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Prevention and Control of Seasonal Influenza with Vaccines

Recommendations of the Advisory Committee on Immunization Practices — United States, 2013–2014

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CDC Adoption of ACIP Recommendations

ACIP is chartered as a federal advisory committee to provide expert external advice and guidance to the Director of the Centers for Disease Control and Prevention (CDC) on use of vaccines and related agents for the control of vaccine-preventable diseases in the civilian population of the United States. Recommendations for routine use of vaccines in children and adolescents are harmonized to the greatest extent possible with recommendations made by the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), and the American College of Obstetricians and Gynecologists. Recommendations for routine use of vaccines in adults are reviewed and approved by the American College of Physicians (ACP), AAFP, the American College of Obstetricians and Gynecologists, and the American College of Nurse-Midwives. ACIP recommendations adopted by the CDC Director become agency guidelines on the date published in the *Morbidity and Mortality Weekly Report* (*MMWR*).

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Prevention and Control of Seasonal Influenza with Vaccines

Recommendations of the Advisory Committee on Immunization Practices — United States, 2013–2014

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SUMMARY

This report updates the 2012 recommendations by CDC's Advisory Committee on Immunization Practices (ACIP) regarding the use of influenza vaccines for the prevention and control of seasonal influenza (CDC. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2012;61:613–8). Routine annual influenza vaccination is recommended for all persons aged ≥6 months. For the 2013–14 influenza season, it is expected that trivalent live attenuated influenza vaccine (LAIV3) will be replaced by a quadrivalent LAIV formulation (LAIV4). Inactivated influenza vaccines (IIVs) will be available in both trivalent (IIV3) and quadrivalent (IIV4) formulations. Vaccine virus strains included in the 2013–14 U.S. trivalent influenza vaccines will be an A/California/7/2009 (H1N1)–like virus, an H3N2 virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011, and a B/Massachusetts/2/2012–like virus. Quadrivalent vaccines will include an additional influenza B virus strain, a B/Brisbane/60/2008–like virus, intended to ensure that both influenza B virus antigenic lineages (Victoria and Yamagata) are included in the vaccine. This report describes recently approved vaccines, including LAIV4, IIV4, trivalent cell culture-based inactivated influenza vaccine (ccIIV3), and trivalent recombinant influenza vaccine (RIV3). No preferential recommendation is made for one influenza vaccine product over another for persons for whom more than one product is otherwise appropriate. This information is intended for vaccination providers, immunization program personnel, and public health personnel. These recommendations and other information are available at CDC's influenza website (http://www.cdc.gov/flu); any updates also will be found at this website. Vaccination and health-care providers should check the CDC influenza website periodically for additional information.

Introduction

Influenza viruses typically circulate widely in the United States annually from the late fall through early spring. Although most persons who become infected with influenza viruses will recover without sequelae, influenza can cause serious illness and death, particularly among persons aged ≥65 years and <2 years and those with medical conditions that confer high risk for complications from influenza (*1–4*). During 30 seasons from the 1976–77 season through the 2005–06 season, estimated influenza-associated deaths ranged from 3,000 to 49,000 annually (*4*).

Annual influenza vaccination is the primary means of preventing influenza and its complications. There are many types of influenza vaccines, and the naming conventions have evolved over time (Box). Routine annual influenza vaccination for all persons aged ≥6 months who do not have contraindications has been recommended by the CDC and CDC's Advisory Committee on Immunization Practices (ACIP) since 2010 (*5*). This report provides updated recommendations and guidance for vaccination providers regarding the use of influenza vaccines for the 2013–14 season.

The material in this report originated in the National Center for Immunization and Respiratory Diseases, Anne Schuchat, MD, Director; Influenza Division, Nancy Cox, PhD, Director; and the National Center for Emerging and Zoonotic Infectious Diseases, Beth Bell, MD, Director; Immunization Safety Office, Frank DeStefano, MD, Director.
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BOX. Naming conventions for influenza vaccines

- The former abbreviation TIV (Trivalent Inactivated Influenza Vaccine, previously used for inactivated influenza vaccines) has been replaced with the new abbreviation IIV (Inactivated Influenza Vaccine). For the 2013–14 season, IIVs as a class will include:
  - egg-based and cell culture-based trivalent inactivated influenza vaccines (IIV3), and
  - egg-based quadrivalent inactivated influenza vaccine (IIV4).
- RIV refers to recombinant hemagglutinin influenza vaccine, available as a trivalent formulation (RIV3) for the 2013–14 season.
- LAIV refers to live-attenuated influenza vaccine, available as a quadrivalent formulation (LAIV4) for the 2013–14 season.
- LAIV, IIV, and RIV denote vaccine categories; numeric suffix specifies the number of antigens in the vaccine.
- When necessary to refer specifically to cell culture-based vaccine, the prefix "cc" is used (e.g., "ccIIV3").

Methods

ACIP provides annual recommendations for the prevention and control of influenza. The ACIP Influenza Work Group* meets by teleconference every 2–4 weeks throughout the year. Work Group membership includes several voting members of ACIP and representatives of ACIP Liaison Organizations. Discussions include topics such as influenza surveillance, vaccine effectiveness and safety, vaccine coverage, program feasibility, cost-effectiveness, and vaccine supply. Presentations are requested from invited experts, and published and unpublished data are discussed. For newly licensed influenza vaccines, discussion pertaining to new recommendations in this report included presentations of clinical data. For minor modifications to the recommendations for vaccination of persons with egg allergy, discussion included a review of influenza vaccine safety surveillance data from the Vaccine Adverse Event Reporting System (VAERS) for the 2012–13 season (see Surveillance for Anaphylaxis Following Influenza Vaccination).

Information presented in this report reflects recommendations presented during public meetings of the ACIP and approved on February 21, 2013, and on June 20, 2013. Meeting minutes and information on ACIP membership and conflicts of interest are available on the ACIP website (http://www.cdc.gov/vaccines/acip/meetings/meetings-info.html). Modifications were made to the ACIP statement during subsequent review at CDC to update and clarify wording in the document. Further updates, if needed, will be posted at CDC's influenza website (http://www.cdc.gov/flu).

Primary Changes and Updates in the Recommendations

Routine annual influenza vaccination of all persons aged ≥6 months continues to be recommended. No preferential recommendation is made for one influenza vaccine product over another for persons for whom more than one product is otherwise appropriate. Updated information and guidance in this document include the following:

- 2013–14 U.S. trivalent influenza vaccines will contain an A/California/7/2009 (H1N1)–like virus, an H3N2 virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011, and a B/Massachusetts/2/2012–like virus. Quadrivalent vaccines will include an additional vaccine virus strain, a B/Brisbane/60/2008–like virus.
- Several new, recently licensed vaccines will be available for the 2013–14 season and are acceptable alternatives to other licensed vaccines indicated for their respective age groups. These vaccines include the following:
  - A quadrivalent live attenuated influenza vaccine (LAIV4; Flumist Quadrivalent [MedImmune, Gaithersburg, Maryland]) is expected to replace the trivalent (LAIV3) formulation. FluMist Quadrivalent is indicated for healthy, nonpregnant persons aged 2 through 49 years.
  - A quadrivalent inactivated influenza vaccine (IIV4; Fluarix Quadrivalent [GlaxoSmithKline, Research Triangle Park, North Carolina]) will be available, in addition to the previous trivalent formulation. Fluarix Quadrivalent is indicated for persons aged ≥3 years.
  - A quadrivalent inactivated influenza vaccine (IIV4; Fluzone Quadrivalent [Sanofi Pasteur, Swiftwater, Pennsylvania]) will be available, in addition to the previous trivalent formulation. Fluzone Quadrivalent is indicated for persons aged ≥6 months.
  - A quadrivalent inactivated influenza vaccine (IIV4; FluLaval Quadrivalent [ID Biomedical Corporation/GlaxoSmithKline]) will be available, in addition to the previous trivalent formulation. FluLaval Quadrivalent is indicated for persons aged ≥3 years.
  - A trivalent cell culture-based inactivated influenza vaccine (ccIIV3; Flucelvax [Novartis Vaccines and

*A list of the members of the ACIP Influenza Vaccine Work Group appears on page 43. The contributors to this report have disclosed that they have no financial interest, relationship, affiliation, or other association with any organization that might represent a conflict of interest.

Diagnostics, Cambridge, Massachusetts]) is indicated for persons aged ≥18 years.
  - A recombinant hemagglutinin (HA) vaccine (RIV3; FluBlok [Protein Sciences, Meriden, Connecticut]) is indicated for persons aged 18 through 49 years.
- RIV3, an egg-free vaccine, is now an option for vaccination of persons aged 18 through 49 years with egg allergy of any severity.
- For persons with egg allergy who have no known history of egg exposure but for whom results suggestive of egg allergy have been obtained on previous allergy testing, consultation with a physician with expertise in the management of allergic conditions is recommended before vaccination.

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 based upon characterization of two surface antigens: hemagglutinin (HA) and neuraminidase (NA). Since 1977, influenza A(H1N1) viruses, influenza A(H3N2) viruses, and influenza B viruses have co-circulated globally. Influenza A virus subtypes and B viruses are further separated into groups on the basis of antigenic similarities. New influenza virus variants emerge via frequent antigenic change (i.e., antigenic drift), resulting from point mutations and recombination events that occur during viral replication (*6*). Immunity to surface antigens, HA and NA, reduces likelihood of infection (*7,8*). Antibody against one influenza virus type or subtype confers limited or no protection against another type or subtype. Moreover, antibody to one antigenic type or subtype of influenza virus might not confer immunity to a new antigenic variant of the same type or subtype (*9*). Frequent emergence of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics, and necessitates consideration for adjustment of vaccine viruses each season.

Larger genetic changes, or antigenic shifts, occur among influenza A viruses, less frequently than antigenic drift events (*6*). The new or substantially different influenza A virus subtypes resulting from antigenic shifts have the potential to cause pandemics when they cause human illness, because they are efficiently transmitted from human to human in a sustained manner, and there is little or no pre-existing immunity among humans (*6*). In April 2009, human infections with a novel influenza A(H1N1) virus caused a worldwide pandemic. While not a new influenza A virus subtype, most humans had limited or no pre-existing antibody to key HA epitopes, and thus widespread transmission occurred. This virus is antigenically distinct from human influenza A(H1N1) viruses in circulation from 1977 through spring 2009. The HA gene is most closely related to that of contemporary influenza A viruses circulating among pigs during several preceding decades. This HA gene is believed to have evolved from the avian-origin 1918 pandemic influenza A(H1N1) virus, which is thought to have entered human and swine populations at about the same time (*10,11*).

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 (*12*). Influenza B viruses from both lineages have co-circulated in most recent influenza seasons (*13,14*). The trivalent influenza vaccines available in recent seasons have contained one influenza B virus, representing only one lineage. The proportion of circulating influenza B viruses that are of the lineage represented in the vaccine has varied. During the 10 seasons from 2001–02 through 2010–11, the predominant circulating influenza B virus lineage was represented in the trivalent vaccine in only five seasons (*15*).

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. Studies that report rates of clinical outcomes without laboratory confirmation of influenza (e.g., respiratory illness requiring hospitalization during influenza season) can be difficult to interpret because of coincident circulation of other respiratory pathogens (e.g., respiratory syncytial virus) (*16–18*). However, increases in health-care provider visits for acute febrile respiratory illness occur annually, coinciding with periods of increased influenza activity, making influenza-like illness surveillance systems valuable in understanding the seasonal and geographic occurrence of influenza each year (*19*).

In typical winter influenza seasons, increases in deaths and hospitalizations are observed during periods when influenza viruses are circulating. Excess deaths and hospitalizations occurring during influenza season have been estimated for decades. Although not all excess events occurring during periods when influenza viruses are circulating can be attributed to influenza, these estimates are useful for following season-to-season trends in influenza-associated outcomes. Estimates that include only outcomes attributed to pneumonia and influenza likely underestimate the burden of severe illnesses that are at least partly attributable to influenza because this category excludes deaths caused by exacerbations of underlying cardiac and pulmonary conditions that are associated with influenza

virus infection (*20–22*). Thus, use of a broader category of respiratory and circulatory excess events are at times preferred for influenza burden estimates. During seasonal influenza epidemics from 1979–80 through 2000–01, 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) (*21*). Between the 1976–77 season and 2006–07 season, estimated annual deaths attributable to influenza ranged from 3,000 to 49,000 each season (*4*).

Influenza viruses cause illness among persons of all ages (*1–3,23–25*). Infection rates are highest among children, but complications, hospitalizations, and deaths from seasonal influenza are typically greatest among persons aged ≥65 years, children aged <5 years and particularly those aged <2 years, and persons of any age who have medical conditions that confer increased risk for complications from influenza (*1,2,25–29*). Estimated rates of influenza-associated deaths vary substantially by age group. 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 through 49 years, 7.5 among persons aged 50 through 64 years, and 98.3 among persons aged ≥65 years (*20*).

Children: Among children aged <5 years, influenza is a common cause of outpatient medical visits. During the 2002–03 and 2003–04 seasons, 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 and 6%–29% of emergency department (ED) visits. From these data, the rate of clinic visits for influenza was estimated to be 50–95 visits per 1,000 children aged <5 years, and the rate of ED visits was 6–27 visits per 1,000 children aged <5 years (*3*). In a retrospective cohort study of children aged <15 years covering 19 consecutive seasons, an annual average of 6–15 additional outpatient visits and 3–9 additional antibiotic courses per 100 children were estimated to be attributable to influenza (*29*). During 1993–2004 in the Boston area, the rate of ED visits for respiratory illness attributed to influenza based on viral surveillance data among children aged 6 months through 7 years during the winter respiratory illness season ranged from 22.1 per 1,000 children aged 6–23 months to 5.4 per 1,000 children aged 5 through 7 years (*30*).

Estimated rates of influenza-associated hospitalization are substantially higher among infants and younger children than among older children and are similar to rates for other groups considered at higher risk for influenza-related complications (*31–36*), including persons aged ≥65 years. During 1993–2008, the estimated rate of influenza-associated hospitalizations was 91.5 per 100,000 for among children aged <1 year and 21.9 per 100,000 for children aged 1 through 4 years (*37*). 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 (*3,35,38–40*). Annual hospitalization rates for laboratory-confirmed influenza decrease with increasing age, ranging from 240–720 hospitalizations per 100,000 children aged <6 months to approximately 20 hospitalizations per 100,000 children aged 2 through 5 years (*3*). Hospitalization rates for children aged <5 years with high-risk medical conditions are higher, with estimates of 250–500 hospitalizations per 100,000 children in some studies (*27,41,42*).

In the United States, death associated with laboratory-confirmed influenza virus infection among children aged <18 years has been a nationally reportable condition since 2004 (*43*). Since reporting began, the annual number of influenza-associated pediatric deaths during regular influenza seasons has ranged from 34 deaths during the 2011–12 season to 122 deaths during the 2010–11 season (*43,44*). However, between April 15, 2009 and October 2, 2010 (the period of the 2009 H1N1 influenza pandemic), approximately 300 deaths attributed to laboratory-confirmed 2009 H1N1 influenza occurred among children aged <18 years (*44*), the majority of whom had one or more underlying medical conditions previously associated with conferring a greater risk for influenza complications (*45*).

Adults: Hospitalization rates during typical influenza seasons are highest for adults aged ≥65 years. One retrospective analysis of data from managed-care organizations collected during 1996–2000 estimated that the risk during influenza season among persons aged ≥65 years with high-risk underlying medical conditions was approximately 560 influenza-associated hospitalizations per 100,000 persons compared with approximately 190 per 100,000 among lower risk persons in this age group. Persons aged 50 through 64 years who have underlying medical conditions also were at substantially increased risk for hospitalization during influenza season compared with healthy adults aged 50 through 64 years (*26*).

Deaths associated with influenza are also most frequent among older adults. From the 1976–77 season through the 2006–07 season, an estimated yearly average of 21,098 influenza-related deaths occurred among adults aged ≥65 years, comprising approximately 90% of estimated annual average deaths across all age groups. In comparison, the average annual mortality was estimated to be 124 deaths among persons aged <19 years and 2,385 deaths among persons aged 19 through 64 years (*4*).

Among healthy younger adults, illness caused by seasonal influenza is typically less severe and results less frequently in hospitalization, as compared with children aged <5 years, adults aged ≥65 years, pregnant women, or persons with chronic

medical conditions. However, influenza is an important cause of outpatient medical visits and worker absenteeism among healthy adults aged 19 through 49 years. In one economic modeling analysis, the average annual burden of seasonal influenza among adults aged 18 through 49 years without medical conditions that confer 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 (*46*). Studies of worker vaccination programs have reported lower rates of influenza like illness (ILI) (*47,48*), lost work time (*47–50*), and health-care visits (*48,49*) in association with vaccination.

