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Prevention and Control of Seasonal Influenza with Vaccines Recommendations of the Advisory Committee on Immunization Practices — United States, 2016–17 Influenza Season

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CDC Adoption of ACIP Recommendations

Recommendations for routine use of vaccines in children, adolescents and adults are developed by the Advisory Committee on Immunization Practices (ACIP). ACIP is chartered as a federal advisory committee to provide expert external advice and guidance to the Director of 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 Obstetrics and Gynecology (ACOG). Recommendations for routine use of vaccines in adults are harmonized with recommendations of AAFP, ACOG, and the American College of Physicians (ACP). ACIP recommendations adopted by the CDC Director become agency guidelines on the date published in *MMWR*. Additional information regarding ACIP is available at http://www.cdc.gov/vaccines/acip).

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Prevention and Control of Seasonal Influenza with Vaccines Recommendations of the Advisory Committee on Immunization Practices — United States, 2016–17 Influenza Season

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Summary

This report updates the 2015–16 recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding the use of seasonal influenza vaccines (Grohskopf LA, Sokolow LZ, Olsen SJ, Bresee JS, Broder KR, Karron RA. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices, United States, 2015–16 influenza season. MMWR Morb Mortal Wkly Rep 2015;64:818–25). Routine annual influenza vaccination is recommended for all persons aged ≥6 months who do not have contraindications. For the 2016–17 influenza season, inactivated influenza vaccines (IIVs) will be available in both trivalent (IIV3) and quadrivalent (IIV4) formulations. Recombinant influenza vaccine (RIV) will be available in a trivalent formulation (RIV3). In light of concerns regarding low effectiveness against influenza A(H1N1)pdm09 in the United States during the 2013–14 and 2015–16 seasons, for the 2016–17 season, ACIP makes the interim recommendation that live attenuated influenza vaccine (LAIV4) should not be used. Vaccine virus strains included in the 2016–17 U.S. trivalent influenza vaccines will be an A/California/7/2009 (H1N1)–like virus, an A/Hong Kong/4801/2014 (H3N2)–like virus, and a B/Brisbane/60/2008–like virus (Victoria lineage). Quadrivalent vaccines will include an additional influenza B virus strain, a B/Phuket/3073/2013–like virus (Yamagata lineage).

Recommendations for use of different vaccine types and specific populations are discussed. A licensed, age-appropriate vaccine should be used. No preferential recommendation is made for one influenza vaccine product over another for persons for whom more than one licensed, recommended product is otherwise appropriate. This information is intended for vaccination providers, immunization program personnel, and public health personnel. Information in this report reflects discussions during public meetings of ACIP held on October 21, 2015; February 24, 2016; and June 22, 2016. These recommendations apply to all licensed influenza vaccines used within Food and Drug Administration–licensed indications, including those licensed after the publication of this report. Updates and other information are available at CDC's influenza website (http://www.cdc.gov/flu). Vaccination and health care providers should check CDC's 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 older adults, very young children, pregnant women, and those with chronic medical conditions (*1*–*3*). During 31 seasons from the 1976–77 through the 2006–07 season, estimated influenza-associated deaths ranged from approximately 3,300 to 49,000 annually (*4*). Annual influenza vaccination is the primary means of preventing influenza and its complications. A variety of different types of influenza vaccine are available. Abbreviation conventions for the different types of vaccine have evolved over time (Box). Routine annual influenza vaccination for all persons aged ≥6 months who do not have contraindications has been recommended by CDC and CDC's

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BOX. Abbreviation conventions for influenza vaccines used in this report

- Inactivated influenza vaccines are abbreviated IIV. For the 2016–17 season, IIVs as a class will include:
  - Egg-based, unadjuvanted, and adjuvanted trivalent influenza vaccines (IIV3s); and
  - Egg-based or cell culture-based unadjuvanted quadrivalent influenza vaccines (IIV4s).
- RIV refers to recombinant hemagglutinin influenza vaccine, available as a trivalent formulation (RIV3) for the 2016–17 season.
- LAIV refers to live-attenuated influenza vaccine, available as a quadrivalent formulation (LAIV4) since the 2013–14 season.
- IIV, RIV, and LAIV denote vaccine categories; numeric suffix specifies the number of HA antigens in the vaccine.
- When necessary to refer specifically to cell culture-based vaccine, the prefix "cc" is used (e.g., "ccIIV4").
- When necessary to refer specifically to adjuvanted vaccine, the prefix "a" is used (e.g., "aIIV3").

Advisory Committee on Immunization Practices (ACIP) since 2010 (*5*). This report updates the 2015–16 ACIP recommendations regarding the use of seasonal influenza vaccines (*6*) and provides recommendations and guidance for vaccination providers regarding the use of influenza vaccines for the 2016–17 season.

Methods

ACIP provides annual recommendations for the prevention and control of influenza. The ACIP Influenza Work Group meets by teleconference once to twice per month 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 unchanged recommendations, literature published since release of the last ACIP influenza Recommendations and Reports in *MMWR* (September, 2013) (*7*) was reviewed. Updates to the recommendations described in in this document are of three types: 1) the vaccine viruses included in the 2016–17 seasonal influenza vaccines, 2) new vaccine licensures and approvals, and 3) an interim recommendation that live attenuated influenza vaccine (LAIV4) not be used during the 2016–17 season.

Recommendations for vaccine viruses to be included in Northern Hemisphere influenza vaccines are made by the World Health Organization (WHO), which organizes a consultation, generally in February of each year, to make recommendations for vaccine composition. Surveillance data are reviewed and candidate vaccine viruses are discussed. A summary of the WHO meeting for selection of the 2016–17 Northern Hemisphere vaccine viruses is available at http://www.who.int/influenza/vaccines/virus/recommendations/201602_recommendation.pdf?ua=1. Subsequently, the Food and Drug Administration (FDA), which has regulatory authority over vaccines in the United States, convenes a meeting of its Vaccines and Related Biologic Products Advisory Committee (VRBPAC), which considers the recommendations of WHO, reviews and discusses similar data, and makes a final decision regarding vaccine virus composition for influenza vaccines licensed and marketed in the United States. A summary of the FDA VRBPAC meeting of March 4, 2016, at which composition of the 2016–17 U.S. influenza vaccines was discussed, is available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM494071.pdf.

With regard to recommendations for newly licensed influenza vaccines and changes to the licensed indications for existing vaccines, ACIP relies on FDA, which has regulatory authority for review of safety, immunogenicity, and effectiveness data and licensure of influenza vaccines. Regulatory information pertinent to the two recently licensed products discussed in this report may be found at http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm473989.htm (for Fluad; Seqirus, Holly Springs, North Carolina) and at http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm502844.htm (for Flucelvax; Seqirus, Holly Springs, North Carolina).