During the 2009 H1N1 pandemic, adults aged <65 years appeared to be at higher risk for influenza-related complications (*51,52*) compared with typical influenza seasons. 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 (*51–55*). 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 higher rates of deaths among American Indians/Alaska Natives and indigenous populations in other countries (*56–61*). 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 (*61,62*).

The duration of influenza symptoms might be prolonged and the severity of influenza illness increased among persons with human immunodeficiency virus (HIV) infection (*63–66*). A retrospective study of women aged 15 through 64 years enrolled in Tennessee's Medicaid program determined that the attributable risk for cardiopulmonary hospitalizations and deaths among women with HIV infection was higher during influenza seasons than it was either before or after periods when influenza viruses were circulating. The risk for these events was higher for HIV-infected women (influenza attributable risk 152 per 10,000) than it was for women with other underlying medical conditions evaluated (including an influenza-attributable risk of 35 per 10,000 for chronic renal disease, 27 per 10,000 for chronic heart disease, and 25 per 10,000 for chronic lung disease) (*67*). Another study estimated that the excess death rate attributable to influenza 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 through 54 years and 64–70 deaths per 100,000 persons in the general population aged ≥65 years (*68*).

Increased severity of influenza among pregnant women was reported during the pandemics of 1918–1919, 1957–1958, and 2009–2010 (*69–74*). Severe infections among postpartum (delivered within previous 2 weeks) women also were observed in the 2009–10 pandemic (*69,73*). In a case series conducted during the 2009 H1N1 pandemic, 56 deaths were reported among 280 pregnant women admitted to intensive care units. Among the deaths, 36 (64%) occurred in the third trimester. Pregnant women who were treated with antivirals more than 4 days after symptom onset were more likely to be admitted to an intensive care unit (57% versus 9%; relative risk [RR] = 6.0; 95% confidence interval [CI] 3.5–10.6) than those treated within 2 days after symptom onset (*75*).

Case reports and some observational studies suggest that pregnancy also increases the risk for seasonal influenza complications for the mother (*76–78*). Most of these studies have measured changes in excess hospitalizations or outpatient visits for respiratory illness during influenza season rather than laboratory-confirmed influenza. 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 134,188 pregnant women, 510 (0.4%) were hospitalized, and 33,775 (25%) visited a clinician during pregnancy for a respiratory illness (*78*).

With regard to pregnancy outcomes, one cohort study noted that pregnant women with respiratory hospitalizations during the influenza season did not have an increase in adverse perinatal outcomes or delivery complications compared with pregnant controls without an influenza hospitalization (*79*); another study indicated an increase in delivery complications, including fetal distress, preterm labor, and cesarean delivery (*80*). However, infants born to women with laboratory-confirmed influenza during pregnancy do not have higher rates of low birthweight, congenital abnormalities, or lower Apgar scores compared with infants born to uninfected women (*81,82*).

Influenza Vaccine Effectiveness

Evaluating Influenza Vaccine Efficacy and Effectiveness Studies

Estimates of efficacy (i.e., prevention of illness among vaccinated persons enrolled in controlled clinical trials) and vaccine effectiveness (i.e., prevention of illness in vaccinated populations) of influenza vaccines depend on many factors, including the age and immunocompetence of the vaccine recipient, the degree of similarity between the viruses in the vaccine and those in circulation, study design, and the outcome being measured. Studies of influenza vaccine efficacy and effectiveness have used a variety of outcome measures, including the prevention of medically attended acute respiratory illness (MAARI), prevention of laboratory-confirmed influenza

illness, prevention of influenza or pneumonia-associated hospitalizations or deaths, or prevention of seroconversion to circulating influenza virus strains. Efficacy or effectiveness for more specific outcomes such as laboratory-confirmed influenza typically will be higher than for less specific outcomes such as MAARI because the causes of MAARI include infections with other pathogens that influenza vaccination would not be expected to prevent (*83*). Observational studies that compare less-specific outcomes among vaccinated populations to those among unvaccinated populations might be more subject to biases than studies using laboratory outcomes. For example, an observational study that finds that influenza vaccination reduces overall mortality among elderly persons might be biased if healthier persons in the study are more likely to be vaccinated, and thus less likely to die for any reason (*84,85*). For studies assessing laboratory-confirmed outcomes, estimates of vaccine efficacy may also be affected be the sensitivity of the diagnostic tests used. A 2012 simulation study found that for each percentage point decrease in diagnostic test specificity for influenza virus infection, vaccine effectiveness would be underestimated by approximately 4% (*86*). Randomized controlled trials that measure laboratory-confirmed influenza virus infections as the outcome are the most persuasive evidence of vaccine efficacy, but such data are not available for all populations. Such trials might be difficult to conduct among groups recommended to receive vaccine annually.

Immune Response Following Vaccination

Humoral and cell-mediated responses to influenza vaccination have been studied among children and adults. Serum antibodies (*7,87*) are considered to be correlates of vaccine-induced protection. Increased levels of antibody induced by vaccination decrease the risk for illness caused by strains that are antigenically similar to those strains of the same type or subtype included in the vaccine (*8,88–90*). Most healthy children and adults have high titers of strain-specific antibody after vaccination (*89,91*). However, although immune correlates such as achievement of certain antibody titers after vaccination correlate well with immunity on a population level, reaching certain antibody threshold (typically defined as a hemagglutination inhibition antibody or HAI titer of 32 or 40) might not predict protection from infection on the individual level.

While LAIV induces lower levels of serum antibodies compared with IIV, LAIV more effectively induces cellular immune responses than IIV. The magnitude of this effect differs among adults and children. One study of children aged 6 months through 9 years and adults aged 22 through 49 years noted a significant increase in influenza A-specific interferon ϒ-producing CD4+ and CD8+ T-cells among children following LAIV but not following IIV. No significant increase in these parameters was noted among adults following either vaccine (*92*).

Antibody elicited by vaccination is generally strain-specific, such that antibody against one influenza virus type or subtype confers limited or no protection against another type or subtype, nor does it confer protection against antigenic variants of the same virus that arise by antigenic drift. Cellular immune responses might arise from more conserved viral epitopes and thus potentially provide broader heterosubtypic immunity. Administration of 2007–08 seasonal vaccine to adults boosted T-cell responses to both seasonal and pandemic 2009(H1N1) HA (*93*); this effect was significantly greater for LAIV. Among children aged 6 through 35 months, LAIV (but not IIV) induced T-cell responses to highly conserved viral peptides (*94*).

Duration of Immunity

The composition of influenza vaccines is changed in most seasons, with one or more vaccine strains replaced annually to provide protection against viruses that are anticipated to circulate. Evidence from some clinical trials indicates that that protection against viruses that are antigenically similar to those contained in the vaccine extends at least for 6–8 months, particularly in nonelderly populations. In some situations, duration of immunity might be longer, and such effects can be detected if circulating influenza virus strains remain antigenically similar for multiple seasons. For example, 3 years after vaccination with the A/Hong Kong/68 vaccine (i.e., the 1968 pandemic vaccine), effectiveness was 67% for prevention of influenza caused by the A/Hong Kong/68 virus (*95*). In randomized trials conducted among healthy college students, immunization with IIV provided 92% and 100% efficacy against influenza H3N2 and H1N1 illnesses, respectively, during the first year after vaccination, and a 68% reduction against H1N1 illness during the second year after vaccination (when the predominant circulating virus was H1N1) without revaccination (*96*). In a similar study of young adults conducted in 1986–1987, IIV reduced influenza A(H1N1) illness by 75% in the first year after vaccination, reduced H3N2 illness by 45% in the second year, and reduced H1N1 illness by 61% during the third year after vaccination (*96*). Serum HAI influenza antibodies and nasal IgA elicited by vaccination remain detectable in children vaccinated with LAIV for >1 year after vaccination (*97*). 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 previous 1999–00 season (*98*). A review

of four trials (three randomized blinded and one open-label) of LAIV conducted among young children aged 6 months through 18 years reported that efficacy against A(H1N1) and A(H3N2) was similar at 9–12 months postvaccination to efficacy at 1–<5 months postvaccination; for B strains efficacy was still comparable at 5–7 months postvaccination. Two randomized trials and one open label study reported residual efficacy through a second season without revaccination, albeit at lower levels than observed in the first season (*98–102*).

Adults aged ≥65 years typically have diminished immune responses to influenza vaccination compared with healthy younger adults (*103,104*). One review of the published literature concluded that no clear evidence existed that vaccine-induced antibody declined more rapidly in the elderly (*105*). A case-control study conducted in Navarre, Spain during the 2011–12 season revealed a decline in vaccine effectiveness from 61% (95% CI = 5–84) in the first 100 days postvaccination, to 42% (95% CI = -39–75) for days 110–119 days postvaccination, to -35% (95% CI = -211–41) thereafter. This decline primarily affected persons aged ≥65 years, among whom effectiveness declined from 85% (95% CI = -8–98) to 24% (95% CI = -224–82) to -208 (95% CI = -1,563–43) over the same time intervals. However, most viruses isolated among infected vaccinees did not match the vaccine strains (*106*). In addition, the wide CIs surrounding the point estimates indicate that larger studies are needed to further characterize the magnitude of possible declines in vaccine effectiveness through the season. Limited available data suggest that administration of additional vaccine doses during the same season does not increase the antibody response among elderly vaccinees (*107*).

Immunogenicity, Efficacy, and Effectiveness of IIV

Inactivated vaccines, which are administered by intramuscular or intradermal injection, contain nonreplicating virus. Immunogenicity, effectiveness, and efficacy have been evaluated in children and adults, although fewer data from randomized studies are available for some age groups (e.g., persons aged ≥65 years).

Children

Children aged ≥6 months typically develop protective levels of antibodies against specific influenza virus strains after receiving the recommended number of doses of seasonal inactivated influenza vaccine (*87,91,108–111*). Immunogenicity studies using the influenza A(H1N1) 2009 monovalent vaccine indicated that 80%–95% of vaccinated children developed protective antibody levels to the 2009 H1N1 influenza virus after 2 doses (*112,113*); response after 1 dose was 50% for children aged 6 through 35 months and 75% for those aged 3 through 9 years (*114*). Studies involving seasonal inactivated influenza vaccine among young children have demonstrated that 2 vaccine doses provide better protection than 1 dose during the first season a child is vaccinated. In a study of children aged 5 through 8 years who received trivalent inactivated vaccine (TIV) for the first time, the proportion of children with protective antibody responses was significantly higher after 2 doses than after 1 dose and higher after 2 doses than after 1 dose of TIV for each antigen (p = 0.001 for influenza A[H1N1]; p = 0.01 for influenza A[H3N2]; and p = 0 0.001 for influenza B) (*115*). Vaccine effectiveness is lower among children aged <5 years who have never received influenza vaccine previously or who received only 1 dose in their first year of vaccination than it is among children who received 2 doses in their first year of being vaccinated. Two retrospective studies of children who had received only 1 dose of IIV in their first year of being vaccinated determined that no decrease was observed in ILI-related office visits compared with unvaccinated children (*116,117*). Similar results were reported in a case-control study of approximately 2,500 children aged 6 through 59 months in which laboratory-confirmed influenza was the outcome measured (*118*). The results of these studies support the recommendation that all children aged 6 months through 8 years who are being vaccinated for the first time should receive 2 vaccine doses separated by at least 4 weeks.

Some studies suggest that antibody responses among children at higher risk for influenza-related complications (i.e., children with chronic medical conditions) are lower than those reported typically among healthy children (*119,120*). However, another study found that 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 (*121*).

Estimates of the efficacy or effectiveness of inactivated vaccine among children aged ≥6 months vary by season and study design. Limited efficacy data are available for children from studies that used culture- or reverse transcription–polymerase chain reaction (RT-PCR)–confirmed influenza virus infections as the primary outcome. A recent large randomized trial compared rates of RT-PCR–confirmed influenza virus infections among 4,707 children aged 6 through 71 months who received inactivated vaccine, inactivated vaccine with MF59 oil-in-water adjuvant, or a control vaccine (meningococcal conjugate vaccine or tick-borne encephalitis vaccine). During the two seasons of the study (2007–08 and 2008–09), efficacy of inactivated vaccine versus control vaccine was 43% (95% CI = 15%–61%) and of inactivated vaccine plus MF59 versus control was 86% (95% CI = 74%–93%) (*122*). In a randomized trial conducted during five influenza

seasons (1985–1990) in the United States among children aged 1 through 15 years, receipt of inactivated vaccine reduced culture-confirmed influenza A by 77% (95% CI = 20%–93%) (*89*). A single season placebo-controlled study that enrolled 192 children aged 3 through 19 years found the efficacy of inactivated vaccine was 56% among healthy children aged 3 through 9 years and 100% among healthy children and adolescents aged 10 through 18 years (*123*); influenza infection was defined either by viral culture or, in the absence of a positive culture, by a postseason antibody rise in HI titer among symptomatic children from whom no other virus was isolated and whose symptoms began within 10 days of isolation of influenza from a household contact or during peak influenza activity in the community. In a randomized, double-blind, placebo-controlled trial conducted during two influenza seasons among 786 children aged 6 through 24 months, estimated efficacy was 66% (95% CI = 34%–82%) against culture-confirmed influenza illness during the 1999–00 influenza season but did not reduce culture-confirmed influenza illness significantly during the 2000–01 season, when influenza attack rates were lower (3% versus 16% during the 1999–00 season) (*124*).

Studies using a serological definition of influenza virus infection have raised concerns that dependence on a serological diagnosis of influenza in clinical trials might lead to overestimation of vaccine efficacy because of an "antibody ceiling" effect in adult subjects with historic exposures to both natural infections and vaccination. This could result in the decreased likelihood that antibody increases can be observed in vaccinated subjects after influenza infection with circulating viruses, as compared with adult subjects in control arms of trials. Thus, vaccinated subjects might be less likely to show a fourfold increase in antibody levels can after influenza infection with circulating viruses compared with unvaccinated subjects in such studies. Whether there is a substantial antibody ceiling effect in children, particularly younger children without extensive experience with influenza antigens, is not known.

Several observational studies to assess vaccine effectiveness were conducted during the 2003–04 influenza season, when the match between vaccine virus antigens and circulating viruses was suboptimal. A case-control study conducted during the 2003–04 season estimated vaccine effectiveness among fully vaccinated children aged 6 through 59 months to be 49% (95% CI = 30%–60%) against influenza diagnosed by a positive antigen-detection test with a specificity of 96% (*125*). An observational study among children aged 6 through 59 months with culture- or PCR-confirmed influenza compared with children who tested negative for influenza reported vaccine effectiveness of 44% (95% CI = -42%–78%) in the 2003–04 influenza season and 57% (95% CI = 28%–74%) during the 2004–05 season (*118*). Receipt of only 1 vaccine dose among children being vaccinated for the first time was not effective in either season. A retrospective cohort study conducted during the 2003–04 season among approximately 30,000 children aged 6 months through 8 years reported vaccine effectiveness of 51% (95% CI = 33%–64%) against medically attended, clinically diagnosed pneumonia or influenza (i.e., there was no laboratory confirmation of influenza infection). Estimated vaccine effectiveness was 49% (95% CI = 9%–71%) among children aged 6 through 23 months (*117*). Another retrospective cohort study of similar size that used a syndromically defined outcome and was conducted during the 2003–04 season among healthy children aged 6 through 21 months estimated effectiveness of 2 IIV doses to be 87% (95% CI = 78%–92%) against pneumonia/influenza-related office visits (*116*). It is difficult to reconcile the high effectiveness estimate in this study with others from the same season because it focused on younger children and used a nonspecific outcome.

Among children, IIV effectiveness might be lower in very young children compared with older children (*122,126*). A 2012 systematic review of published studies estimated vaccine effectiveness among healthy children was 40% (95% CI = 6%–61%) for those aged 6 through 23 months and 60% (95% CI = 30%–78%) for those aged 24 through 59 month (*127*). However, during the 2010–11 season, when all three vaccine virus strains appeared antigenically similar to circulating strains, vaccine effectiveness among children was similar to that observed for those of all ages in a large multisite observational study that used RT-PCR–confirmed medically attended influenza virus infections as the outcome (all ages: 60%; 95% CI = 54%–66%; vaccine effectiveness among children aged 6 months through 2 years: 58%; 95% CI = 31%–74%; among children aged 3 through 8 years: 69%; 95% CI = 56%–77%) (*128*).

Because of the long-standing recommendation for annual influenza vaccination of immunosuppressed children and those with chronic medical conditions, randomized placebo-controlled studies to study efficacy specifically in these children are lacking. In a nonrandomized controlled trial among children aged 2 through 6 years and 7 through 14 years who had asthma, vaccine efficacy was 54% and 78% against laboratory-confirmed influenza A(H3N2) infection and 22% and 60% against laboratory-confirmed influenza B infection, respectively. However, vaccine effectiveness was not significant against B viruses for vaccinated children aged 2 through 6 years with asthma who did not have substantially fewer type B influenza virus infections compared with the control group in this study (*129*). The association between vaccination and prevention of asthma exacerbations is unclear.