For interim changes in the recommendation for use of LAIV4, in June 2016, ACIP reviewed newly available data concerning the effectiveness of LAIV4 for the 2015–16 season. The information reviewed comes from three unpublished observational studies. Presentations of preliminary data reviewed by the ACIP may be found at http://www.cdc.gov/vaccines/acip/meetings/meetings-info.html. Minutes of the June ACIP meeting may be found at http://www.cdc.gov/vaccines/acip/meetings/minutes-archive.html. ACIP will review subsequent data as they become available.

Information presented in this report reflects recommendations presented during ACIP public meetings and approved on October 21, 2015; February 24, 2016; and June 22, 2016. Meeting minutes and information on ACIP membership and

*A list of the members may be found on page 52 of this report.

conflicts of interest are available on the ACIP website (http://www.cdc.gov/vaccines/acip). Modifications were made to the ACIP recommendations 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 without contraindications continues to be recommended. No preferential recommendation is made for one influenza vaccine product over another for persons for whom more than one licensed, recommended product is otherwise appropriate. Updated information and guidance in this document includes the following:

- In light of low effectiveness against influenza A(H1N1)pdm09 in the United States during the 2013–14 and 2015–16 seasons, for the 2016–17 season, ACIP makes the interim recommendation that LAIV4 should not be used. Because LAIV4 is still a licensed vaccine that might be available and that some providers might elect to use, for informational purposes, reference is made to previous recommendations for its use.
- 2016–17 U.S. trivalent influenza vaccines will contain an A/California/7/2009 (H1N1)–like virus, an A/Hong Kong/4801/2014 (H3N2)–like virus and a B/Brisbane/60/2008–like virus (Victoria lineage). Quadrivalent vaccines will include an additional vaccine virus strain, a B/Phuket/3073/2013–like virus (Yamagata lineage).
- Recent new vaccine licensures are discussed:
  - An MF59-adjuvanted trivalent inactivated influenza vaccine (aIIV3), Fluad (Seqirus, Holly Springs, North Carolina), was licensed by FDA in November 2015 for persons aged ≥65 years. Regulatory information is available at http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm473989.htm. aIIV3 is an acceptable alternative to other vaccines licensed for persons in this age group. ACIP and CDC do not express a preference for any particular vaccine product.
  - A quadrivalent formulation of Flucelvax (cell culture-based inactivated influenza vaccine [ccIIV4], Seqirus, Holly Springs, North Carolina) was licensed by FDA in May 2016, for persons aged ≥4 years. Regulatory information is available at: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm502844.htm. ccIIV4 is an acceptable alternative to other vaccines licensed for persons in this age group. No preference is expressed for any particular vaccine product.
- Recommendations for influenza vaccination of persons with egg allergy have been modified, including
  - Removal of the recommendation that egg-allergic recipients should be observed for 30 minutes postvaccination for signs and symptoms of an allergic reaction. Providers should consider observing all patients for 15 minutes after vaccination to decrease the risk for injury should they experience syncope, per the ACIP General Recommendations on Immunization (*8*).
  - A recommendation that persons with a history of severe allergic reaction to egg (i.e., any symptom other than hives) should be vaccinated in an inpatient or outpatient medical setting (including but not necessarily limited to hospitals, clinics, health departments, and physician offices), under the supervision of a health care provider who is able to recognize and manage severe allergic conditions.

Background and Epidemiology

Biology of Influenza

Influenza A and B are the two types of influenza viruses that cause epidemic human disease. Influenza A and B viruses are further separated into subtypes (for A viruses) and lineages (for B viruses) on the basis of antigenic differences. Influenza A viruses are categorized into subtypes on the basis of characterization of two surface antigens: hemagglutinin (HA) and neuraminidase (NA). Influenza A(H1N1) viruses, influenza A(H3N2) viruses, and influenza B viruses co-circulate globally. New influenza virus variants emerge as a result of point mutations and recombination events that occur during viral replication, resulting in frequent antigenic change (i.e., antigenic drift) (*9*). Immunity to surface antigens, HA and NA, reduces likelihood of infection (*10*,*11*). Antibody against one influenza virus type or subtype confers limited or no protection against another type or subtype (*12*). 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. 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 might be transmitted efficiently from human to human in a sustained manner and because there is little or no pre-existing immunity among humans (*9*). In April 2009, human infections with a novel

influenza A(H1N1) virus caused a worldwide pandemic. This virus was antigenically distinct from human influenza A(H1N1) viruses in circulation from 1977 through spring 2009. The HA gene is related most closely 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 and is thought to have entered human and swine populations at about the same time (*13*,*14*).

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 (*15*). Influenza B viruses from both lineages have co-circulated in most influenza seasons since the 1980s (*16*,*17*). 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 in the United States was represented in the trivalent vaccine in only five seasons (*18*). During the 11 seasons from 2004–05 through 2015–16 (the 2009 pandemic period was excluded because there was minimal influenza B activity), the more prevalent circulating B lineage was represented in the vaccine in eight seasons (CDC, unpublished data, 2016).

Burden of Influenza Illness

Although precise timing of the onset, peak, and end of influenza activity varies from one season to the next, annual epidemics of seasonal influenza typically occur in the United States between October and April. 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) (*19*–*21*). 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 (ILI) surveillance systems valuable in understanding the seasonal and geographic occurrence of influenza each year (*22*).

Persons of all age groups are susceptible to influenza. Data from the Influenza Incidence Surveillance Project (IISP) covering the 2009–10 through 2012–13 seasons revealed the highest rates of outpatient visits for influenza-positive ILI occurred among children aged 2 through 17 years (*23*). 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*–*4*,*24*–*29*).

In typical winter influenza seasons, increases in deaths and hospitalizations are observed during periods when influenza viruses are circulating. 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 (P&I) likely underestimate the burden of severe illnesses that are at least partly attributable to influenza because this category excludes deaths and hospitalizations caused by exacerbations of underlying cardiac and pulmonary conditions that are associated with influenza infection (*30*–*32*). Thus, some authors use the broader category of respiratory and circulatory excess events for influenza burden estimates. During seasonal influenza epidemics from 1979–1980 through 2000–2001, the estimated annual overall number of influenza-associated hospitalizations in the United States ranged from approximately 55,000 to 431,000 per annual epidemic, with a mean of 226,000 (*31*). Between the 1976–77 and the 2006–07 seasons, estimated annual deaths in the United States attributable to influenza ranged from 3,349 to 48,614 each season (*4*). A subsequent modeling analysis of population-based surveillance data for seasons following the 2009 pandemic (2010–2011 through 2012–2013), which used a multiplier method developed to correct for underdetection in hospitalizations attributable to cases for which influenza testing was not performed and for insufficient test sensitivity, estimated that influenza was associated with 114,018–633,001 hospitalizations, 18,476–96,667 intensive care unit (ICU) admissions, and 4,866–27,810 deaths per year. Among these, an estimated 54%–70% of hospitalizations and 71%–85% of deaths occurred among adults aged ≥65 years (*33*).

Children

Influenza is an important cause of outpatient medical visits and hospitalizations among young children. In a population-based study conducted in three metropolitan areas (Nashville, Tennessee; Rochester, New York; and Cincinnati, Ohio) during the 2002–03 and 2003–04 seasons, children aged <5 years with acute respiratory illness or fever caused by laboratory-confirmed influenza (LCI) accounted for 10% (2002–03) and 19% (2003–04) of medical office visits and 6% (2002–03) and 29% (2003–04) of emergency department (ED) visits (*3*) From these data, the rate of clinic visits for influenza was estimated to be 50 (2002–03) and 95 (2003–04) visits per 1,000 children aged <5 years, and the rate of ED visits was 6 (2002–03) and 27 (2003–04) visits per 1,000 children aged

<5 years. In a retrospective cohort study of children aged <15 years over 19 seasons (1974–75 through 1992–93), an estimated average of 6–15 additional outpatient visits and 3–9 additional antibiotic courses per 100 children per season were attributed to influenza (*25*). 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–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 5–7 years (*34*). In a study conducted in a single county in Tennessee during the 2000–01 through 2010–11 seasons, estimated rates of influenza-related hospitalizations among children aged 6 through 59 months varied from 1.9 to 16 per 10,000 children per year; estimated rates of ED visits ranged from 89 to 620 per 10,000 children per year (*35*).

Estimated rates of influenza-associated hospitalization generally are substantially higher among infants and children aged <5 years than among older children (*36–42*). During 1993–2008, estimated annual rates of influenza-associated hospitalizations were 151.0 per 100,000 among children aged <1 years and 38.8 per 100,000 among children aged 1–4 years, compared with 16.8 per 100,000 among persons aged 5 through 49 years (*40*). Estimates of influenza-related hospitalization rates for children with high-risk medical conditions are higher than for those without such conditions (*26*,*43*,*44*).

In the United States, death associated with LCI among children aged <18 years has been a nationally reportable condition since October 2004 (*45*). Since reporting began, the annual number of influenza-associated pediatric deaths during regular influenza seasons has ranged from 37 to 171 deaths per season. A larger number of deaths were reported during the 2009 pandemic, for which 358 pediatric deaths were reported to CDC from April 15, 2009 through October 2, 2010 (*46*).

Younger Adults

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. In one economic modeling analysis that used health insurance claims data and projections of either earnings or statistical life values, the average annual burden of seasonal influenza among adults aged 18–49 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 (*47*). Studies of worker vaccination have reported lower rates of ILI (*48*,*49*), lost work time (*48–51*), and health care visits (*49*,*50*) in association with vaccination as compared with no vaccine or placebo.

During the 2009 influenza A(H1N1)pdm09 pandemic (2009[H1N1] pandemic), adults aged <65 years appeared to be at higher risk for influenza-related hospitalizations and deaths (*52*) as compared with typical influenza seasons. During the 2009 influenza A (H1N1) pandemic period (for the period April 2009 through May 1, 2010), the cumulative rates of LCI-related hospitalization for the Emerging Infections Program (EIP; http://www.cdc.gov/ncezid/dpei/eip/index.html) sites were 3.0 per 10,000 persons aged 18–49 years, 3.8 per 10,000 persons aged 50–64 years, and 3.2 per 10,000 persons aged ≥65 years. During the previous three seasons, rates had ranged from 0.3–0.7 per 10.000 persons aged 18–49 years to 0.4–1.5 per 10.000 persons aged 50–64 years and 1.4–7.5 per 10.000 persons aged ≥65 years (*53*). Adults aged 50–64 years had the highest mortality rate during the 2009 pandemic. This group was again severely affected during the 2013–14 season when H1N1pdm09 was the predominant virus, sustaining higher hospitalization rates than in previous seasons since the pandemic (*54*).

Older Adults

Hospitalization rates during typical influenza seasons are highest for adults aged ≥65 years. One retrospective analysis of data from three managed-care organizations collected during 1996–1997 through 1999–2000 estimated that the risk during influenza season among persons aged ≥65 years with high-risk underlying medical conditions was 55.6 pneumonia and influenza-associated hospitalizations per 10,000 persons, compared with 18.7 per 10,000 among lower risk persons in this age group. Persons aged 50–64 years who had underlying medical conditions also were at substantially increased risk for hospitalization during influenza season compared with healthy adults aged 50–64 years (12.3 versus 1.8 per 10,000 person-periods) (*28*).

Deaths associated with influenza are most frequent among older adults. From the 1976–2007 seasons, an estimated yearly average of 21,098 influenza-related deaths occurred among adults aged ≥65 years, corresponding to 90% of estimated annual average deaths across all age groups (*4*). In comparison, the average annual mortality was estimated to be 124 deaths among persons aged <19 years and 2,385 deaths among persons aged 19–64 years. In a later modeling analysis of population-based surveillance data covering the 2010–11 through the 2012–13 seasons, an estimated 71%–85% of deaths occurred among adults aged ≥65 years (*33*).

Pregnant Women and Neonates

Pregnant women are vulnerable to severe symptoms and illness attributable to influenza. Physiologic changes associated with pregnancy, such as altered respiratory mechanics and changes in cell mediated immunity, might contribute to enhanced susceptibility (*55*). In a case-cohort study of 1,873 pregnant women conducted over the 2010–11 and 2011–12 seasons, among 292 women with acute respiratory illnesses, those with influenza reported greater symptom severity than those with noninfluenza acute respiratory illness (*56*). Case reports and some observational studies suggest that pregnancy increases the risk for hospitalization and serious maternal medical complications (*57–59*). Most of these studies have measured changes in excess hospitalizations or outpatient visits for respiratory illness during influenza season rather than LCI. A retrospective cohort study of pregnant women conducted in Nova Scotia during 1990–2002 compared medical record data for 134,188 pregnant women to data from the same women during the year before pregnancy. During the influenza seasons, the rate ratio of hospital admissions during the third trimester compared with admissions in the year before pregnancy was 7.9 (95% confidence interval [CI] = 5.0–12.5) among women with comorbidities and 5.1 (95% CI = 3.6–7.3) among those without comorbidities (*59*).