One study suggested that vaccination might provide protection against asthma exacerbations (*130*).

Receipt of IIV was associated with a reduction in acute otitis media in some studies, but no effect was observed in others. Two studies reported that IIV decreases the risk for influenza-related otitis media among children (*131,132*). However, a large study conducted among young children (mean age: 14 months) indicated that IIV did not reduce the proportion of children who developed acute otitis media during the study (*124*). Influenza vaccine effectiveness against a nonspecific clinical outcome such as acute otitis media, which is caused by a variety of pathogens and typically is not diagnosed by use of influenza virus detection methods, would be expected to be lower than effectiveness against laboratory-confirmed influenza.

Adults Aged <65 Years

One dose of IIV tends to be highly immunogenic in healthy adults aged <65 years. For example, monovalent influenza A(H1N1)pdm09 (2009[H1N1]) vaccines were highly immunogenic, with approximately 90% of vaccinated adults aged 18 through 64 years demonstrating antibody levels considered protective (*133,134*). A 2012 meta-analysis found that IIV efficacy against RT-PCR or culture-confirmed influenza was 59% (95% CI = 51%–67%) among adults aged 18 through 65 years in eight of twelve seasons analyzed in ten randomized controlled trials (*135*). A 2010 meta-analysis of randomized clinical trial results among healthy adults aged 16 through 65 years suggested that when vaccine and circulating influenza viruses strains were well-matched, efficacy against influenza symptoms was 73% (95% CI = 54%–84%) whereas it was 44% (95% CI = 23%–59%) when they were not well-matched. However, a standard definition of "matched" was not specified (*136*). Vaccination of healthy adults was associated with decreased work absenteeism and use of health-care resources in some studies, when the vaccine and circulating viruses are well-matched (*48,137*).

Adults with Chronic Medical Conditions

There is some evidence to suggest that vaccine effectiveness among adults aged <65 years who have medical conditions conferring higher risk for influenza complications typically might be 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 (tests used not specified) illness among adults aged 50 through 64 years with high-risk conditions was 48% (95% CI = 21%–66%) compared with 60% (95% CI = 43%–72%) for healthy adults. By contrast, for the subset of cases who were hospitalized (n = 106), effectiveness varied more substantially by risk status: among those with high-risk conditions vaccine effectiveness was 36% (95% CI = 0–63%) while it was 90% (95% CI = 68%–97%) among healthy adults (*138*). Adults with immunocompromising conditions (e.g., solid organ transplant and HIV infection with low CD4 counts) have lower serum antibody responses after vaccination compared with healthy young adults (*139,140*).

A randomized controlled trial conducted among adults (median age: 68 years) in Thailand with chronic obstructive pulmonary disease (COPD) observed that vaccine efficacy was 76% (95% CI = 32%–93%) in preventing influenza-associated acute respiratory infection (defined as respiratory illness associated with HAI titer increase and/or positive influenza antigen on indirect immunofluorescence testing) during a season when circulating influenza viruses were well-matched to vaccine viruses (*141*). A meta-analysis that examined effectiveness among persons with chronic obstructive pulmonary disease identified evidence of reduced risk for exacerbation from vaccination (*142*). However, another meta-analysis of published studies concluded that evidence was insufficient to demonstrate that persons with asthma benefit from vaccination (*143*).

A few randomized controlled trials have studied the effects of influenza vaccination on outcomes not usually associated with influenza virus infection. There is evidence suggesting that acute respiratory infections might trigger acute vascular events mediated by atherosclerosis (*144*). In particular, respiratory infections coded as influenza or occurring when influenza viruses were circulating transiently increase the risk for acute myocardial infarctions (*145*). A meta-analysis of two small randomized trials of influenza vaccination in persons with cardiovascular disease yielded a pooled efficacy estimate of 49% for prevention of acute myocardial infarction or cardiac death, although this effect was not statistically significant (95% CI = -76%–85%) (*146*).

Some observational studies that have provided estimates of vaccine effects for serious complications of influenza infections without laboratory confirmation of influenza have found large reductions in hospitalizations or deaths. For example, in a case-control study conducted during the 1999–00 season in the Netherlands among 75,227 persons aged <65 years with underlying medical conditions, vaccination was reported to reduce deaths attributable to any cause by 78% and reduce hospitalizations attributable to respiratory infections or cardiopulmonary diseases by 87% (*147*). The benefit was greater among those who had been vaccinated previously than among first-time vaccinees (*147*). 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 (*148*). Effects of this magnitude on nonspecific outcomes might have been caused by confounding from unmeasured factors (e.g., dementia and difficulties with

self-care) that are associated strongly with the measured outcomes (*84,85*). Recent studies using methods to account for unmeasured confounding have indicated that vaccine effectiveness among community-dwelling older persons for nonspecific serious outcomes such as pneumonia/influenza hospitalizations or all-cause mortality is <10%, which is much more plausible than higher estimates from earlier studies (*149–151*).

Immunocompromised Persons

In general, HIV-infected persons with minimal AIDS-related symptoms and normal or near-normal CD4+ T-lymphocyte cell counts who receive IIV develop adequate antibody response (*152–154*). Among persons who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, IIV might not induce protective antibody titers (*154,155*); a second dose of vaccine does not improve the immune response in these persons (*155,156*). A recent immunogenicity study of HIV-infected persons aged ≥18 years indicated that seroprotection rates were higher for persons given high-dose IIV (containing 60 μg of HA per vaccine virus) than those given standard-dose vaccine (which contains 15 μg of HA per vaccine virus); the high-dose vaccine is not licensed for persons aged <65 years (*157*). In an investigation of an influenza A outbreak at a residential facility for HIV-infected persons, vaccine was most effective at preventing ILI among persons with >100 CD4+ cells and among those with <30,000 viral copies of HIV type-1/mL (*64*). In a randomized placebo-controlled trial conducted in South Africa among 506 HIV-infected adults, including 349 persons on antiretroviral treatment and 157 who were antiretroviral treatment-naïve, efficacy for culture- or RT-PCR–confirmed influenza illness was 75% (95% CI = 9%–96%) (*158*).

Several relatively small observational studies have suggested that immunogenicity among persons with solid organ transplants varies according to transplant type. Among persons with kidney or heart transplants, the proportion that developed seroprotective antibody concentrations was similar or slightly reduced compared with healthy persons (*159–161*). However, a study among persons with liver transplants indicated reduced immunologic responses to influenza vaccination (*162–164*), especially if vaccination occurred within the 4 months after the transplant procedure (*162*).

Pregnant Women and Neonates

Pregnant women have protective levels of anti-influenza antibodies after vaccination (*165*). Passive transfer of anti-influenza antibodies that might provide protection from vaccinated women to neonates has been reported (*165–169*). One randomized controlled trial conducted in Bangladesh that provided IIV3 vaccination to pregnant women during the third trimester demonstrated a 29% reduction in respiratory illness with fever among the infants and a 36% reduction in respiratory illness with fever among their mothers during the first 6 months after birth, compared with pregnant women receiving 23-valent pneumococcal polysaccharide vaccine. In addition, infants born to vaccinated women had a 63% reduction in laboratory-confirmed influenza illness during the first 6 months of life (*170*). All women in this trial breastfed their infants (mean duration: 14 weeks). Maternal influenza vaccination during pregnancy was associated with significantly reduced risk for influenza virus infection (relative risk: 0.59; 95% CI = 0.37–0.93) and hospitalization for influenza-like illness (ILI) (relative risk: 0.61; 95% CI = 0.45–0.84) among infants aged <6 months in a nonrandomized prospective cohort study; increased antibody titers were also noted in infants through age 2 to 3 months (*171*). 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 (*172*). In a retrospective cohort study conducted during 1995–2001, medical visits for respiratory illness among the infants of vaccinated mothers were not substantially reduced (*173*).

Older Adults

Most studies suggest that antibody responses to influenza vaccination are decreased in older adults, and it is likely that increasing dysregulation of the immune system with aging contributes to the increased likelihood of serious complications of influenza infection (*174*). A review of HAI antibody responses in 31 studies among adults aged ≥58 years found that 42%, 51%, and 35% of older persons seroconverted to H1N1, H3N2, and B vaccine antigens, respectively, compared with 60%, 62%, and 58% of younger persons (*104*). When seroprotection (defined as an HAI titer ≥40) was the outcome, 83%, 84%, and 78% of younger adults versus 69%, 74%, and 67% of older adults achieved protective titers to H1N1, H3N2, and B antigens, respectively (*104*). Although an HAI titer ≥40 is associated with approximately 50% clinical protection from infection, this standard was established in young healthy adults (*8*), and there are few data to suggest that such antibody titers represent a correlate of protection among elderly adults. Limited or no increase in antibody response is reported among elderly adults when a second dose is administered during the same season (*175–177*).

The desire to improve HI responses among adults aged ≥65 years led to the development and licensure of a vaccine with more antigen than standard-dose IIV. Immunogenicity data

from 3 studies of high-dose IIV (Fluzone High-Dose, Sanofi Pasteur) among persons aged ≥65 years indicated that vaccine with four times the HA antigen content of standard-dose vaccine elicited substantially higher HAI titers (*178–180*). Pre-specified criteria for superiority in one clinical trial study was defined by a lower bound of a two-sided CI for the ratio of geometric mean HI titers >1.5 and a difference in fourfold rise of HI titers >10%. These criteria were met for influenza A(H1N1) and influenza A(H3N2) virus antigens (*181*), but not for the influenza B virus antigen (for which criteria for noninferiority were met) (*179*).

The only large randomized placebo-controlled trial conducted among community-dwelling persons aged ≥60 years reported a vaccine efficacy of 58% (95% CI = 26%–77%) against serologically confirmed clinical influenza illness during a season when the vaccine strains were considered to be well-matched to circulating strains (*182*). The outcome used for measuring the efficacy estimate was seroconversion to a circulating influenza virus and a symptomatic illness compatible with a clinical influenza infection. As noted previously, there is concern that seroconversion after symptomatic illness will be less likely among vaccinated persons who have higher levels of pre-existing anti-HA antibody that than among those not vaccinated. Such a situation would lead to an overestimate of the true vaccine efficacy, as was demonstrated in a recent clinical trial conducted among healthy adults aged 18 through 49 years (*183*). Additional information from this trial published after the main results indicated that efficacy among those aged ≥70 years was 57% (95% CI = -36%–87%), similar to the point estimate found among younger persons. However, few persons aged ≥70 years participated in this study, and the wide CI for the estimate of efficacy for persons in this age group included no efficacy (*184*). Influenza vaccine effectiveness in preventing MAARI among elderly persons residing in nursing homes has been estimated at 20%–40% (*185,186*), 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 (*187,188*). Influenza vaccination might reduce the frequency of secondary complications and might reduce the risk for influenza-related hospitalization and death among community-dwelling adults aged ≥65 years with and without high-risk medical conditions (*189–193*). However, these 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. Such methods have been challenged because analyses might not be adjusted adequately to control for the possibility that healthier persons may be more likely to be vaccinated than less healthy persons (*84,85,194–198*).

Immunogenicity, Efficacy, and Effectiveness of LAIV

LAIV virus strains replicate 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, as well as cell-mediated immune responses. The immunogenicity of LAIV has been assessed in multiple studies (*97,199–205*).

Healthy Children

A randomized, double-blind, placebo-controlled trial among 1,602 healthy children aged 15 through 71 months assessed the efficacy of LAIV against culture-confirmed influenza during two seasons (*206,207*). 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 for 1 dose was 86%. The overall efficacy during the two influenza seasons was 92%. Receipt of LAIV also resulted in 21% fewer febrile illnesses and a significant decrease in influenza A-associated otitis media (vaccine efficacy: 94%; 95% CI = 78%–99%) (*206,207*). In a randomized placebo-controlled trial among vaccine-naïve children aged 6 through <36 months which compared 1 versus 2 doses of LAIV, efficacy against culture-confirmed influenza was 58% (95% CI = 45%–68%) after 1 dose of LAIV and 74% (95% CI = 64%–81%) after 2 doses (*100*). 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 through 35 months attending child care centers during consecutive influenza seasons (*208*) in which 85%–89% efficacy was observed. Another study conducted among children aged 12 through 36 months living in Asia during consecutive influenza seasons reported efficacy of 64%–70% (*101*). In one community-based, nonrandomized open-label study, reductions in MAARI were observed among children who received 1 dose of LAIV during the 1999–00 and 2000–01 influenza seasons even though antigenically drifted influenza A/H1N1 and B viruses were circulating during the latter season (*98*). LAIV efficacy in preventing laboratory-confirmed influenza also has been demonstrated in studies comparing the efficacy of LAIV with

IIV rather than with a placebo (see Comparisons of LAIV and IIV Efficacy or Effectiveness).

A meta-analysis of six placebo-controlled studies concluded that the efficacy of LAIV against acute otitis media associated with culture-confirmed influenza among children aged 6 through 83 months was 85% (95% CI = 78%–90%) (*209*). In clinical trials, an increased risk for wheezing postvaccination was observed in LAIV recipients aged <24 months. An increase in hospitalizations was also observed in children aged <24 months after vaccination with LAIV (*210*).

Healthy Adults

A randomized, double-blind, placebo-controlled trial of LAIV effectiveness among 4,561 healthy working adults aged 18 through 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) viruses were not well-matched. The frequency of febrile illnesses was not significantly decreased among LAIV recipients compared with those who received placebo. However, vaccine recipients had significantly fewer severe febrile illnesses (19% reduction) and febrile upper respiratory tract illnesses (24% reduction); and significant reductions in days of illness, days of work lost, days with health-care provider visits, and use of prescription antibiotics and over-the-counter medications (*211*). Estimated efficacy of LAIV against influenza confirmed by either culture or RT-PCR in a randomized, placebo-controlled study among approximately 2,000 young adults was 48% (95% CI = -7%–74%) in the 2004–05 influenza season, 8% (95% CI = -194%–67%) in the 2005–06 influenza season, and 36% (95% CI = 0–59%) in the 2007–08 influenza season; efficacy in the 2004–05 and 2005–06 seasons was not significant (*212–214*).

Comparisons of LAIV and IIV Efficacy or Effectiveness

Both IIV and LAIV have been demonstrated to be effective in children and adults. Studies comparing the efficacy of IIV to that of LAIV have been conducted in a variety of settings and populations using several different outcomes. Among adults, most comparative studies have demonstrated either that LAIV and IIV were of similar efficacy or that IIV was more efficacious (*215*). One randomized, double-blind, placebo-controlled challenge study that was conducted among 92 healthy adults aged 18 through 41 years assessed the efficacy of both LAIV and IIV in preventing influenza infection when artificially challenged with wild-type strains that were antigenically similar to vaccine strains (*205*). The overall efficacy in preventing laboratory-documented influenza illness (defined as respiratory symptoms with either isolation of wild-type influenza virus from nasal secretions or fourfold and/or greater HAI antibody response to challenge) from all three influenza strains combined was 85% for LAIV and 71% for IIV when study participants were challenged 28 days after vaccination by viruses to which they were susceptible before vaccination. The difference in efficacy between the two vaccines was not statistically significant in this small study. No additional challenges were conducted to assess efficacy at time points later than 28 days (*205*). 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 IIV against culture-confirmed influenza was 57% (95%CI = -3%–82%) and 77% (95% CI = 37%–92%), respectively. The difference in efficacy was not statistically significant and was attributable primarily to a difference in efficacy against influenza B (*212*). Similar studies conducted among adults during the 2005–06 and 2007–08 influenza seasons found no significant difference in vaccine efficacy in 2005–06 (*213*) but did find a 50% relative efficacy of IIV compared with LAIV in the 2007–08 season (*214*). An observational study conducted among military personnel aged 17–49 years over the 2004–05, 2005–06, and 2006–07 influenza seasons indicated that persons who received IIV had a significantly lower incidence of health-care encounters resulting in diagnostic coding for pneumonia and influenza compared with those who received LAIV (adjusted incidence rate ratio of 0.57 [95% CI = 0.51–0.64] for the 2004–05 season, of 0.79 [95% CI = 0.72–0.87] for the 2005–06 season, and of 0.80 [95% CI = 0.74–0.86] for the 2006–07 season) (*216*). However, in a retrospective cohort study comparing LAIV and IIV among 701,753 nonrecruit military personnel and 70,325 new recruits, among new recruits, incidence of ILI was lower among those who received LAIV than IIV. The previous vaccination status of the recruits was not known; it is possible that this population was relatively naïve to vaccination compared with previous service members who are vaccinated routinely each year (*217*).

Several studies have demonstrated superior efficacy of LAIV as compared with IIV among children (*215*). A randomized controlled clinical trial conducted among 7,852 children aged 6 through 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 IIV (*218*). In this study, LAIV efficacy was higher compared with IIV against antigenically drifted viruses and well-matched viruses (*218*). An open-label,

nonrandomized, community-based influenza vaccine trial conducted among 7,609 children aged 5 through 18 years during an influenza season when circulating H3N2 strains were poorly matched with strains contained in the vaccine also indicated that LAIV, but not IIV, was effective against antigenically drifted H3N2 viruses. In this study, children who received LAIV had significant protection against laboratory-confirmed influenza (37%) and pneumonia/influenza events (50%) (*219*). LAIV provided 32% increased protection in preventing culture-confirmed influenza compared with IIV in one study conducted among children aged ≥6 years and adolescents with asthma (*220*) and 52% increased protection compared with IIV among children aged 6 through 71 months with recurrent respiratory tract infections (*221*).

Safety of Influenza Vaccines

Inactivated Influenza Vaccines

Children: A large postlicensure population-based study assessed IIV3 safety in 251,600 children aged <18 years (including 8,476 vaccinations in children aged 6 through 23 months) enrolled in one of five health-care organizations within the Vaccine Safety Datalink (VSD) (http://www.cdc.gov/vaccinesafety/activities/vsd.html) 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 (*222*). In a retrospective cohort study using VSD data from 45,356 children aged 6 through 23 months during 1991–2003, IIV3 was not associated with statistically significant increases in any clinically important medically attended events other than gastritis/duodenitis during the 2 weeks after vaccination compared with control time periods before and after vaccination. Most vaccinated children with a diagnosis of gastritis/duodenitis had self-limited vomiting or diarrhea. Several diagnoses, including acute upper respiratory illness, otitis media and asthma, were significantly less common during the 2 weeks after influenza vaccination. Although there was a temporal relationship with vaccination, the vaccine did not necessarily cause nor prevent these conditions (*223*). A subsequent VSD study of 66,283 children aged 24 through 59 months noted diagnoses of fever, gastrointestinal tract symptoms, and gastrointestinal disorders to be significantly associated with IIV3. Upon medical record review, none of the events appeared to be serious, and none were associated with complications (*224*).

In a study of 791 healthy children aged 1 through 15 years, postvaccination fever was noted among 12% of those aged 1 through 5 years, 5% among those aged 6 through 10 years, and 5% among those aged 11 through 15 years (*89*). Fever, malaise, myalgia, and other systemic symptoms that can occur after vaccination with IIV most often affect persons who have had no previous exposure to the influenza virus antigens in the vaccine (e.g., young children) (*225*). These reactions are generally self-limited and subside after 1–2 days.

Febrile seizures associated with IIV and pneumococcal conjugate vaccine (PCV13): Febrile seizures are common in young children. At least one febrile seizure is experienced by 2%–5% of children aged 6 through 60 months; nearly all children who have a febrile seizure recover quickly and are healthy afterwards (*226*). Prior to the 2010–11 influenza season, an increased risk for febrile seizures following IIV3 had not been observed in the United States (*223,227*). During the 2010–11 influenza season, CDC and the Food and Drug Administration (FDA) conducted enhanced monitoring for febrile seizures following influenza vaccines after reports of an increased risk for fever and febrile seizures in young children in Australia associated with a 2010 Southern Hemisphere IIV3 produced by CSL Biotherapies (up to nine febrile seizures per 1,000 doses) (*228*). Because of the findings in Australia, ACIP does not recommend the U.S.-licensed CSL Biotherapies' IIV3, Afluria, for children aged <9 years (Table 1).

Surveillance among children receiving U.S.-licensed influenza vaccines during the 2010–11 influenza season subsequently detected safety concerns for febrile seizures in young children following IIV3 (*229,230*). Further assessment through a VSD study determined that the increased risk was in children aged 6 months through 4 years on the day of vaccination to the day after (risk window: Day 0–1). The risk was higher when children received concomitant PCV13 (i.e., when the two vaccines are given at the same health-care visit) and peaked at approximately age 16 months (*230*). No increased risk was observed in children aged >4 years after IIV3 or in children of any age after LAIV. The magnitude of the increased risk for febrile seizures in children aged 6 through 23 months in the United States observed in this study (<1 per 1,000 children vaccinated) was substantially lower than the risk observed in Australia in 2010 (*228*). Findings from surveillance for febrile seizures in young children following influenza vaccine for the 2011–12 influenza season (which had the same formulation as that of the 2010–11 season) were consistent with the 2010–11 influenza season; however, an increased risk for febrile seizures following IIV3 was not observed during the 2012–13 influenza season (CDC, unpublished data, 2013). After evaluating the data on febrile seizures from the 2010–11 influenza season and taking into consideration benefits and risks of vaccination, no policy change was recommended for use of IIV or PCV13 (*231,232*). Surveillance for febrile seizures after IIV is ongoing through VAERS.

TABLE 1. Influenza vaccines — United States, 2013–14 influenza season*

Trade name	Manufacturer	Presentation	Mercury content (μg Hg/0.5 mL)	Ovalbumin content (μg/0.5mL)	Age indications	Route
Inactivated Influenza Vaccine, Trivalent (IIV3), Standard Dose						
Afluria	CSL Limited	0.5 mL single-dose prefilled syringe	0	≤1.0	≥9 yrs†††	IM†
		5.0 mL multi-dose vial	24.5	≤1.0		
Fluarix	GlaxoSmithKline	0.5 mL single-dose prefilled syringe	0	≤0.05	≥3 yrs	IM†
Flucelvax	Novartis Vaccines and Diagnostics	0.5 mL single-dose prefilled syringe	0	NI§§§	≥18 yrs	IM†
FluLaval	ID Biomedical Corporation of Quebec (distributed by GlaxoSmithKline)	5.0 mL multi-dose vial	<25.0	≤0.3	≥3 yrs	IM†
Fluvirin	Novartis Vaccines and Diagnostics	0.5 mL single-dose prefilled syringe	≤1.0	≤1.0	≥4 yrs	IM†
		5.0 mL multi-dose vial	25.0	≤1.0		
Fluzone	Sanofi Pasteur	0.25 mL single-dose prefilled syringe	0	—¶¶¶	6–35 mos	IM†
		0.5 mL single-dose prefilled syringe	0	—	≥36 mos	IM†
		0.5 mL single-dose vial	0	—	≥36 mos	IM†
		5.0 mL multi-dose vial	25.0	—	≥6 mos	IM†
Fluzone Intradermal††	Sanofi Pasteur	0.1 mL prefilled microinjection system	0	—	18–64 yrs	ID§
Inactivated Influenza Vaccine, Trivalent (IIV3), High Dose						
Fluzone High-Dose**	Sanofi Pasteur	0.5 mL single-dose prefilled syringe	0	—	≥65 yrs	IM†
Inactivated Influenza Vaccine, Quadrivalent (IIV4), Standard Dose						
Fluarix Quadrivalent	GlaxoSmithKline	0.5 mL single-dose prefilled syringe	0	≤0.05	≥3 yrs	IM†
Flulaval Quadrivlalent	ID Biomedical Corporation of Quebec (distributed by GlaxoSmithKline)	5.0 mL multi-dose vial	<25.0	≤0.3	≥3 yrs	IM†
Fluzone Quadrivalent	Sanofi Pasteur	0.25 mL single-dose prefilled syringe	0	—	6–35 mos	IM†
		0.5 mL single-dose prefilled syringe	0	—	≥36 mos	IM†
		0.5 mL single-dose vial	0	—	≥36 mos	IM†
Recombinant Influenza Vaccine, Trivalent (RIV3)						
FluBlok	Protein Sciences	0.5 mL single-dose vial	0	0	18–49 yrs	IM†
Live Attenuated Influenza Vaccine, Quadrivalent (LAIV4)						
FluMist Quadrivalent§§	MedImmune	0.2 mL single-dose prefilled intranasal sprayer	0 (per 0.2 mL)	<0.24 (per 0.2mL)	2–49 yrs***	INL

Abbreviations: IM = intramuscular; ID = intradermal; INL = intranasal; NI = not included.

* Immunization providers should check Food and Drug Administration–approved prescribing information for 2013–14 influenza vaccines for the most complete and updated information, including (but not limited to) indications, contraindications, and precautions. Package inserts for US-licensed vaccines are available at http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm.

† 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. Specific guidance regarding site and needle length for intramuscular administration may be found in the ACIP General Recommendations on Immunization (CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices, 2011. MMWR 2011;60[No. RR-2]).

§ The preferred site is over the deltoid muscle. Fluzone Intradermal is administered using the delivery system included with the vaccine.

** Inactivated influenza vaccine, high-dose: A 0.5-mL dose contains 60 μg of each vaccine antigen (180 μg total).

†† Inactivated influenza vaccine, intradermal: A 0.1-mL dose contains 9 μg of each vaccine antigen (27 μg total).

§§ It is anticipated that the quadrivalent formulation of FluMist will replace the trivalent formulation for the 2013–14 season. FluMist is shipped refrigerated and stored in the refrigerator at 35°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 through 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 through 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.

*** Flumist is indicated for healthy, nonpregnant persons aged 2–49 years. Persons who care for severely immunosuppressed persons who require a protective environment should not receive FluMist given the theoretical risk of transmission of the live attenuated vaccine virus.

††† Age indication per package insert is ≥5 years; however, ACIP recommends that Afluria not be used in children aged 6 months through 8 years because of increased risk for febrile reactions noted in this age group with CSL's 2010 Southern Hemisphere IIV3. If no other age-appropriate, licensed inactivated seasonal influenza vaccine is available for a child aged 5–8 years who has a medical condition that increases the child's risk for influenza complications, Afluria can be used; however, providers should discuss with the parents or caregivers the benefits and risks of influenza vaccination with Afluria before administering this vaccine. Afluria may be used in persons aged ≥9 years.

§§§ Information not included in package insert. The total egg protein is estimated to be less than 50 femtograms (5x10-14 grams) total egg protein (of which a fraction is ovalbumin) per 0.5 mL dose of Flucelvax.

¶¶¶ Available on request from Sanofi Pasteur, telephone 1-800-822-2463 or e-mail MIS.Emails@sanofipasteur.com.

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 (*233,234*). These local reactions typically were mild and rarely interfered with the recipients' ability to conduct usual daily activities. Placebo-controlled trials demonstrate that among older persons and healthy young adults, administration of IIV3 is not associated with higher rates for systemic symptoms (e.g., fever, malaise, myalgia, and headache) when compared with placebo injections (*233–235*). Adverse events in adults aged ≥18 years reported to VAERS during 1990–2005 were analyzed. The most common adverse events for adults described in 18,245 VAERS reports included injection site reactions, pain, fever, myalgia, and headache. The VAERS review identified no new safety concerns. Fourteen percent of the IIV3 VAERS reports in adults were classified as serious adverse events (defined as those involving death, life-threatening illness, hospitalization or prolongation of hospitalization, or permanent disability [*236*]), similar to proportions seen in VAERS for other adult vaccines. The most common serious adverse event reported after IIV3 in VAERS in adults was Guillain-Barré syndrome (GBS) (*237*). The potential association between IIV3 and GBS is an area of ongoing research (see Guillain-Barré Syndrome and IIV).

Injection site reactions and systemic adverse events were more frequent after vaccination with a vaccine containing 180 μg of HA antigen (Fluzone High-Dose, Sanofi Pasteur, Swiftwater, Pennsylvania) than after standard-dose (45 μg) (Fluzone, Sanofi Pasteur) but were typically mild and transient. In one study, 915 (36%) of 2,572 persons who received Fluzone High-Dose, compared with 306 (24%) of those who received Fluzone, reported injection site pain. Only 1.1% of Fluzone High Dose recipients reported moderate to severe fever, but this was significantly higher than the 0.3% of Fluzone recipients who reported this systemic adverse event (RR: 3.6, 95% CI = 1.3–10.1) (*179*). A randomized study of high-dose versus standard-dose vaccine including 9,172 participants found no difference in occurrence of serious adverse events or several specific adverse events of interest (including GBS, Bell's Palsy, encephalitis/myelitis, optic neuritis, Stevens-Johnson syndrome, and toxic epidermal necrolysis) (*238*). Safety monitoring of high-dose vaccine in VAERS during the first year after licensure indicated a higher than expected number of gastrointestinal events compared with standard-dose vaccine, but otherwise no new safety concerns were identified. Most of the reported gastrointestinal reports were nonserious (*239*). CDC and FDA will continue to monitor the safety of high-dose vaccine through VAERS.

Intradermal IIV has been observed to be associated with higher rates of some injection site reactions as compared with intramuscularly administered influenza vaccines. In a randomized study of intradermal versus intramuscular vaccine among approximately 4,200 adults aged 18 through 64 years, erythema, induration, swelling, and pruritus occurred with greater frequency following intradermal vaccine compared with intramuscular vaccine; rates of injection site pain were not significantly different (*240*). A recent review of studies comparing intradermal and intramuscular vaccine similarly noted higher rates of erythema, induration, swelling, and pruritus among adults aged 18 through 60 years within the first 7 days after receiving intradermal vaccine; local pain and ecchymosis and systemic reactions occurred with similar frequency (*241*).

Pregnant women and neonates: Currently available IIVs are classified as either Pregnancy Category B or Category C† medications, depending upon whether adequate animal reproduction studies have been conducted. Available data indicate that influenza vaccine does not cause fetal harm when administered to a pregnant woman. However, data on the safety of influenza vaccination in the early first trimester are limited (*242*). One study of approximately 2,000 pregnant women who received IIV3 during pregnancy demonstrated no increase in malignancies during infancy or early childhood (*243*). A matched case-control study of 252 pregnant women who received IIV3 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 (*244*). A case-control analysis of data from six health-care organizations participating in the VSD found no significant increase in the risk for pregnancy loss in the 4 weeks following seasonal influenza vaccination (*245*). A review of health registry data in Norway noted an increased risk for fetal death associated with pandemic 2009(H1N1) infection, but no increased risk of fetal mortality associated with vaccination (*246*). During 2000–2003, when an estimated 2 million pregnant women were vaccinated, only 20 adverse events among women who received IIV3 were reported to VAERS, including nine injection site reactions, eight systemic reactions (e.g., fever, headache, and myalgia), and three miscarriages (*247*). Background rates of miscarriage vary from 10.4% in women aged <25 years to 22.4% in women

† Pregnancy Category B indicates that 1) animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in humans or 2) that animal studies have shown an adverse effect, but adequate and well-controlled studies in humans have failed to demonstrate a risk to the fetus in any trimester. Pregnancy Category C indicates that animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Additional information about pregnancy categories is available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm.

aged >34 years (*248*); considering the number of pregnant women vaccinated, miscarriage following (but not attributable to) influenza vaccination would not be an unexpected event. Recent reviews of studies pertaining to seasonal (*249–251*) and monovalent 2009(H1N1) (*250,251*) inactivated influenza vaccines in pregnancy concluded that no evidence exists to suggest harm to the fetus from maternal vaccination.

Persons with chronic medical conditions: In a blinded, randomized crossover study of 1,952 children and adults with asthma, no increase in asthma exacerbations was reported for either age group. Only myalgias were reported more frequently after IIV3 (25%) than placebo-injection (21%) (*252*). Among children with high-risk medical conditions, one study of 52 children aged 6 months through 3 years reported fever among 27% and irritability and insomnia among 25% (*108*); and a study among 33 children aged 6 through 18 months reported that one child had irritability and one had a fever and seizure after vaccination (*253*). No placebo comparison group was used in these studies. One prospective cohort study found that the rate of adverse events was similar among hospitalized persons who either were aged ≥65 years or were aged 18 through 64 years and had one or more chronic medical conditions compared with outpatients (*254*).

Immunocompromised persons: Data demonstrating safety of IIV3 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 increase in HIV RNA (ribonucleic acid) levels in one HIV-infected person after influenza virus infection (*255*). While some earlier studies demonstrated a transient increase in replication of HIV-1 in the plasma or peripheral blood mononuclear cells of HIV-infected persons after vaccine administration (*154,256*), more recent and better-designed studies have not documented a substantial increase in the replication of HIV (*257–260*). CD4+ T-lymphocyte cell counts or progression of HIV disease have not been demonstrated to change substantially after influenza vaccination among HIV-infected persons compared with unvaccinated HIV-infected persons (*154,261*). Limited information is available about the effect of antiretroviral therapy on increases in HIV RNA levels after either influenza virus infection or influenza vaccination (*63,262*).

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 (*159,160*), heart transplants (*161*), or liver transplants (*162*). Limited data are available on influenza vaccination in the setting of solid organ transplantation. A recent literature review concluded that there is no convincing epidemiologic link between vaccination and allograft dysfunction (*263*). Case reports of corneal graft rejection have been reported following IIV (*264–266*), but no studies demonstrating an association have been conducted.