Increased severity of influenza among pregnant women was reported during the pandemics of 1918–1919, 1957–1958, and 2009–2010 (*60–65*). Severe infections among postpartum (delivered within previous 2 weeks) women also were observed in the 2009(H1N1) pandemic (*60*,*64*). 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 >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% CI = 3.5–10.6) than those treated within 2 days after symptom onset (*66*).

Some studies of pregnancy outcomes have suggested increased risk for pregnancy complications attributable to maternal influenza illness; others have not. A review of data from the National Inpatient Sample (a publicly available hospital discharge database; http://www.hcup-us.ahrq.gov/nisoverview.jsp) covering the 1998–99 through the 2001–02 seasons and including over 6.2 million hospitalizations of pregnant women, reported increased risk for fetal distress, preterm labor, and cesarean delivery among those women with respiratory illness during influenza seasons, compared with women without respiratory illness (*67*). A study of 117,347 pregnancies in Norway during the 2009–10 pandemic noted an increased risk for fetal death among pregnant women with a clinical diagnosis of influenza (adjusted hazard ratio [aHR]: 1.91; 95% CI = 1.07–3.41) (*68*). A cohort study conducted among 221 hospitals in the United Kingdom observed an increased risk for perinatal death, stillbirth, and preterm birth among women admitted with confirmed 2009(H1N1) infection (*69*). However, other studies of infants born to women with LCI during pregnancy have not shown higher rates of prematurity, preterm labor, low birth weight, congenital abnormalities, or lower Apgar scores compared with infants born to uninfected women (*70–72*). A cohort study of 58,640 pregnant women enrolled in the Tennessee Medicare Program during the 1985–86 through the 1992–93 seasons noted that pregnant women with respiratory hospitalizations during the influenza season had similar odds of preterm labor, prematurity, and low birth weight compared with pregnant women in a control group without an influenza hospitalization; modes of delivery and length of stay were also similar between the two groups (*72*).

Notably, influenza symptoms often include fever, which during pregnancy might be associated with neural tube defects and other adverse outcomes (*73*). A meta-analysis of 22 observational studies of congenital anomalies following influenza exposure during the first trimester of pregnancy noted associations with several types of congenital anomalies, including neural tube defects, hydrocephaly, heart and aortic valve defects, digestive system defects, cleft lip, and limb reduction defects. However, many of the included studies were conducted during the 1950s through 1970s, and a nonspecific definition of influenza exposure was used (any reported influenza, ILI, or fever with influenza, with or without serological or clinical confirmation) (*74*). Additional studies are needed to further elucidate the association between influenza and congenital anomalies and other birth outcomes.

Persons with Increased Risk for Severe Influenza Illness and Complications

In the first U.S. recommendations for annual influenza vaccination, published by the Surgeon General in 1960, persons with "chronic debilitating diseases" (particularly cardiovascular disease, pulmonary disease, and diabetes) were cited as being among the groups contributing most to the excess deaths observed during the 1957 influenza pandemic (*75*). Persons with certain chronic medical conditions, in particular (but not limited to) chronic cardiovascular and pulmonary disease, have been observed to be at increased risk for severe influenza illness. In a study of 4,756 adults hospitalized with influenza from October 2005 through April 2008, characteristics significantly associated with pneumonia included underlying chronic lung

disease, asthma, and immunosuppression (*76*). Among patients with pneumonia, patients with a poor outcome (defined as ICU admission, need for mechanical ventilation, or death) were more likely to be affected by chronic lung disease, cardiovascular disease, renal disease, or immunosuppression. Observational studies have noted increased likelihood of hospitalization (*77–79*) and death (*79*,*80*) among persons with HIV infection.

Prior to the 2009 pandemic, obesity had not been recognized as a risk factor for severe influenza illness. However, several studies during the 2009 pandemic noted a high prevalence of obesity among persons with severe illness attributable to A(H1N1)pdm09 (*81–83*). In a case-cohort study, among persons aged ≥20 years, hospitalization with illness attributable to influenza A(H1N1)pdm09 was associated with extreme obesity (body mass index [BMI] ≥40) even in the absence of other risk factors for severe illness (odds ratio [OR]: 4.7; 95% CI = 1.3–17.2) (*84*). Death was associated with both obesity, defined as BMI ≥30 (OR: 3.1; 95% CI = 1.5–6.6) and extreme obesity (OR: 7.6; 95% CI = 2.1–27.9). A Canadian cohort study covering 12 seasons (1996–97 through 2007–08) found that persons with a BMI of 30.0–34.9 and those with a BMI ≥35 were more likely than normal-weight persons to have a respiratory hospitalization during influenza seasons (OR: 1.45; 95% CI = 1.03–2.05 for BMI 30–34.9 and OR: 2.12; 95% CI = 1.45–3.10 for BMI ≥35) (*85*). Conversely, a two-season study (2007–09) in the United States found no association between obesity and medically attended LCI, including both seasonal and pandemic virus circulation (*86*).

The 2009 pandemic also emphasized racial and ethnic disparities in the risk for influenza-related complications among adults, including higher rates of severe influenza illness among blacks and among American Indians/Alaska Natives and indigenous populations in other countries (*87–92*). These disparities might be attributable in part to the higher prevalence of underlying medical conditions or disparities in medical care among these racial/ethnic groups (*92*,*93*). A more recent case-control study of risk factors for death from 2009 pandemic influenza that adjusted for factors such as pre-existing medical conditions, barriers to health care access, and delayed receipt of antivirals found that American Indian/Alaska Native status was not independently associated with death (*94*).

Influenza Vaccine Immunogenicity and Effectiveness

Estimates of vaccine 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, diagnostic testing measures, and the outcome being measured. Studies of influenza vaccine efficacy and effectiveness have used a variety of outcome measures, including the prevention of ILI, medically attended acute respiratory illness (MAARI), LCI, P&I-associated hospitalizations or deaths, and prevention of seroconversion to circulating influenza virus strains. Efficacy or effectiveness for more specific outcomes such as LCI typically are 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 (*95*).

Observational studies, particularly those that compare less-specific outcomes among vaccinated populations to those among unvaccinated populations, are more subject to biases than studies using laboratory-confirmed 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 (*96*,*97*). Observational studies that use a case-positive, control test-negative study design (in which all participants present with illness, and case/control status is assigned on the basis of influenza testing) might be less subject to frailty bias (*98*).

For studies assessing laboratory-confirmed outcomes, estimates of vaccine efficacy and effectiveness also might be affected by the specificity 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% (*99*). Randomized controlled trials that measure LCI virus infections (by viral culture or reverse transcription polymerase chain reaction [RT-PCR]) as the outcome are the most persuasive evidence of vaccine efficacy, but such data are not available for all populations.