Immediate hypersensitivity reactions after influenza vaccines: Vaccine components can occasionally cause allergic reactions, also called immediate hypersensitivity reactions. Immediate hypersensitivity reactions are mediated by preformed immunoglobulin E (IgE) antibodies against a vaccine component and usually occur within minutes to hours of exposure (*267*). Symptoms of immediate hypersensitivity range from urticaria (hives) to angioedema and 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, tongue 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 (*267,268*).

Allergic reactions might be caused by the vaccine antigen, residual animal protein, antimicrobial agents, preservatives, stabilizers, or other vaccine components (*269*). 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 (*270*). The Clinical Immunization Safety Assessment (CISA) network, a collaboration between CDC and medical research centers with expertise in vaccinology and vaccine safety, has developed an algorithm to guide evaluation and revaccination decisions for persons with suspected immediate hypersensitivity after vaccination (*267*).

Anaphylaxis after IIV and LAIV is rare. A study conducted in VSD during 2005–2008 observed that the incidence of anaphylaxis in the 0–2 days after IIV3 was 0.45–1.98 cases per million IIV3 doses administered in all ages (*227*). Anaphylaxis occurring after receipt of IIV3 and LAIV3 has rarely been reported to VAERS (*237,271*). A VSD study of children aged <18 years in four HMOs during 1991–1997 estimated the overall risk for postvaccination anaphylaxis after any type of childhood vaccine to be approximately 1.5 cases per million doses administered. In this study, no cases were identified in IIV3 recipients (*272*).

Some immediate hypersensitivity reactions after IIV or LAIV might be caused by the presence of residual egg protein in the vaccines (*273*). Although influenza vaccines contain only a limited quantity of egg protein, this protein can potentially induce immediate hypersensitivity reactions among persons who have severe egg allergy. Specific recommendations pertaining to the use of influenza vaccines for egg-allergic

persons are provided (see Influenza Vaccination for Persons with a History of Egg Allergy).

Ocular and respiratory symptoms after receipt of IIV: Oculorespiratory syndrome (ORS), an acute, self-limited reaction to IIV 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 IIV, and resolving within 48 hours of onset: red eyes, cough, wheeze, chest tightness, difficulty breathing, sore throat, or facial swelling (*274*). ORS was 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 (*275*). 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 (*276–278*).

The cause of ORS has not been established; however, studies suggest that the reaction is not IgE-mediated (*279*). After changes in the manufacturing process of the vaccine preparation associated with ORS during the 2000–01 season, the incidence of ORS in Canada was reduced greatly (*277*). 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 (*280*).

Ocular and respiratory symptoms reported after IIV 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 IIV that did not involve the lower respiratory tract have been revaccinated without reports of serious adverse events after subsequent exposure to IIV (*281*).

When assessing whether a patient who experienced ocular and respiratory symptoms should be revaccinated, providers should determine if concerning signs and symptoms of IgE mediated immediate hypersensitivity are present (see Immediate Hypersensitivity after Influenza Vaccines). Health-care providers who are unsure whether symptoms reported or observed after receipt of IIV 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 IIV should not receive influenza vaccination unless hypersensitivity is ruled out or revaccination is administered under close medical supervision (*267*).

Ocular or respiratory symptoms observed after receipt of IIV often are coincidental and unrelated to IIV 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 IIV without other concerning signs or symptoms of hypersensitivity can receive IIV in subsequent seasons without further evaluation. Two studies indicated that persons who had symptoms of ORS after receipt of IIV were at a higher risk for ORS after subsequent IIV administration; however, these events usually were milder than the first episode (*281,282*).

Guillain-Barré syndrome and IIV: The annual incidence of GBS is 10–20 cases per 1 million adults (*283*). Evidence exists that multiple infectious illnesses, most notably *Campylobacter jejuni* gastrointestinal infections and upper respiratory tract infections, are associated with GBS (*284–286*). A recent study identified an association between serologically confirmed influenza virus infection and 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 cases per 100,000 persons compared with one case per 1 million persons following vaccination with TIV) (*287*).

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 (*288,289*). The risk for influenza vaccine–associated GBS was higher among persons aged ≥25 years than among persons aged <25 years (*290*). No subsequent study 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 the 1976–77 season. During three of four influenza seasons studied during 1977–1991, the overall relative risk estimates for GBS after influenza vaccination were not statistically significant (*291–293*). 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. GBS cases peaked 2 weeks after vaccination (*289*). 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 (relative incidence: 1.45; 95% CI = 1.05–1.99). 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 (*294*). Published data from the United Kingdom's General Practice Research Database (GPRD) found influenza vaccination to be associated with a decreased risk for GBS (odds ratio: 0.16; 95% CI = 0.02–1.25), 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) is unclear (*295*). A separate GPRD analysis found 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 (*296*). A third GPRD analysis found that GBS was associated with recent ILI, but not influenza vaccination (*297*).

The estimated risk for GBS (on the basis of the few studies that have demonstrated an association between seasonal IIV and GBS) is low; approximately one additional case per 1 million persons vaccinated (*288,294*). In addition, data from the systems monitoring influenza A(H1N1) 2009 monovalent vaccines suggest that the risk for GBS associated with these inactivated vaccines is approximately one or two additional cases per 1 million persons vaccinated, which is similar to that observed in some seasons for IIV (*298–304*).

The incidence of GBS among the general population is low (0.75 to 2 cases per 100,000 persons annually) (*283*), but persons with a history of GBS have a substantially greater likelihood of subsequently experiencing GBS than persons without such a history (*283*). 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 (*305*). In a Kaiser Permanente Northern California database study among more than 3 million members conducted over an 11-year period, no cases of recurrent GBS were identified after influenza vaccination in 107 persons with a documented prior diagnosis of GBS, two of whom had initially developed GBS within 6 weeks of influenza vaccination (*306*).

As a precaution, persons who are not at high risk for severe influenza complications (see Persons at Risk for Medical Complications Attributable to Influenza) and who are known to have experienced GBS within 6 weeks of influenza vaccination generally should not be vaccinated. As an alternative, physicians might consider using influenza antiviral chemoprophylaxis for these persons. However, the benefits of influenza vaccination might outweigh the risks for certain persons who have a history of GBS and who also are at high risk for severe complications from influenza.

Thimerosal in multidose vials of IIV: Thimerosal, a mercury-containing antibacterial compound, is used in multidose vial preparations of IIV to reduce the likelihood of bacterial growth. While accumulating evidence shows no increased risks from exposure to thimerosal-containing vaccines (*307–316*), 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 (*307,308*). LAIV, RIV, and most single-dose vial or syringe preparations of IIV are thimerosal-free. Persons recommended to receive IIV may receive any age- and risk factor–appropriate vaccine preparation, depending on availability.

Live Attenuated Influenza Vaccines

Shedding, transmission, and stability of vaccine viruses: 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. Rarely, 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 through 36 months in a child care center assessed transmissibility of vaccine viruses from 98 vaccinated children to the 99 unvaccinated children; 80% of vaccine recipients shed one or more virus strains (mean duration: 7.6 days). One influenza B vaccine virus strain isolate was recovered from a placebo recipient and was confirmed to be vaccine-type virus. The influenza B virus isolate retained the cold-adapted, temperature-sensitive, attenuated phenotype. The placebo recipient from whom the influenza B vaccine virus strain was isolated had symptoms of a mild upper respiratory illness. The estimated probability of acquiring vaccine virus after close contact with a single LAIV recipient in this population was 1%–2% (*317*).

Studies assessing shedding of vaccine virus have been based on viral cultures or RT-PCR detection of vaccine viruses in nasal aspirates from LAIV recipients. A study of 345 subjects aged 5 through 49 years who received LAIV indicated that 30% had detectable virus in nasal secretions obtained by nasal swabbing. The duration of virus shedding and the amount of virus shed was inversely correlated 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 (*318*).

Other smaller studies have reported similar findings (*319,320*). In an open-label study of 200 children aged 6 through 59 months who received a single dose of LAIV, shedding of at least one vaccine virus was detected on culture in 79% of children, and was more common among the younger recipients (89% of children aged 6 through 23 months compared with 69% of children aged 24 through 59 months) (*321*). The incidence of shedding was highest on day 2 postvaccination. Mean duration of shedding was 2.8 days (3.0 days and 2.7 days for the younger and older age groups, respectively); shedding detected after 11 days postvaccination was uncommon and nearly all instances occurred among children aged 6 through 23 months (an age group for which LAIV is not licensed). Titers of shed virus were low (*321*). Vaccine virus was detected from nasal secretions in one (2%) of 57 HIV-infected adults who received LAIV compared with none of 54 HIV-negative participants (*322*), and in three (13%) of 24 HIV-infected children compared with seven (28%) of 25 children who were not HIV-infected (*323*).

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. 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 (*324*). A study conducted in a child care setting demonstrated that limited genetic change occurred in the LAIV strains following replication in the vaccine recipients (*317*).

Healthy children aged 2 through 18 years: In a subset of healthy children aged 60 through 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 myalgia (6% and 4%, respectively) (*325*). 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 myalgia (0–21%) (*199,201,202,208,326–329*). These symptoms were associated more often with the first dose and were self-limited. In a placebo-controlled trial in 9,689 children aged 1–17 years assessed pre-specified medically attended outcomes during the 42 days after vaccination, LAIV was associated with increased risk 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). In this study, the proportion of serious adverse events was 0.2% in LAIV and placebo recipients; none of the serious adverse events was judged to be related to the vaccine by the study investigators (*328*).

In a randomized trial published in 2007, LAIV and IIV were compared among children aged 6 through 59 months (*218*). Children with medically diagnosed or treated wheezing in the 42 days before enrollment or with a history of severe asthma were excluded from participation. Among children aged 24 through 59 months who received LAIV, the proportion of children who experienced medically significant wheezing, using a prespecified definition, was not greater compared with those who received IIV (*218*). Wheezing was observed more frequently following the first dose among previously unvaccinated, younger LAIV recipients, primarily those aged <12 months; LAIV is not licensed for this age group. In a previous randomized placebo-controlled safety trial among children aged 12 months through 17 years without a history of asthma by parental report, an increased risk for asthma events (RR: 4.1; 95% CI = 1.3–17.9) was documented among 728 children aged 18 through 35 months who received LAIV. Of the 16 children with asthma-related events in this study, seven had a history of asthma on the basis of subsequent medical record review. None required hospitalization, and increased risk for asthma events were not observed in other age groups (*328*).

An open-label field trial was conducted among approximately 11,000 children aged 18 months through 18 years in which 18,780 doses of vaccine were administered between 1998–2002 For children aged 18 months through 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 (*330*). This trial later assessed LAIV safety among 2,196 children aged 18 months through 18 years with a history of intermittent wheezing 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 (*331*).

In a postlicensure observational study of 28,226 children aged 24 through 59 months, asthma and wheezing medically attended events were not statistically increased after LAIV during three influenza seasons (2007–08, 2008–09, and 2009–10) (*332*). Safety monitoring for wheezing events after LAIV is ongoing through VAERS.

Adults aged 19 through 49 years: In one clinical trial among a subset of healthy adults aged 18 through 49 years, signs and symptoms reported significantly more often ($p<0.05$; Fisher exact test) 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) (*325*). 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 (*271*). Few (9%) of the LAIV VAERS reports concerned serious adverse events; respiratory events were the most common conditions reported.

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 57 HIV-infected persons aged 18 through 58 years with CD4+ counts >200 cells/mm3 who received LAIV, no serious adverse events attributable to vaccines were reported during a 1-month follow-up period (*322*). Similarly, one study demonstrated no significant difference in the frequency of adverse events or viral shedding among 24 HIV-infected children aged 1 through 8 years on effective antiretroviral therapy who were administered LAIV compared with 25 HIV-uninfected children receiving LAIV (*323*). LAIV was well-tolerated among adults aged ≥65 years with chronic medical conditions (*333*). Among 27 reports to VAERS involving inadvertent administration of LAIV to pregnant women during 1990–2009, no unusual patterns of maternal or fetal outcomes were observed (*334*); among 138 reports noted in a health insurance claims database, all outcomes occurred at similar rates to those observed in unvaccinated women (*335*). These findings suggest that persons at risk for influenza complications who have inadvertent exposure to LAIV are not expected to 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.

Recombinant Influenza Vaccine

FluBlok, the first RIV licensed in the United States, was approved in January 2013. Postmarketing safety data have not yet accumulated. Prelicensure data are discussed (see New and Recently Approved Influenza Vaccine Products).

Dosage, Administration, and Storage of Influenza Vaccines

The composition of influenza vaccines varies among different products. For all vaccines, package inserts should be consulted for authoritative guidance regarding storage conditions and administration. Influenza vaccine manufactured for a previous season should not be administered in any subsequent season and should not be administered after the expiration date.

Inactivated Influenza Vaccine

IIVs are available in both single-dose and multidose formulations. Multidose vials contain the vaccine preservative thimerosal. Single-dose, unpreserved products should not be used for multiple doses. IIV should be stored at 35°F–46°F (2°C–8°C) and should not be frozen. IIV that has been frozen should be discarded. Dosage recommendations and schedules vary according to age group (Table 1). Vaccine prepared for a given influenza season should not be administered to provide protection for any subsequent season.

With the exception of Fluzone Intradermal (Sanofi Pasteur), IIV should be administered intramuscularly. For adults and older children, the deltoid is the preferred site. Infants and younger children should be vaccinated in the anterolateral thigh. Specific guidance regarding site and needle length for intramuscular administration can be found in the ACIP General Recommendations on Immunization (*270*). Fluzone Intradermal is administered intradermally, preferably over the deltoid muscle, using the delivery system included in the vaccine package. No influenza vaccines are licensed in the United States for administration via jet-injector device (*336*).

Live Attenuated Influenza Vaccine (LAIV)

LAIV contains live, attenuated, cold-adapted, temperature-sensitive vaccine viruses which replicate efficiently only at temperatures present in the nasal mucosa. Providers should refer to the package insert, which contains additional information about the formulation of this vaccine and other vaccine components (*210*). LAIV does not contain thimerosal. 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 (*210*).

LAIV is intended for intranasal administration only. 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.

Recombinant Influenza Vaccine

RIV should be stored refrigerated between 36°F–46°F (2°C–8°C). It should not be frozen. Vaccine which has frozen should be discarded. Vials should be protected from light. RIV has a shorter shelf life than IIV. Vaccine should not be used past its expiration date. RIV is administered intramuscularly.

Influenza Vaccine Composition for the 2013–14 Season

All influenza vaccines licensed in the United States will contain hemagglutinin (HA) derived from influenza viruses antigenically identical to those recommended by FDA (*337*). This season, for the first time, both trivalent and quadrivalent influenza vaccines will be available in the United States Trivalent influenza vaccines will contain HA derived from three vaccine virus strains: one A(H1N1), one A(H3N2), and one B vaccine virus strain. Quadrivalent vaccines will contain the same the HA antigens as trivalent vaccines, but will also contain HA from a second B virus strain (one B virus strain from each lineage will be represented) (see Quadrivalent Influenza Vaccines).

Trivalent influenza vaccines will contain HA derived from the following:

- an A/California/7/2009 (H1N1)-like virus,
- an (H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011 (A/Texas/50/2012 is recommended to replace the A/Victoria/361/2011–like virus used in the 2012–13 vaccine because egg-adaptation of the A/Victoria/361/2011–like virus resulted in mutations that altered antigenicity), and
- a B/Massachusetts/2/2012–like (Yamagata lineage) virus.

Quadrivalent influenza vaccines will contain these three antigens, and

- a B/Brisbane/60/2008–like (Victoria lineage) virus.

New and Recently Approved Influenza Vaccine Products

Since early 2012, six new influenza vaccines have been approved for use by FDA. These include 1) Flumist Quadrivalent (MedImmune, Gaithersburg, Maryland), a quadrivalent live attenuated influenza vaccine (LAIV4); 2) Fluarix Quadrivalent (Glaxo Smith Kline, Research Triangle Park, North Carolina), a quadrivalent inactivated influenza vaccine (IIV4); 3) Fluzone Quadrivalent (Sanofi Pasteur, Swiftwater, Pennsylvania), an IIV4; 4) Flulaval Quadrivalent, (ID Biomedical Corportation of Quebec/GlaxoSmith Kline, Research Triangle Park, North Carolina), an IIV4; 5) Flucelvax (Novartis Vaccines and Diagnostics, Cambridge, Massachusetts), a cell culture-based trivalent inactivated influenza vaccine (ccIIV3); and 6) FluBlok (Protein Sciences, Meriden, Connecticut), a trivalent recombinant HA influenza vaccine (RIV3). These products all are expected to be available for the 2013–14 influenza season.

Quadrivalent Influenza Vaccines

All inactivated influenza vaccines available during recent seasons have been trivalent, containing A(H1N1), A(H3N2), and B viral antigens. There are two antigenically distinct lineages of influenza B viruses, referred to as Victoria and Yamagata lineages (*13,14*). Immunization against influenza B virus strains of one lineage provides only limited cross-protection against strains in the other lineage (*338*). Given this, and the challenge of predicting which B virus lineage will predominate during a given season, inclusion of two B virus strains (one from each lineage) in seasonal influenza vaccines may improve protection against circulating seasonal B virus strains. A recent modeling analysis indicates that the impact of a quadrivalent vaccine could result in a modest reduction in influenza-associated outcomes (by 2,200–970,000 cases, 14–8,200 hospitalizations, and 1–485 deaths annually), depending upon adequate vaccine supply, coverage, effectiveness, and incidence of influenza associated with the two B lineages (*339*).

The World Health Organization (WHO) (*340*) and FDA (*337*) have made recommendations for inclusion of a second influenza B vaccine virus in quadrivalent influenza vaccines for the 2013–14 season. This strain will be included in addition to the A(H1N1), A(H3N2), and B vaccine virus strains contained in trivalent vaccines. For the 2013–14 season, quadrivalent influenza vaccines will include a Victoria lineage B/Brisbane/60/2008–like vaccine virus strain, in addition to the Yamagata lineage B/Massachusetts/2/2012–like virus strain contained in trivalent influenza vaccines.

As of August 15, 2013, four quadrivalent seasonal influenza vaccines are expected to be available for the 2013–14 influenza season. Other quadrivalent vaccines might become available in future seasons. New vaccines will be addressed in the ACIP influenza statement as they are approved and become commercially available.

Flumist Quadrivalent: Flumist Quadrivalent (MedImmune), an LAIV4, was approved by FDA in February 2012. All LAIV available in the United States for the 2013–14 season is expected to be the quadrivalent formulation. As with the prior trivalent formulation, Flumist Quadrivalent is approved for persons aged 2 through 49 years (*210*) and is an alternative for healthy, non-pregnant persons within this age range.

Flumist Quadrivalent contains $10^{6.5}$–$10^{7.5}$ fluorescent focus units (FFU) of live attenuated influenza virus reassortants of each of the four vaccine virus strains recommended for inclusion in quadrivalent influenza vaccines. It is supplied in a single-dose, 0.2 mL intranasal sprayer, and is administered intranasally (0.1 mL per nostril). Contraindications and

precautions to the administration of FluMist are similar to those described for LAIV3 (see Contraindications and Precautions for the Use of LAIV; Table 2) (*210*).

In randomized trials comparing FluMist Quadrivalent with FluMist among children aged 2 through 17 years (*210,341*) and adults aged 18 through 49 years (*210,342*) with the exception of fever in children aged 2 through 8 years, similar rates of solicited adverse reactions were observed. Fever was more common after dose 1 in children aged 2 through 8 years following FluMist Quadrivalent (5.1%) compared with FluMist (3.1%). Assessment of the immunogenicity of Flumist Quadrivalent was based upon multicenter, randomized, double-blind, active-controlled non-inferiority studies of immunogenicity performed among children aged 2 through 17 years and adults. In immunogenicity assessments in each study, Flumist Quadrivalent was found to be non-inferior to FluMist. Comparison of the strain-specific serum HAI antibody geometric mean titers (GMTs) postvaccination indicated that the addition of the second B strain was not associated with immune interference to other strains included in the vaccine (*344*).

Fluarix Quadrivalent: Fluarix Quadrivalent (GlaxoSmithKline), an IIV4, was approved by FDA in December 2012. Fluarix Quadrivalent will be available alongside the trivalent formulation of Fluarix during the 2013–14 season. Both the trivalent and quadrivalent formulations of Fluarix are approved for persons aged ≥3 years (*343*).

Fluarix Quadrivalent is formulated to contain 60 μg HA per 0.5 mL dose (15 μg HA of each of the four influenza virus strains recommended for inclusion in quadrivalent influenza vaccines). It is supplied in 0.5 mL single-dose prefilled syringes, and is administered by intramuscular injection. Contraindications and precautions to the administration of Fluarix Quadrivalent are similar to those described for the trivalent formulation of Fluarix (see Contraindications and Precautions for the Use of IIV; Table 2).

Two studies evaluated safety and immunogenicity of Fluarix Quadrivalent (*343*). Both involved subjects randomized to receive either Fluarix Quadrivalent or one of two formulations of comparator trivalent influenza vaccine (IIV3), each containing an influenza type B virus corresponding to one of the two type B viruses in Fluarix Quadrivalent. One study evaluated adults aged ≥18 years, and the other focused on children aged 3 through 17 years. In adults, the most common (≥10%) injection site adverse reaction was pain (36%); the most common systemic adverse events were muscle aches (16%), headache (16%), and fatigue (16%). Among children aged 3 through 17 years, the most common injection site adverse reactions were pain (44%), redness (23%), and swelling (19%). In children aged 3 through 5 years, the most common (≥10%) systemic adverse events were drowsiness (17%), irritability (17%), and loss of appetite (16%); in children aged 6 through 17 years, the most common systemic adverse events were fatigue (20%), muscle aches (18%), headache (16%), arthralgia (10%), and gastrointestinal symptoms (10%). Overall frequencies of most solicited adverse events associated with Fluzone Quadrivalent in these studies were generally similar to these reported for the comparator trivalent vaccines

In immunogenicity analyses, Fluarix Quadrivalent was noninferior to both comparator IIV3s based on adjusted GMTs and seroconversion rates. The antibody response to influenza B strains contained in Fluarix Quadrivalent was higher than the antibody response after vaccination with a trivalent IIV containing an influenza B strain from a different lineage. No evidence indicated that the addition of the second B strain resulted in immune interference to other strains included in the vaccine (*343*).

Fluzone Quadrivalent: Fluzone Quadrivalent (Sanofi Pasteur), an IIV4, was approved by FDA in June 2013. Fluzone Quadrivalent will be available alongside the trivalent formulation of Fluzone during the 2013–14 season. Both the trivalent and quadrivalent formulations of Fluzone are approved for persons aged ≥6 months (*344*).

Fluzone Quadrivalent is formulated to contain 60 μg HA per 0.5 mL dose (15 μg HA of each of the four influenza virus strains recommended for inclusion in quadrivalent influenza vaccines). It is available in three presentations (0.25 and 0.5 mL single-dose prefilled syringes and 0.5 mL single-dose vials), and is administered by intramuscular injection. Contraindications and precautions to the administration of Fluzone Quadrivalent are similar to those described for the trivalent formulation of Fluzone (see Contraindications and Precautions for the Use of IIV; Table 2).

Safety of Fluzone Quadrivalent was evaluated in three studies including participants aged ≥6 months who were randomized to receive either Fluzone Quadrivalent or one of two formulations of comparator trivalent influenza vaccine (IIV3), each containing an influenza type B virus corresponding to one of the two type B viruses in Fluzone Quadrivalent (*344*). Among children aged 6 through 35 months, the most common local reactions (reported in ≥10% of participants) included pain (57%), tenderness (54%), erythema (37%), and swelling (22%); the most common solicited systemic reactions were irritability (54%), abnormal crying (41%), drowsiness (38%), malaise (38%), myalgia (27%), appetite loss (32%), fever (14%), and vomiting (15%). Among children aged 3 through 8 years, the most frequently reported local reactions included pain (67%), erythema (34%), and swelling (25%); the most common solicited systemic reactions were malaise (32%), myalgia (39%), and headache (23%). Among adults aged

≥18 years, the most common injection site adverse reaction was pain (47% among those aged ≥18 years and 33% among those aged ≥65 years); the most common systemic adverse events were myalgia (24% among those aged ≥18 years and 18% among those aged ≥65 years), headache (16% among those aged ≥18 years and 13% among those aged ≥65 years), and malaise (11% among those in both age groups). Overall frequencies of most solicited adverse events associated with Fluzone Quadrivalent in these studies were generally similar to these reported for the comparator trivalent vaccines (*344*).

In immunogenicity analyses performed in these studies, Fluzone Quadrivalent was noninferior to both IIV3s based on adjusted GMTs and seroconversion rates for all four strains contained in the vaccine for children and for adults aged ≥18 years. For adults aged ≥65 years, GMTs were noninferior for all four strains; seroconversion rates were non-inferior to those for IIV3 for the included influenza A(H3N2), and both the Victoria and Yamagata B strains, but not for the included influenza A(H1N1). Overall, antibody response to influenza B strains contained in Fluzone Quadrivalent was higher than the antibody response after vaccination with a trivalent IIV containing an influenza B strain from a different lineage (*344*).

Flulaval Quadrivalent: Flulaval Quadrivalent (ID Biomedical Corporation/GlaxoSmithKline), an IIV4, was approved by FDA in August 2013. Fluarix Quadrivalent will be available alongside the trivalent formulation of Flulaval during the 2013–14 season. Both the trivalent and quadrivalent formulations of Flulaval are approved for persons aged ≥3 years (*345*).

Flulaval Quadrivalent is formulated to contain 60 μg HA per 0.5 mL dose (15 μg HA of each of the four influenza virus strains recommended for inclusion in quadrivalent influenza vaccines). It is supplied in 5.0 mL multi-dose vials and is administered by intramuscular injection. Contraindications and precautions to the administration of Fluarix Quadrivalent are similar to those described for the trivalent formulation of Flulaval (see Contraindications and Precautions for the Use of IIV; Table 2) (*345*).

In clinical studies, the most common (≥10%) solicited local adverse reaction to Flulaval Quadrivalent among adults was pain (60%); the most common solicited systemic adverse events were muscle aches (26%), headache (22%), fatigue (22%), and arthralgia (15%). Among children aged 3 through 17 years, the most common (≥10%) solicited local adverse reaction was pain (65%). Among children aged 3 through 4 years, the most common (≥10%) solicited systemic adverse events were irritability (26%), drowsiness (21%), and loss of appetite (17%). Among children aged 5 through 17 years, the most common (≥10%) solicited systemic adverse events were muscle aches (29%), fatigue (22%), headache (22%), arthralgia (13%), and gastrointestinal symptoms (10%) (*345*).

In immunogenicity studies, there was no evidence that the addition of a second B strain resulted in immune interference to other strains included in the vaccine. In a randomized, observer-blind, non-influenza vaccine-controlled study of FluLaval Quadrivakent vs. Havrix (hepatitis A vaccine, GlaxoSmithKline) conducted among children aged 3 through 8 years, vaccine efficacy was vaccine efficacy was vaccine efficacy was 55.4% (95% CI = 39.1–67.3) for RT-PCR-confirmed influenza, and 55.9% (97.5% CI = 35.4–69.9) for culture confirmed influenza (*345*).

Vaccines Produced via Non-Egg Based Technologies

For the 2013–14 season, two new vaccines for adults will be available that are manufactured using newer technologies that minimize or avoid entirely the use of eggs. A primary advantage of these manufacturing methods is that they might permit more rapid scale up of vaccine production when needed (e.g., response to a pandemic). These include Flucelvax (Novartis, Cambridge, Massachusetts), which is produced using cell culture technology, and FluBlok (Protein Sciences, Meriden, Connecticut), which contains recombinant HA.

Flucelvax: Flucelvax, a ccIIV3, was approved by FDA in November 2012. It is a trivalent subunit IIV prepared from virus propagated in Madin Darby Canine Kidney (MDCK) cells. It is approved for persons aged ≥18 years (*346*).

Flucelvax contains a total of 45 μg HA (15 μg HA of each of the included influenza A(H1N1), influenza A(H3N2), and influenza B vaccine virus strains) per 0.5 mL dose. It is supplied in single-dose, prefilled syringes and is administered via intramuscular injection. Contraindications are similar to those for other IIVs (see Contraindications and Precautions for the Use of IIV; Table 2) (*346*).

In clinical studies of Flucelvax, the most common (≥10%) solicited adverse reactions among adults aged 18 through 64 years occurring within 7 days of vaccination were injection-site pain (28%), erythema at the injection site (13%), headache (16%), fatigue (12%), myalgia (11%), and malaise (10%). The most common (≥10%) solicited adverse reactions occurring in adults aged ≥65 years within 7 days of vaccination were erythema at the injection site (10%), fatigue (11%), headache (10%) and malaise (10%) (*346–348*). Injection site pain was reported significantly more frequently than with a licensed comparator egg-based IIV3 in one study, but was of mild or moderate severity in >99% of reports and usually resolved within 48 hours (*348*). In a multinational placebo-controlled study conducted during the 2007–08 influenza season among

persons aged 18–49 years, Flucelvax was 83.8% effective (lower limit of one-sided 97% CI = 61%) against culture-confirmed influenza caused by viruses antigenically matched to the vaccine. In three studies in adults aged ≥18 years, Flucelvax demonstrated comparable immunogenicity to U.S.-licensed comparator vaccines for all three vaccine strains (*346*).

Although manufacture of the Flucelvax does not use eggs, the vaccine cannot be considered to be egg-free. Before beginning production, seed viruses are created using reference virus strains supplied by the World Health Organization that have been passaged in eggs. The total egg protein is estimated to be less than 50 femtograms ($5x10^{-14}$ grams or $5x10^{-8}$ μg) total egg protein (of which a fraction is ovalbumin) per 0.5 mL dose of Flucelvax (Novartis, personal communication, 2013).

FluBlok: Approved in January 2013, FluBlok is a trivalent recombinant HA influenza vaccine (RIV3) containing purified HA proteins produced in a continuous insect cell line using a baculovirus vector. This process uses neither live influenza viruses nor eggs. Flublok is approved for persons aged 18 through 49 years (*349*).

FluBlok contains 135 μg HA per 0.5 mL dose (45 μg of each of the three HA antigens recommended for inclusion in trivalent influenza vaccines). It is supplied in 0.5 mL single-dose vials and is administered by intramuscular injection. Contraindications include severe allergic reaction to any component of the vaccine (*349*).

Safety, immunogenicity, and efficacy of FluBlok were evaluated in randomized, double-blind, placebo-controlled studies (*350,351*) conducted among healthy adults aged 18 through 49 years that compared recombinant HA vaccines containing a total of 135 μg HA with placebo. The most frequently reported injection site reaction (reported in ≥10% of the 135 μg-dose recipients) was pain (>37%); the most common solicited systemic reactions were headache (>15%), fatigue (>15%), and myalgias (>11%) (*349,351*). Local pain and tenderness were reported significantly more frequently with FluBlok than placebo; however, 94% of reports of pain following FluBlok were rated as mild. In a randomized placebo-controlled efficacy study of the 135 μg HA dose of FluBlok conducted among healthy adults during the 2007–08 influenza season (*349,351*), estimated vaccine effectiveness for CDC-defined ILI with a positive culture for influenza virus was 75.4% (95% CI = -148.0%–99.5%) against matched strains; more precise estimation of vaccine effectiveness was not possible because 96% of isolates in this study did not antigenically match the strains represented in the vaccine (*349*). Estimated vaccine effectiveness without regard to match was 44.6% (95% CI = 18.8%–62.6%) (*351*).

Recommendations for the Use of Influenza Vaccines, 2013–14 Influenza Season

Groups Recommended for Vaccination

Routine annual influenza vaccination is recommended for all persons aged ≥6 months who do not have contraindications. Recommendations pertaining to the use of specific vaccines and populations are summarized below.

Timing of Vaccination

In general, health-care providers should begin offering vaccination soon after vaccine becomes available and, if possible, by October. All children aged 6 months through 8 years who are recommended for 2 doses should receive their first dose as soon as possible after vaccine becomes available; these children 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. 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 be structured to ensure the vaccination of as many persons as possible before influenza activity in the community begins. In any given year, the optimal time to vaccinate 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 (*5*).

In recent seasons, initial shipments of influenza vaccine have arrived to some vaccine providers as early as July. Very early availability of vaccine as compared with typical onset and peak of influenza activity raises questions related to the ideal time to begin vaccination. Antibody levels induced by vaccine decline over the months after vaccination (*99,352–354*). Although a 2008 literature review found no clear evidence of more rapid decline among the elderly (*105*), a 2010 study noted significant decline in titers 6 months postvaccination among persons aged ≥65 years (though titers still met European Medicines Agency levels considered adequate for protection) (*354*). More recently, some investigators have estimated vaccine effectiveness over the course of a season, as a function of time since vaccination.