A study of data from the National Inpatient Sample (a large database of hospital discharge data comprising approximately 8 million records annually from approximately 1,000 hospitals, representing 46 states as of 2011) noted a decrease in the number of hospitalizations associated with P&I of 295,000 (95% CI = 139,000–451,000) and a decrease of 13,600 P&I-associated inpatient deaths (95% CI = 2,700–24,400) for October 2008 through December 2011, compared with what would have been expected on the basis of previous rates (*100*). This time period correlates with that of expansion of the target groups for annual influenza vaccination to include all persons aged ≥6 months. However, it is not possible to definitively attribute these decreases directly to increased vaccination.

Immune Response Following Vaccination

Humoral and cell-mediated responses to influenza vaccination among children and adults have been studied. Serum antibodies (*10*,*101*) are considered to be correlates of vaccine-induced protection for inactivated influenza vaccines (IIVs). 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 (*11*,*102*–*104*). Most healthy children and adults have high titers of strain-specific antibody after IIV vaccination (*103*,*105*). However, although immune correlates such as achievement of certain antibody titers after vaccination correlate well with immunity on a population level, reaching a 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.

Compared with IIV, LAIV induces lower levels of serum antibodies but induces cellular immune responses more effectively. The magnitude of this effect differs among adults and children. One study of children aged 6 months–9 years and adults aged 22–49 years noted a significant increase in influenza A-specific interferon γ-producing CD4+ and CD8+ T-cells among children following receipt of LAIV but not following receipt of IIV. No significant increase in these parameters was noted among adults following receipt of either vaccine (*106*).

Immune responses elicited by influenza vaccines are generally strain-specific. Antibody against one influenza virus type or subtype generally confers limited or no protection against another type or subtype, nor does it typically confer protection against antigenic variants of the same virus that arise by antigenic drift. However, among adults, vaccination can cause a "back boost" of antibody titers against influenza A(H3N2) viruses that have been encountered previously either by vaccination or natural infection (*107*).

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 participants with historic exposures to both natural infections and vaccination (*108*). This could result in the decreased likelihood that antibody increases can be observed in vaccinated participants after influenza infection with circulating viruses, as compared with adult participants in control arms of trials. Thus, vaccinated participants might be less likely to show a fourfold increase in antibody levels after influenza infection with circulating viruses compared with unvaccinated participants 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.

Influenza Vaccine Effectiveness and Match Between Vaccine and Circulating Viruses

The viral composition of influenza vaccines must be determined months in advance of the start of each season, to allow enough time for manufacture and distribution of vaccine. Selection of viruses is based on consideration of global influenza surveillance data, from which decisions are made regarding the viruses most likely to circulate during the upcoming season. During some seasons, because of antigenic drift among influenza A viruses or change in predominant lineage among B viruses, circulating viruses might differ from those included in the vaccine. Seasonal influenza vaccine effectiveness can be influenced by mismatches to circulating influenza viruses. Good match between vaccine and circulating viruses was associated with increased protection against MAARI-related ED visits and hospitalizations among older persons (*109*), ILI in younger working adults (*49*), and LCI (*110*) in observational studies. Results from other investigations suggest that influenza vaccine can still provide some protection against influenza and outcomes such as influenza-associated hospitalizations, even in seasons when match is suboptimal (*111*,*112*). In addition to antigenic drift of circulating influenza viruses, vaccine viruses might undergo adaptive mutations during propagation in eggs that also can contribute to an antigenic differences between vaccine virus and circulating viruses, which in some cases, has been suggested to contribute to reducing vaccine effectiveness (*113*).

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 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, three 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 (*114*). Serum HAI influenza antibodies elicited by vaccination remained detectable in children vaccinated with LAIV for >1 year after vaccination (*115*). 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 LAIV3 during the previous season (*116*). A review of four

trials (three randomized blinded and one open-label) of LAIV3 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 (*117*).

Several more recent observational studies have attempted to evaluate changes in influenza vaccine effectiveness over the course of a single influenza season. Some of these studies have noted a decrease in vaccine effectiveness, particularly against influenza A(H3N2) viruses, most markedly among older adults (*118–121*). However, this effect has not been observed consistently across age groups and seasons, and might be partially attributable to factors such as increased circulation of antigenically drifted variants over the course of the influenza season. These issues are discussed in more detail below (see Timing of Vaccination).

Immunogenicity, Efficacy, and Effectiveness of IIV

IIVs are administered by intramuscular or intradermal injection and contain nonreplicating virus. Immunogenicity, effectiveness, and efficacy have been evaluated in children and adults, although fewer data from randomized studies are available for certain age groups (e.g., persons aged ≥65 years). Since the introduction of quadrivalent IIV in the United States during the 2013–14 season, both trivalent (IIV3) and quadrivalent (IIV4) IIVs have been available. Both IIV3s and IIV4s contain an A(H1N1) virus, an A(H3N2) virus, and a B virus. IIV4s contain the viruses selected for IIV3s, and in addition contain a fourth virus, which is a B virus selected from the opposite lineage of that selected for IIV3s. Data directly comparing effectiveness of IIV3 versus IIV4 are not available. However, the U.S. Influenza Vaccine Effectiveness Network found that IIV3 provided statistically significant protection against both the included B lineage (66%; 95% CI = 58–73) and the nonincluded B lineage (51%; 95% CI = 36–63) during the 2012–13 season when both lineages co-circulated (*122*). In general, prelicensure studies of immunogenicity of the currently licensed IIV4s compared with corresponding IIV3 products (e.g., Fluzone Quadrivalent versus Fluzone, Fluarix Quadrivalent versus Fluarix, and Flulaval Quadrivalent versus Flulaval) demonstrated superior immunogenicity for IIV4 for the added influenza B virus without interfering with immune responses to the remaining three vaccine viruses (*123–130*).

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 IIV (*101*,*105*,*131–134*). Immunogenicity studies using the A(H1N1)pdm09 monovalent vaccine indicated that 80%–95% of vaccinated children developed protective antibody levels to the 2009 A(H1N1) influenza virus after 2 doses (*135*,*136*); response after 1 dose was 50% for children aged 6–35 months and 75% for those aged 3–9 years (*137*).

Studies involving seasonal IIV 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 during the 2004–05 season of children aged 5–8 years who received IIV3 for the first time, the proportion of children with protective antibody responses was significantly higher after 2 doses than after 1 dose of IIV3 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) (*138*). 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. A retrospective study of billing and registry data among children aged 6–21 months conducted during the 2003–04 season found that although receipt of 2 doses of IIV3 was protective against office visits for ILI, receipt of 1 dose was not (*139*). Another retrospective cohort study of children aged 6 months through 8 years, the majority of whom received IIV3 (0.8% received LAIV3), also conducted during the 2003–04 season, found no effectiveness against ILI among children who had received only 1 dose (*140*). In a case-control study of approximately 2,500 children aged 6–59 months conducted during the 2003–04 and 2004–05 seasons, being fully vaccinated (having received the recommended number of doses) was associated with 57% effectiveness (95% CI = 28–74) against LCI for the 2004–05 season; a single dose was not significantly effective (too few children in the study population were fully vaccinated during the 2003–04 season to draw conclusions) (*141*). The results of these studies support the recommendation that all children aged 6 months–8 years who are being vaccinated for the first time should receive 2 doses separated by at least 4 weeks (see Children Aged 6 Months Through 8 Years).

Estimates of the efficacy of IIV among children aged ≥6 months vary by season and study design. Limited efficacy data are available for children from studies that used culture- or RT-PCR–confirmed influenza virus infections as the primary outcome. A large randomized trial compared rates

of RT-PCR–confirmed influenza virus infections among 4,707 children aged 6–71 months who received IIV3, IIV3 with MF59 adjuvant (aIIV3; not currently licensed for children in the United States), or a control vaccine (meningococcal conjugate vaccine or tickborne encephalitis vaccine). During the two seasons of the study (2007–08 and 2008–09), efficacy of IIV3 versus control vaccine was 43% (95% CI = 15–61). Efficacy of aIIV3 versus control was 86% (95% CI = 74–93) (*142*). In a randomized trial conducted during five influenza seasons (1985–90) in the United States among children aged 1–15 years, receipt of IIV3 reduced culture-positive influenza by 77% (95% CI = 20–93) during A(H3N2) years and 91% (95% CI = 64–98) during A(H1N1) years (*103*). A single-season placebo-controlled study that enrolled 192 healthy children aged 3–19 years found the efficacy of IIV3 was 56% ($p<0.05$) among those aged 3–9 years and 100% among those aged 10–18 years (*143*); influenza infection was defined either by viral culture or by a postseason antibody rise in HI titer among symptomatic children from whom no other virus was isolated. In a randomized, double-blind, placebo-controlled trial conducted during two influenza seasons among 786 children aged 6–24 months, estimated efficacy was 66% (95% CI = 34–82) against culture-confirmed influenza illness during 1999–2000. However, vaccination did not reduce culture-confirmed influenza illness significantly during 2000–2001, when influenza attack rates were lower (3% versus 16% during 1999–2000 season) (*144*).

Receipt of IIV was associated with a reduction in acute otitis media in some studies but not in others. Two studies reported that IIV3 decreases the risk for otitis media among children (*145*,*146*). However, a randomized, placebo-controlled trial conducted among 786 children aged 6 through 24 months (mean age: 14 months) indicated that IIV3 did not reduce the proportion of children who developed acute otitis media during the study (*144*). 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 LCI.

Younger Adults

One dose of IIV tends to be immunogenic in healthy adults aged <65 years. A 2012 meta-analysis found a pooled IIV3 efficacy against RT-PCR or culture-confirmed influenza of 59% (95% CI = 51–67) among adults aged 18–65 years for eight of twelve seasons analyzed in 10 randomized controlled trials (*147*). 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 (*49*,*148*). In another study of healthy working adults conducted during the 2012–13 season, no significant difference in missed work hours between vaccinated and unvaccinated subjects was noted (*149*).

Older Adults

Older adults have long been recognized as a high-risk group for severe influenza illness, and have been recommended to receive annual influenza vaccination since the 1960s (*75*). Historically, most effectiveness data in this population pertain to standard-dose IIVs, which contain 15 μg of HA of each vaccine virus per dose. Discussion of the more recently licensed high-dose IIV3 occurs below.

Most studies suggest that antibody responses to influenza vaccination are decreased in older adults. It is likely that increasing dysregulation of the immune system with aging contributes to the increased likelihood of serious complications of influenza infection (*150*). A review of HAI antibody responses to IIV3 in 31 studies found that 42%, 51%, and 35% of older adults (aged ≥58 years) seroconverted to A(H1N1), A(H3N2), and B vaccine antigens, respectively, compared with 60%, 62%, and 58% of younger persons (aged <58 years) (*151*). When seroprotection (defined as an HAI titer ≥40) was the outcome, 69%, 74%, and 67% of older adults versus 83%, 84%, and 78% of younger adults achieved protective titers to A(H1N1), A(H3N2), and B antigens, respectively. Although an HAI titer ≥40 is considered to be associated with approximately 50% clinical protection from infection, this standard was established in young healthy adults (*11*), and few data suggest that such antibody titers represent a correlate of protection among elderly adults. An analysis of serologic data from a randomized controlled efficacy trial of high-dose IIV among the elderly found that an HAI titer of ≥40 corresponded to 50% protection (similar to the recognized threshold for younger adults) when the assay virus was well-matched to the circulating virus but higher titers were required with poor match (*152*). Limited or no increase in antibody response is reported among elderly adults when a second dose is administered during the same season (*153*–*155*).

Most data concerning vaccine effectiveness among community-dwelling older adults comes from observational studies. One randomized controlled trial conducted among community-dwelling persons aged ≥60 years found IIV3 to be 58% effective (95% CI = 26–77) against serologically confirmed influenza illness during the 1991–92 season, during which vaccine viruses were considered to be well-matched to circulating strains (*156*). The outcome used for measuring the efficacy estimate was seroconversion to a circulating influenza virus and symptomatic illness compatible with clinical influenza infection, rather than viral culture or PCR-confirmed influenza infection. Use

of such outcomes raises 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, leading to an overestimate of the true vaccine efficacy. This phenomenon was demonstrated in a clinical trial conducted among healthy adults aged 18 through 49 years (*108*).