TABLE 2. Contraindications and precautions to the use of influenza vaccines — United States, 2013–14 influenza season*

Vaccine	Contraindications	Precautions
IIV (includes IIV3, II4, and ccIIV)	History of severe allergic reaction to any component of the vaccine, including egg protein, or after previous dose of any influenza vaccine.	Moderate to severe illness with or without fever. History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine.
RIV	History of severe allergic reaction to any component of the vaccine	Moderate to severe illness with or without fever. History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine.
LAIV	History of severe allergic reaction to any component of the vaccine, including egg protein, gentamicin, gelatin, and arginine, or after a previous dose of any influenza vaccine; Concomitant Aspirin therapy in children and adolescents. In addition, ACIP recommends against use in the following: • Children aged <2 years • adults aged ≥50 years • children aged 2 through 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 (see screening guidance, footnote in Table 1); • persons with asthma; • children and adults who have chronic pulmonary, cardiovascular (except isolated hypertension), renal, hepatic, neurologic/neuromuscular, hematologic, or metabolic disorders; • children and adults who have immunosuppression (including immunosuppression caused by medications or by HIV); • persons with egg allergy; • close contacts and caregivers of severely immunosuppressed persons who require a protected environment; • pregnant women	Moderate to severe illness with or without fever. History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine.

Abbreviations: IIV = inactivated influenza vaccine; IIV3 = inactivated influenza vaccine, trivalent; IIV4 = inactivated influenza vaccine, quadrivalent; RIV = recombinant influenza vaccine; LAIV = live-attenuated influenza vaccine.

* Immunization providers should check Food and Drug Administration–approved prescribing information for 2013–14 influenza vaccines for the most complete and updated information, including (but not limited to) indications, contraindications, and precautions. Package inserts for U.S.-licensed vaccines are available at http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm.

A case-control study conducted in Navarre, Spain, during the 2011–12 season revealed a decline in vaccine effectiveness from 61% (95% CI = 5–84) in the first 100 days postvaccination to 42% (95% CI = -39–75) for 100–119 days postvaccination and to -35% (95% CI = -211–41) thereafter. This decline primarily affected persons aged ≥65 years, among whom vaccine effectiveness declined from 85% (95% CI = -8–98) to 24% (95% CI = -224–82) to -208 (95% CI = -1,563–43) over these intervals. Most viruses isolated among those infected which were characterized did not match the vaccine strains (*106*). A case-control study conducted in the United Kingdom during the same season estimated an overall vaccine effectiveness against A(H3N2) of 53% (95% CI = 0–78) among those vaccinated less than 3 months, and 12% (95% CI = -31–41) for those vaccinated 3 months or more. The proportion of persons aged ≥65 years was too small to detect a substantial difference in vaccine effectiveness among this age group (*355*). Further evaluation of this effect in larger studies and in different seasons is needed. ACIP will continue to evaluate further data as they become available.

While delaying vaccination until later in the season might permit greater immunity later in the season, such deferral might result in missed opportunities to vaccinate, as well as difficulties in vaccinating a population within a more constrained time period. Community vaccination programs should balance maximizing likelihood of persistence of vaccine-induced protection through the season with avoiding missed opportunities to vaccinate or vaccinating after influenza circulation occurs.

Vaccination efforts should continue throughout the season, because the duration of the influenza season varies and influenza activity might not occur 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 (*356,357*).

Available Vaccine Products and Indications

No preferential recommendation is made for one influenza vaccine product over another for persons for whom more than one product is otherwise appropriate. A variety of influenza vaccine products are available (Table 1), including (as of August 2013) six newly approved vaccines (see New and Recently Approved Influenza Vaccine Products). For many vaccine recipients, more than one type or brand of vaccine may be appropriate within indications and ACIP recommendations. Considerations for selection of a given vaccine when several appropriate options are available are discussed below. However, not all products are likely to be uniformly available in any practice setting or locality. For newer vaccines, supplies might be limited during the 2013–14 season; moreover, postmarketing safety and effectiveness data are as yet unavailable, prohibiting a full risk-benefit analysis of newer versus previously available products. Therefore, within these guidelines and approved indications, where more than one type of vaccine is appropriate and available, no preferential recommendation is made for use of any influenza vaccine product over another.

Inactivated Influenza Vaccines

IIVs comprise a large group of products. For the 2013–14 season, most IIVs will be trivalent (IIV3), with some quadrivalent (IIV4) also available. Among IIV3 preparations, cell-culture based IIV will be available (ccIIV3). As a class, IIVs include products which might be administered to all persons aged ≥6 months. However, approved age indications for the various IIV products differ (Table 1). Only age-appropriate products should be administered. Providers should consult package inserts and updated CDC/ACIP guidance for current information. Of particular note, although Afluria (CSL Limited) is FDA-approved for children aged >5 years, CDC and ACIP recommend against use of Afluria in persons aged <9 years because of increased risk for febrile reactions noted in this age group with CSL's 2010 Southern Hemisphere IIV3 (*228*). If no other age-appropriate, licensed inactivated seasonal influenza vaccine is available for a child aged 5 through 8 years who has a medical condition that increases the child's risk for influenza complications, Afluria can be used; however, providers should discuss with the parents or caregivers the potential benefits and risks of influenza vaccination with Afluria in this age group before administering this vaccine (*358*).

All IIV preparations contain the same quantity of HA (15 μg per vaccine virus strain per 0.5 mL dose; 45 μg total), except Fluzone Intradermal and Fluzone High-Dose (Sanofi Pasteur). Fluzone Intradermal is approved for persons aged 18 through 64 years, and contains 9 μg of each HA per vaccine virus strain (27 μg total). Fluzone High-Dose is approved for persons aged ≥65 years and contains 60 μg of each HA per vaccine virus strain (180 μg total). Within specified age indications, ACIP expresses no preference for any given IIV over another.

The one IIV product licensed by FDA for children aged 6 through 36 months contains 0.25 mL/dose. The 0.25 mL dose may be administered from a prefilled single-dose syringe, single-use vial, or multi-dose vial of this age-appropriate formulation. Children aged 36 months through 18 years, and adults receiving IM preparations of IIV, should receive a 0.5 mL dose. If a pediatric vaccine dose (0.25 mL) is administered inadvertently to an adult, an additional pediatric dose (0.25 mL) should be administered to provide a full adult dose (0.5 mL). 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 (*5*).

With the exception of Fluzone Intradermal (Sanofi Pasteur), IIVs should be administered intramuscularly. For adults and older children, the deltoid is the preferred site. Infants and younger children should be vaccinated in the anterolateral thigh. Additional specific guidance regarding site selection and needle length for intramuscular administration are provided in ACIP's General Recommendations on Immunization (*270*). Fluzone Intradermal is administered intradermally, preferably over the deltoid muscle, using the included delivery system (*240*).

Trivalent versus Quadrivalent IIVs: For the first time, during the 2013–14 influenza season, both trivalent (IIV3) and quadrivalent (IIV4) IIVs will be available. The relative quantity of doses of IIV4 that will be available is not certain; however, it is expected that the supply of IIV4 might be limited. Quadrivalent vaccines are designed to provide broader protection against circulating influenza B viruses in seasons during which the B virus contained in trivalent vaccines is not an optimal match to the predominant circulating B viruses. However, vaccination should not be delayed if only IIV3 is available. No preference is expressed for IIV4 over IIV3.

IIVs and persons aged ≥65 years: For persons aged ≥65 years, either an age-appropriate standard-dose IIV (IIV3 or IIV4) or high-dose IIV3 are acceptable options. High-dose IIV3 (available as Fluzone High-Dose) is approved for persons aged ≥65 years. Immunogenicity data from three prelicensure studies among persons aged ≥65 years indicated that, compared with standard dose Fluzone, Fluzone High-Dose elicited higher HAI titers against all three influenza virus strains included in seasonal influenza vaccines recommended during the study period (*178–180,359*). Whether the higher postvaccination immune responses observed among Fluzone High-Dose vaccine recipients will result in greater protection against

influenza illness is under study. Some solicited injection site and systemic adverse events were more frequent after vaccination with Fluzone High-Dose compared with standard Fluzone, but typically were mild and transient (*178–180*). No preferential recommendation is made for high-dose IIV over standard dose IIV for persons aged ≥65 years.

IIVs and egg allergy: With the exception of Flucelvax, IIVs are manufactured via propagation of virus in eggs and therefore might contain residual egg protein. Egg protein content (usually described as ovalbumin content as a surrogate measure) is not disclosed on all package inserts (Table 1); where not listed, this information generally can be obtained by contacting the manufacturer. Flucelvax is manufactured from virus propagated in Madin Darby Canine Kidney (MDCK) cells rather than embryonated eggs; however, before production seed virus is created using reference virus strains supplied by WHO, which have been passaged in eggs. Flucelvax can therefore not be considered egg-free. The total egg protein is estimated to be <50 femtograms ($5x10^{-14}$ grams) total egg protein (of which a fraction is ovalbumin) per 0.5 mL dose of Flucelvax (Novartis, unpublished data, 2013). Flucelvax can be administered to persons with a history of mild egg allergy (specifically, those who have experienced only hives following egg exposure; see Influenza Vaccination of Persons with Egg Allergy) who are aged ≥18 years and have no other contraindications. Because no data are available regarding the use of ccIIV among egg-allergic persons, and there is no established safe threshold for ovalbumin content in vaccines, ccIIV should be administered according to the guidance for other IIVs (see Influenza Vaccination of Persons with Egg Allergy).

Contraindications and precautions for use of IIVs: Manufacturer package inserts and updated CDC/ACIP guidance should be consulted for current information on contraindications and precautions for individual vaccine products. In general, IIV is contraindicated for, and should not be administered to, persons known to have anaphylactic hypersensitivity to eggs or to any vaccine components (Table 2). 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.

Moderate or severe acute illness with or without fever is a general precaution for vaccination (*270*). GBS within 6 weeks following a previous dose of influenza vaccine is considered a precaution for use of influenza vaccines (Table 2).

Recombinant Influenza Vaccine

One RIV product, FluBlok, a trivalent recombinant HA vaccine, is expected to be available for the 2013–14 influenza season. This RIV3 is administered by intramuscular injection, and is indicated for persons aged 18 through 49 years. RIV3 is manufactured without the use of influenza viruses; therefore, similarly to IIVs, no shedding of vaccine virus will occur. No preference is expressed for RIV versus IIV within specified indications.

RIV and egg allergy: The currently available RIV, FluBlok, is manufactured without the use of eggs, and does not carry a contraindication for egg allergy. Therefore, Flublok can be administered to persons with egg allergy of any severity who are aged 18 through 49 years and do not have other contraindications. Since 2011, ACIP has recommended that persons with a history of mild egg allergy (specifically, those who experience only hives following egg exposure) can receive IIV, with additional safety precautions. For such persons, vaccination should not be delayed if RIV is not available; IIV should be used in these settings, following the recommendations outlined (see Influenza Vaccination of Persons with Egg Allergy).

Contraindications and precautions for use of RIV: FluBlok is contraindicated in persons who have had a severe allergic reaction to any component of the vaccine. Moderate or severe acute illness with or without fever is a general precaution for vaccination (*270*). GBS within 6 weeks following a previous dose of influenza vaccine is considered a precaution for use of influenza vaccines (Table 2). FluBlok is not licensed for use in children aged <18 years or adults aged >49 years.

Live Attenuated Influenza Vaccine

One LAIV4 product, FluMist Quadrivalent (MedImmune), is expected to be available during the 2013–14 influenza season. Flumist is indicated for nonpregnant persons aged 2 through 49 years who do not have a medical condition that predisposes them to medical complications from influenza. No preference is indicated for LAIV versus other vaccines appropriate for this group.

LAIV is administered intranasally using the supplied 0.2 mL intranasal sprayer (0.1 mL in each nostril). 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 IIV should be administered instead.

LAIV versus IIV: Several randomized studies have evaluated the relative effectiveness of LAIV3 as compared with IIV3 (*205,212–214,218,220,221*). Most studies conducted among adults have noted superior relative efficacy of IIV3 (*205,212–214*). A significantly greater relative efficacy of LAIV3 as compared with IIV3 has been noted in several studies conducted among younger children, including a randomized,

open label study among children aged 6 through 71 months (*221*), a randomized blinded trial of children aged 6 through 59 months (218), and a randomized blinded trial of children with asthma aged 6 through 17 years (*220*). However, no postmarketing safety data are yet available for the new quadrivalent formulation, LAIV4, which will be available for the first time during the 2013–14 season and is expected to replace LAIV3. Therefore, no preferential recommendation is made for LAIV4 over IIV for any age group at this time. This information will be updated as more data become available. Vaccination should not be delayed if LAIV is not available.

LAIV and egg allergy: Because of relative lack of data demonstrating safety of LAIV for persons with egg allergy, egg-allergic persons should receive IIV rather than LAIV (see Influenza Vaccination of Persons with Egg Allergy) (*360*).

Contraindications and precautions to the use of LAIV: LAIV is contraindicated for persons with a history of severe hypersensitivity reaction to any component of the vaccine or to a previous dose of any influenza vaccine, and in children and adolescents receiving concomitant aspirin therapy (Table 2). In addition, LAIV should not be administered to the following groups:

- children aged <2 years;
- adults aged ≥50 years;
- children aged 2 through 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 (Table 1);
- persons with asthma;
- children and adults who have chronic pulmonary, cardiovascular (except isolated hypertension), renal, hepatic, neurologic/neuromuscular, hematologic, or metabolic disorders;
- children and adults who have immunosuppression (including immunosuppression caused by medications or by HIV); and
- pregnant women.

Moderate or severe acute illness with or without fever is a general precaution for vaccination (*270*). GBS within 6 weeks following a previous dose of influenza vaccine is considered a precaution for use of influenza vaccines.

Persons at Risk for Medical Complications Attributable to Severe Influenza

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 (no hierarchy is implied by order of listing):

- all children aged 6 through 59 months;
- all persons aged ≥50 years;
- adults and children who have chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus);
- persons who have immunosuppression (including immunosuppression caused by medications or by HIV infection);
- women who are or will be pregnant during the influenza season;
- children and adolescents (aged 6 months through 18 years) who are receiving long-term aspirin therapy and who might be at risk for experiencing Reye's syndrome after influenza virus infection;
- residents of nursing homes and other long-term care facilities;
- American Indians/Alaska Natives; and
- persons who are morbidly obese (BMI ≥40).

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

All persons aged ≥6 months should be vaccinated annually. Continued emphasis should be placed on vaccination of persons who live with or care for persons at higher risk for influenza-related complications. When vaccine supply is limited, vaccination efforts should focus on delivering vaccination to persons at higher risk for influenza-related complications listed above, as well as these persons:

- health-care personnel;
- household contacts (including children) and caregivers of children aged ≤59 months (i.e., aged <5 years) and adults aged ≥50 years, with particular emphasis on vaccinating contacts of children aged <6 months; and
- household contacts (including children) and caregivers of persons with medical conditions that put them at high risk for severe complications from influenza.

Annual influenza vaccination is recommended for all health-care personnel and persons in training for health-care professions. Personnel in health-care settings who should be vaccinated include physicians, nurses, and other workers in inpatient 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. ACIP guidance for immunization of health-care personnel has been published previously (*361*).

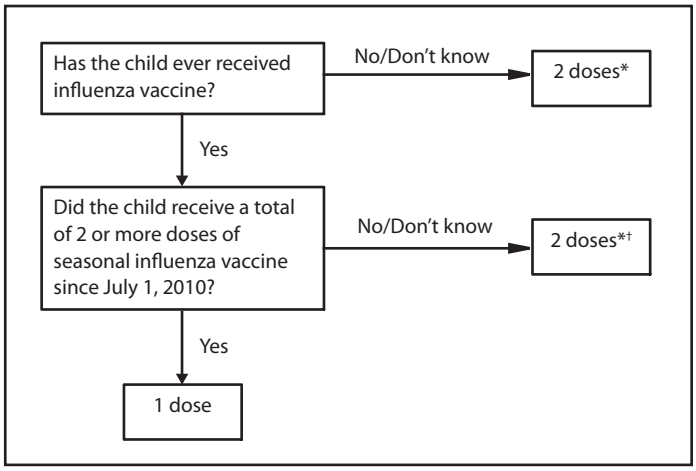
Health-care personnel and persons who are contacts of persons in these groups and who are not contacts of severely immunocompromised persons (those living in a protective environment; see Close Contacts of Immunocompromised Persons) may receive any influenza vaccine that is otherwise indicated. Persons who care for the severely immunocompromised should receive either IIV or RIV3. The rationale for avoiding use of LAIV among health-care personnel or close contacts of severely immunocompromised patients is the theoretical risk that a live attenuated vaccine virus could be transmitted to the severely immunosuppressed person. In addition, to further reduce the theoretical risk of vaccine virus transmission, ACIP/HICPAC has recommended that health-care personnel who receive LAIV should avoid providing care for severely immunosuppressed patients requiring a protected environment for 7 days after vaccination, and that hospital visitors who have received LAIV should avoid contact with severely immunosuppressed persons (i.e., persons requiring a protected environment) for 7 days after vaccination. However, such visitors should not be restricted from visiting less severely immunosuppressed patients (*362*). Healthy nonpregnant persons aged 2 through 49 years, including health-care personnel, 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 LAIV.