Other evidence of effectiveness of influenza vaccines among older adults is derived from observational studies and from analyses of health care system data. A 2010 Cochrane review of influenza vaccine effectiveness studies among community-dwelling persons aged ≥65 years pooled data from 75 studies (randomized, quasi-randomized, cohort, and case-control studies) to assess efficacy against LCI or ILI (*157*). IIV3 was not significantly effective against LCI, ILI, or pneumonia. The quality of the pooled evidence was rated as generally low because of the paucity of randomized clinical trials. A different team of investigators subsequently performed a meta-analysis of these data, but using a different stratification method and examining a smaller number of clinically relevant outcomes. Using these methods, the authors estimated vaccine effectiveness for LCI of approximately 49% (95% CI = 33–62), and for ILI of 39% (95% CI = 35–43) (*158*). A more recent systematic review, published in 2014, included pooled data from 35 test-negative design case-control studies involving community-dwelling elderly. This review concluded that although influenza vaccine was not significantly effective during periods of localized influenza activity (defined as cases limited to one administrative unit of a country or reported from a single site), influenza vaccine was effective against LCI irrespective of vaccine match or mismatch to the circulating viruses during regional (OR: 0.42; 95% CI = 0.30–0.60 when matched; OR 0.57; 95% CI = 0.41–0.79 when not matched) and widespread outbreaks (OR: 0.54; 95% CI = 0.46–0.62 when matched; OR 0.72; 95% CI = 0.60–0.85 when not matched), although the effect was stronger when the vaccine matched (*159*). Vaccine was effective during sporadic activity, but only when vaccine matched (OR: 0.69; 95% CI = 0.48–0.99).

Influenza vaccination might reduce the frequency of secondary complications and risk for influenza-related hospitalization and death among community-dwelling adults aged ≥65 years with and without high-risk medical conditions (*160*–*164*). However, these studies have been conducted using medical record databases and did not use reductions in LCI illness as an outcome of interest. Such methods have been challenged because results might not be adjusted adequately to control for the possibility that healthier persons might be more likely to be vaccinated than less healthy persons (*96*,*97*,*165*–*168*). In a study of medical record data on influenza-associated hospitalizations associated with two A(H3N2) outbreaks in 1982–1983 and 1985–1986, vaccination was associated with a reduction in P&I hospitalizations among those aged ≥65 years (37% [95% CI = 15–53] in 1982–1983 and 39% [95% CI = 19–53] in 1985–1986) (*169*). A test-negative case-control study of community-dwelling adults aged ≥65 years noted that receipt of 2010–11 seasonal influenza vaccine was associated with a 42% reduction (95% CI = 29–53) in hospitalizations for LCI. When analyzed by type/subtype, the reduction was 40% (95% CI = 26–52) for influenza A(H3N2) and 90% (95% CI = 51–98) for influenza A(H1N1); no benefit was seen against influenza B (13%; 95% CI = -77–58) (*170*). A seven-season study (2002–03 through 2008–09) found that in every season, vaccinated elderly participants were significantly less likely to be hospitalized for P&I compared with unvaccinated persons (adjusted odds ratio [aOR] ranged from 0.67 to 0.86 over the seven seasons; $p<0.001$ to <0.030); no significant decrease was observed in the risk for outpatient visits (*171*). Several studies using methods to account for unmeasured confounding have reported that among community-dwelling older persons for nonspecific serious outcomes such as P&I hospitalizations or all-cause mortality is ~10% or less, which is more plausible than higher estimates from earlier studies (*172*–*174*).

Influenza infection is a common cause of morbidity and death among institutionalized older adults. Influenza vaccine effectiveness in preventing respiratory illness among elderly persons residing in nursing homes has been estimated at 20%–40% (*175*,*176*). A Cochrane review of 64 studies demonstrated that vaccination was more effective for persons living in institutional settings than for community-dwellers (*177*). However, documented outbreaks among well-vaccinated nursing-home populations suggest that vaccination might not have discernable effectiveness, particularly when circulating strains are drifted from vaccine strains (*178*,*179*).

The desire to improve immune response and vaccine effectiveness among adults aged ≥65 years has led to the development and licensure of vaccines intended to promote a better immune response in this population. Currently, both a high-dose IIV3 and an aIIV3 are licensed for this age group, in addition to standard-dose unadjuvanted IIV3 and IIV4. The only currently licensed high-dose IIV, Fluzone High-Dose (Sanofi Pasteur, Swiftwater, Pennsylvania), is licensed for persons aged ≥65 years and has been available since the 2010–11 influenza season. It is a trivalent formulation containing 60 μg of HA of each vaccine virus per dose, compared with 15 μg of each vaccine virus per dose in standard-dose IIVs. Licensure was based on superior immunogenicity compared with standard-dose IIV in this age group. Immunogenicity data from three studies of high-dose IIV3 among persons aged ≥65 years

indicated that vaccine with four times the HA antigen content of standard-dose vaccine elicited substantially higher HAI titers (*180*–*182*). Prespecified criteria for superiority in one clinical trial study was defined by a lower bound of the 95% CI for the ratio of geometric mean HI titers of >1.5, and a lower bound of the 95% CI for the difference in seroconversion rates (fourfold rise of HI titers) of >10%. These criteria were met for influenza A(H1N1) and influenza A(H3N2) virus antigens, but not for the influenza B virus antigen (for which criteria for noninferiority were met) (*181*,*183*). Subsequently, a large randomized comparative efficacy trial of high-dose versus standard-dose IIV3 conducted among over 31,000 persons aged ≥65 years over the 2011–12 and 2012–13 influenza seasons found 24.2% greater relative efficacy of the high-dose IIV3 for protection against LCI caused by any viral type or subtype associated with protocol-defined ILI (*184*).

A second vaccine licensed specifically for this age group, Fluad (Seqirus, Holly Springs, North Carolina), is an MF59-adjuvanted trivalent IIV (aIIV3). This new vaccine is anticipated to be available for the 2016–17 season. Further information is provided below (see Recently Licensed Influenza Vaccine Products).

Pregnant Women and Neonates

IIV induces protective levels of antibody in pregnant women (*185*). Passive transfer of anti-influenza antibodies from vaccinated women to neonates has been documented (*185*–*187*). In a randomized controlled trial conducted in Bangladesh, vaccination of pregnant women during the third trimester resulted in a 36% reduction in respiratory illness with fever among these women, as compared with women who received pneumococcal polysaccharide vaccine. In addition, influenza vaccination of mothers was 63% effective (95% CI = 5–85) in preventing LCI in their breastfed infants during the first 6 months of life (*188*). A randomized placebo-controlled trial of IIV3 among HIV-infected and uninfected women in South Africa reported efficacy against RT-PCR–confirmed influenza of 50.4% (95% CI = 14.5–71.2) among the HIV-uninfected mothers and 48.8% (95% CI = 11.6–70.4) among their infants (*189*). In a matched case-control study of infants admitted to a large urban hospital in the United States during 2000–2009, investigators found that maternal vaccination was associated with significantly lower likelihood of hospitalization for LCI among infants aged <6 months (91.5%; 95% CI = 61.7–98.1) (*190*). A prospective cohort study among Native Americans reported that infants aged <6 months of vaccinated mothers had a 41% reduction of the risk for LCI in the inpatient and outpatient settings (RR: 0.59; 95% CI = 0.37–0.93) and a 39% reduction in risk for ILI-associated hospitalization (RR: 0.61; 95% CI = 0.45–0.84) (*191*). In a study of 1,510 infants aged <6 months, those of vaccinated mothers were less likely to be hospitalized with LCI than those of nonvaccinated mothers (aOR: 0.55; 95% CI = 0.32–0.95) (*192*).