Vaccine Dose Considerations for Children Aged 6 Months Through 8 Years

Evidence from several studies indicates that children aged 6 months through 8 years require 2 doses of influenza vaccine (administered a minimum of 4 weeks apart) during their first season of vaccination to optimize immune response. In a study of children aged 5 through 8 years receiving trivalent inactivated influenza vaccine (IIV3) for the first time, the proportion of children with protective antibody responses was significantly higher ($p<0.001$ for influenza A(H1N1), $p = 0.01$ for influenza A(H3N2), and $p<0.001$ for influenza B) after 2 doses as compared with a single dose (*115*). Several studies have indicated that the time interval between two initial doses (from 4 weeks up to 1 year) of the same antigen may not be critical (*363–365*). However, because of the antigenic novelty of the 2009 influenza A(H1N1) pandemic virus, which is anticipated to continue circulating during the 2013–14 influenza season, exposure history to this vaccine virus antigen also must be considered. Children who last received seasonal (trivalent) influenza vaccine before the 2010–11 season but did not receive a vaccine containing 2009(H1N1) antigen (i.e., either in seasonal vaccine since July 2010 or monovalent 2009(H1N1) vaccine) will not have received this antigen. These children are recommended to receive 2 doses this season, even if 2 doses of seasonal influenza vaccine were received before the 2010–11 season. This recommendation is illustrated in the approaches outlined below. These recommendations are consistent with those of the American Academy of Pediatrics (*366*). Two approaches are recommended, both of which are acceptable.

The first approach (Figure 1), takes into consideration only doses of seasonal influenza vaccine received since July 1, 2010. This approach has the advantage of simplicity, particularly in settings in which it is difficult to ascertain vaccination history before the 2010–11 season. Using this approach, children aged 6 months through 8 years need only 1 dose of vaccine in the 2013–14 influenza season if they received a total of 2 or more doses of seasonal vaccine since July 1, 2010. Children who did not receive a total of 2 or more doses of seasonal vaccine since July 1, 2010, require 2 doses in the 2013–14 season.

FIGURE 1. Influenza vaccine dosing algorithm for aged children 6 months through 8 years — Advisory Committee on Immunization Practices, United States, 2013–14 influenza season



* Doses should be administered at least 4 weeks apart.

† For the sake of simplicity, this algorithm takes into consideration only doses of seasonal influenza vaccine received since July 1, 2010. As an alternative approach in settings where vaccination history from before July 1, 2010, is available, if a child aged 6 months through 8 years is known to have received at least 2 seasonal influenza vaccines during any previous season, and at least 1 dose of a 2009(H1N1)-containing vaccine (i.e., 2010–11, 2011–12, or 2012–13 seasonal vaccine or the monovalent 2009[H1N1] vaccine), then the child needs only 1 dose for the 2013–14 season. Using this approach, children aged 6 months through 8 years need only 1 dose of vaccine in the 2013–14 season if they have received any of the following:

- 2 or more doses of seasonal influenza vaccine since July 1, 2010;
- 2 or more doses of seasonal influenza vaccine before July 1, 2010, and 1 or more doses of monovalent 2009(H1N1) vaccine; or
- 1 or more doses of seasonal influenza vaccine before July 1, 2010, and 1 or more doses of seasonal influenza vaccine since July 1, 2010.

Children in this age group for whom one of these conditions is not met require 2 doses in the 2013–14 season.

In settings where adequate vaccination history from before the 2010–11 season is available, the second approach may be used. By this approach, if a child aged 6 months through 8 years is known to have received at least 2 doses of seasonal influenza vaccine during any prior season, and at least 1 dose of a 2009(H1N1)-containing vaccine (i.e., 2010–11, 2011–12, or 2012–13 seasonal vaccine or the monovalent 2009 [H1N1] vaccine) then the child needs only 1 dose for the 2013–14 season. Using this approach, children aged 6 months through 8 years need only 1 dose of vaccine in the 2013–14 season if they have received any of the following:

- 2 or more doses of seasonal influenza vaccine since July 1, 2010 or;
- 2 or more doses of seasonal influenza vaccine before July 1, 2010 and 1 or more doses of monovalent 2009(H1N1) vaccine or;
- 1 or more doses of seasonal influenza vaccine before July 1, 2010, and 1 or more doses of seasonal influenza vaccine since July 1, 2010.

Children aged 6 months through 8 years for whom one of these conditions is not met require 2 doses in the 2013–14 season.

Influenza Vaccination for Pregnant Women

Pregnant and postpartum women are at higher risk for severe illness and complications from influenza than women who are not pregnant because of changes in the immune system, heart, and lungs during pregnancy (*367*). Vaccination during pregnancy has been shown to protect infants from influenza (*170,368*), including infants aged <6 months, for whom no influenza vaccines are currently licensed (*368–370*). The ACIP and American College of Obstetricians and Gynecologists (ACOG) recommends that all women who are pregnant or who might be pregnant in the upcoming influenza season receive IIV because of this increased risk for serious illness and complications from influenza (*371*). Influenza vaccination can be administered at any time during pregnancy, before and during the influenza season.

Women who are or will be pregnant during influenza season should receive IIV. Live attenuated influenza vaccine (LAIV) is not recommended for use during pregnancy. Postpartum women can receive either LAIV or IIV. Pregnant and postpartum women do not need to avoid contact with persons recently vaccinated with LAIV.

Influenza Vaccination of Persons With a History of Egg allergy

Severe allergic and anaphylactic reactions can occur in response to a number of influenza vaccine components, but such reactions are rare. With the exceptions of RIV and ccIIV3, currently available influenza vaccines are prepared by propagation of virus in embryonated eggs. A recent review of published data (including 4,172 patients, 513 of whom were reported to have a history of severe allergic reaction to egg) noted that no occurrences of anaphylaxis were reported, though some milder reactions did occur (*372*), suggesting that severe allergic reactions to egg-based influenza vaccines are unlikely. Vaccines containing as much as 0.7 μg/0.5 mL have been tolerated (*360,373*); however, a threshold below which no reactions would be expected is not known (*360*). Although ovalbumin content is not required to be disclosed on package inserts for vaccines used in the United States, manufacturers either report maximum albumin content in the package inserts or will provide this information on request. Among IIVs for which ovalbumin content was disclosed during the 2011–12 and 2012–13 seasons, reported maximum amounts were ≤1 μg/0.5 mL dose. Ovalbumin is not directly measured for Flucelvax, but it is estimated by calculation from the initial content in the reference virus strains to contain a maximum of $5x10^{-8}$ μg/0.5 mL dose of total egg protein (Novartis, unpublished data, 2013). Flublok is egg-free. It should be noted, however, that neither Flucelvax nor Flublok are licensed for children aged <18 years.

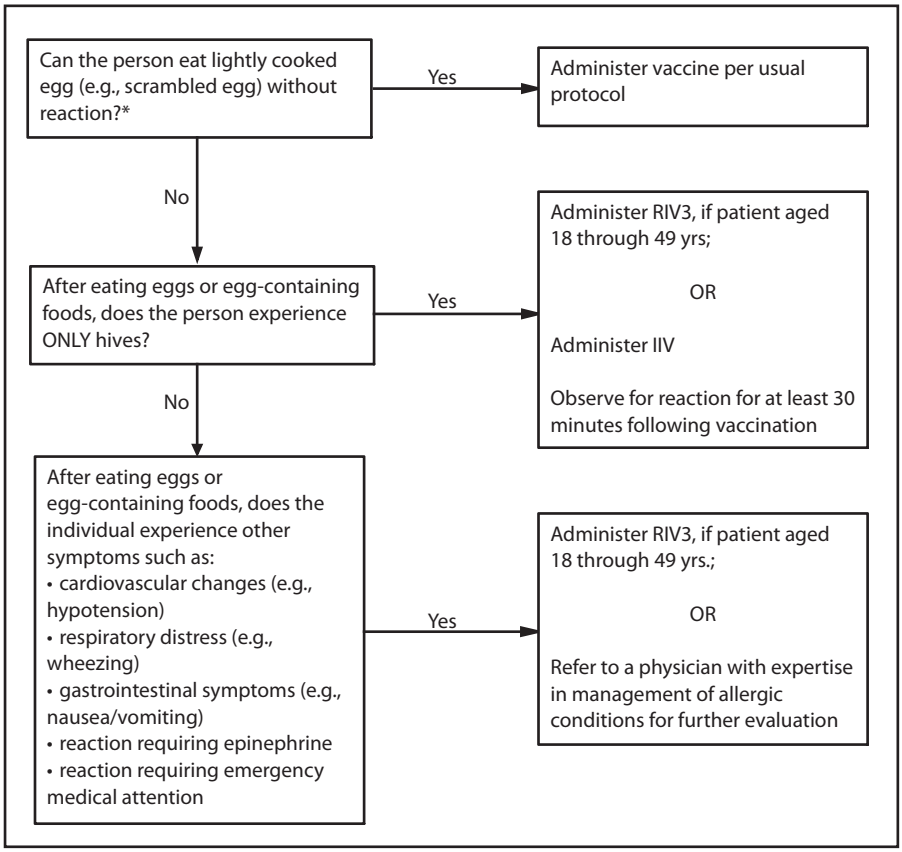
Surveillance for Anaphylaxis Following Influenza Vaccination

Following review of available data, since the 2011–12 influenza season, ACIP has recommended that persons with egg allergy who report only hives after egg exposure should receive IIV, with several additional safety measures (*231*); current FDA-approved packaging for influenza vaccines lists only severe hypersensitivity to egg protein as a contraindication to vaccination. Review of VAERS data for the 2011–12 and 2012–13 seasons indicated no disproportionate reporting of allergic reaction or anaphylaxis after influenza vaccination during the first two seasons the new recommendation was in place (*374,375*). However, during the 2012–13 influenza season, VAERS received one report containing a documented medical history of anaphylaxis following receipt of a first-ever split dose IIV in a child aged 12 months with atopy but no known prior egg ingestion in the past, who had a previous positive allergy skin prick test to ovalbumin. This child had previously received allergy testing attributed to a strong personal and family history of food allergies and other allergies (*375*). For the 2013–14 season, the recommendations which follow include guidance concerning persons who have no history of exposure to egg, but who have documented results potentially suggestive of egg allergy on previously performed allergy testing.

For the 2013–14 influenza season, ACIP recommends the following:

- Persons with a history of egg allergy who have experienced only hives after exposure to egg should receive influenza vaccine. Because relatively few data are available for use of LAIV in this setting, IIV or RIV should be used. RIV is egg-free and may be used for persons aged 18–49 years who have no other contraindications. However, IIV (egg- or cell-culture based) also may be used, with the following additional safety measures (Figure 2):
  - Vaccine should be administered by a health-care provider who is familiar with the potential manifestations of egg allergy; and
  - Vaccine recipients should be observed for at least 30 minutes for signs of a reaction after administration of each vaccine dose (*360*).
- Other measures, such as dividing and administering the vaccine by a two-step approach and skin testing with vaccine, are not necessary (*360*).
- Persons who report having had reactions to egg involving such symptoms as angioedema, respiratory distress, lightheadedness, or recurrent emesis; or who required epinephrine or another emergency medical intervention, particularly those that occurred immediately or within a short time (minutes to hours) after egg exposure, are more likely to have a serious systemic or anaphylactic reaction upon reexposure to egg proteins. These persons may receive RIV3, if aged 18 through 49 years and there are no other contraindications. If RIV3 is not available or the recipient is not within the indicated age range, such persons should be referred to a physician with expertise in the management of allergic conditions for further risk assessment before receipt of vaccine (Figure 2).
- All vaccines should be administered in settings in which personnel and equipment for rapid recognition and treatment of anaphylaxis are available. ACIP recommends that all vaccination providers should be familiar with the office emergency plan (*270*).
- Some persons who report allergy to egg might not be egg-allergic. Those who are able to eat lightly cooked egg (e.g., scrambled egg) without reaction are unlikely to be allergic. Egg-allergic persons might tolerate egg in baked products (e.g., bread or cake). Tolerance to egg-containing foods does not exclude the possibility of egg allergy (*376*). Egg allergy can be confirmed by a consistent medical history of adverse reactions to eggs and egg-containing foods, plus skin and/or blood testing for immunoglobulin E antibodies to egg proteins.
- For persons who have no known history of exposure to egg, but who are suspected of being egg-allergic on the basis of previously performed allergy testing, consultation with a physician with expertise in the management of allergic conditions should be obtained before vaccination (Figure 2). Alternatively, RIV3 may be administered if the recipient is aged 18 through 49 years.
- A previous severe allergic reaction to influenza vaccine, regardless of the component suspected to be responsible

FIGURE 2. Recommendations regarding influenza vaccination of persons who report allergy to eggs — Advisory Committee on Immunization Practices, United States, 2013–14 influenza season



Abbreviations: IIV = inactivated influenza vaccine; RIV3 = recombinant influenza vaccine, trivalent

* Persons with egg allergy might tolerate egg in baked products (e.g. bread or cake). Tolerance to egg-containing foods does not exclude the possibility of egg allergy. For persons who have no known history of exposure to egg but who are suspected of being egg-allergic on the basis of previously performed allergy testing, consultation with a physician with expertise in the management of allergic conditions should be obtained prior to vaccination. Alternatively, RIV3 may be administered if the recipient is aged 18 through 49 years.

for the reaction, is a contraindication to future receipt of any influenza vaccine.

Influenza Vaccines and Use of Influenza Antiviral Medications

Administration of IIV to persons receiving influenza antiviral drugs for treatment or chemoprophylaxis is acceptable. The effect on safety and effectiveness of LAIV co-administration with influenza antiviral medications has not been studied. However, because antiviral drugs reduce replication of influenza viruses, LAIV should not be administered until 48 hours after cessation of influenza antiviral therapy (*210*). If influenza antiviral medications are administered within 2 weeks after receipt of LAIV, the LAIV dose should be repeated 48 or more hours after the last dose of antiviral medication. Alternatively, persons receiving antiviral drugs within the period 2 days before to 14 days after vaccination with LAIV may be revaccinated another approved vaccine formulation (e.g., IIV or RIV).

Concurrent Administration of Influenza Vaccine With Other Vaccines

Limited data are available on the concurrent administration of influenza vaccines with other live vaccines. Use of LAIV3 concurrently with measles, mumps, rubella (MMR) and varicella vaccine among children aged 12 through 15 months has been studied, and no interference with the immunogenicity to antigens in any of the vaccines was observed (*210,377*). Among adults aged ≥50 years, the safety and immunogenicity of zoster vaccine and IIV3 were similar whether administered simultaneously or sequentially spaced 4 weeks apart (*378*).

In the absence of specific data indicating interference, following ACIP's general recommendations for vaccination is prudent (*270*). 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 (such as LAIV), at least 4 weeks should pass before another live vaccine is administered.

Sources of Information Regarding Influenza and Surveillance

Updated information regarding influenza surveillance, prevention, detection, and control is available at http://www.cdc.gov/flu. U.S surveillance data are updated weekly during October–May on FluView (http://www.cdc.gov/flu/weekly). In addition, periodic updates regarding influenza are published in *MMWR* (http://www.cdc.gov/mmwr). Additional information regarding influenza vaccine can be obtained from CDC by calling telephone 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

The National Childhood Vaccine Injury Act of 1986 requires health-care providers to report any adverse event listed by the vaccine manufacturer as a contraindication to further doses of the vaccine, or any adverse event listed in the VAERS Table of Reportable Events Following Vaccination (http://vaers.hhs.gov/resources/VAERS_Table_of_Reportable_Events_Following_Vaccination.pdf) that occurs within the specified time period after vaccination. In addition to mandated reporting, health-care providers are encouraged to report any clinically significant adverse event following vaccination to VAERS. Information on how to report a vaccine adverse event is available 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 request by facsimile 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.

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 (available at http://www.hrsa.gov/vaccinecompensation/vaccinetable.html) lists the vaccines covered by VICP and the associated injuries and conditions (including death) that may receive a legal presumption of causation. 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. Eligibility for compensation is not affected by whether a covered vaccine is used off-label or inconsistently with recommendations.

For a claim to be eligible for compensation under the VICP, it must be filed within 3 years after the first symptom of the vaccine injury. 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 can 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 may be eligible to file a claim. Additional information is available at http://www.hrsa.gov/vaccinecompensation or by calling 1-800-338-2382.

Additional Information Regarding Prevention of Influenza in Specific Populations

- CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices, 2011. MMWR 2011;60(No. RR-2).
- CDC. Immunization of health-care personnel: recommendations of the Advisory Committee on Immunization Practices, 2011. MMWR 2011;60(No. RR-7).
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- CDC. ACIP birth18 years and "catch-up" immunization schedules, United States, 2013 (available at http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html).
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- AAP influenza prevention recommendations (available at http://www.aap.org).

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