Persons with Chronic Medical Conditions

Because of the long-standing recommendation for annual influenza vaccination of persons with chronic medical conditions, there are relatively few published studies describing the efficacy of inactivated influenza vaccines among populations with specific high-risk conditions. In the pediatric literature, most published studies of this nature focus on asthma. In a nonrandomized controlled trial during the 1992–93 season involving 137 children who had moderate to severe asthma, vaccine efficacy against laboratory-confirmed influenza A(H3N2) infection was 54% among children aged 2 through 6 years and 78% among children aged ≥7 through 14 years; vaccine efficacy against laboratory-confirmed influenza B infection was 60% among children aged ≥7 through 14 years, but nonsignificant for the younger age group (*193*). In a two-season study of 349 asthmatic children, IIV3 vaccine was associated with a 55% reduction in the occurrence of ARI in children aged <6 years (95% CI = 20–75; p = 0.01), but no association was noted among children aged 6 through 12 years (*194*).

The association between vaccination and prevention of asthma exacerbations is unclear. A retrospective uncontrolled cohort study based on medical and vaccination records during three seasons (1993–94 through 1995–96) found that asthmatic children aged 1 through 6 years showed an association between receipt of IIV3 and reduced rates of exacerbations in two out of three seasons (*195*). In a study of 80 asthmatic children aged 3–18 years, current influenza vaccination status was associated with a significant reduction (OR: 0.29, 95% CI = 0.10–0.84) in oral steroid use in the 12 months before the survey (*196*). Other studies have failed to show any benefit against asthma exacerbation (*197*,*198*).

A small study evaluated immune response to IIV3 among asthmatic children who were receiving prednisone for asthma exacerbation symptoms. Among 109 children aged 6 months through 18 years, 59 of whom had no asthma symptoms and 50 of whom were symptomatic and required prednisone, no difference was noted in antibody response to A(H1N1) and A(H3N2) following receipt of IIV3. Response to the B component of the vaccine was significantly better in the prednisone group (*199*).

There is some evidence to suggest that vaccine effectiveness among adults aged <65 years with chronic medical conditions 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 LCI (tests used were not specified) illness among adults aged 50–64 years with high-risk conditions was 48% (95% CI = 21–66) compared with 60% (95% CI = 43–72) for healthy adults. For influenza-related hospitalizations, effectiveness varied more substantially by risk status: among those with high-risk conditions, vaccine effectiveness was 36% (95% CI = 0–63) whereas it was 90% (95% CI = 68–97) among healthy adults (*200*).

Some observational studies have found large reductions in hospitalizations or deaths for adults with chronic medical conditions. For example, in a case-control study conducted during 1999–2000 in the Netherlands among 24,928 persons aged 18 through 64 years with underlying medical conditions, vaccination was reported to reduce deaths attributable to any cause by 78% and reduce hospitalizations attributable to acute respiratory or cardiovascular diseases by 87%. (*201*). 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 (*202*). Effects of this magnitude on nonspecific outcomes are likely to have been caused by confounding from unmeasured factors (e.g., dementia and difficulties with self-care) that are associated strongly with the measured outcomes (*96,97*).

A randomized controlled trial conducted among 125 adults 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 (*203*). A systematic review of studies of influenza vaccine among COPD patients identified evidence of reduced risk for exacerbation from vaccination (*204*). Eleven trials were included but only six of these were specifically performed in COPD patients. The others were conducted on elderly and high-risk persons, some of whom had chronic lung disease. However, a systematic review that focused on studies of adults and children with asthma concluded that evidence was insufficient to demonstrate benefit of vaccination in this population (*205*).

Evidence suggests that acute respiratory infections might trigger atherosclerosis-related acute vascular events (*206*). Some studies have attempted to evaluate the impact of vaccination on such events. Several randomized controlled trials have suggested protective efficacy of influenza vaccination against vascular events. The FLUVACS study randomized participants with known coronary artery disease to IIV3 or placebo and followed up at 6 months, 1 year and 2 years. Vaccination was associated with lower cardiovascular mortality (RR: 0.25; 95% CI = 0.07-0.86 at 6 months and RR: 0.34; 95% CI = 0.17–0.71 at 1 year) and lower risk for a composite endpoint including cardiovascular death, nonfatal myocardial infarction, or severe ischemia (RR: 0.50; 95% CI = 0.29-0.85 at 6 months and 0.59; 95% CI = 0.40–0.86 at 1 year) compared with controls (*207*,*208*). In the FLUCAD study, a randomized trial of 658 participants with coronary artery disease, rates of coronary ischemic events at 12 months were significantly lower in the vaccinated group (hazard ratio [HR]: 0.54; 95% CI = 0.29–0.99) (*209*). Another composite endpoint, major CV events (including cardiovascular death, myocardial infarction, or coronary revascularization) was not significantly different between vaccinated and placebo groups. In a trial of 439 participants with acute coronary syndrome, influenza vaccination resulted in a significant reduction of major coronary adverse events (adjusted HR [aHR]: 0.67; 95% CI = 0.51–0.86), but not cardiovascular death (0.62; 95% CI = 0.34–1.12) (*210*). A pooled analysis of these data with those of the FLUVACS study showed a significant reduction of major cardiovascular events (pooled effectiveness 44%; 95% CI = 25–58), cardiovascular deaths (pooled effectiveness: 60%; 95% CI = 29–78); and hospitalization (pooled effectiveness 51%; 95% CI = 16–72) in vaccinated participants at one-year follow up (*211*). A self-controlled case series study conducted through medical record review of over 17,000 persons aged ≥18 years who had experienced a stroke found a reduction of 55% in the risk for stroke in the first 1–3 days after vaccination; subsequent reductions were 36% at 4–7 days, 30% at 8–14 days, 24% at 15–28 days, and 17% at 29–59 days (*212*).

Statin medications, a class of drugs commonly used among persons with vascular disease, are known to have immunomodulatory effects. A posthoc analysis of data from a randomized clinical trial comparing MF59-adjuvanted IIV3 and unadjuvanted IIV3 among persons aged ≥65 years demonstrated lower geometric mean titers following vaccination among persons receiving chronic statin therapy (by 38% [95% CI = 27–50] for A(H1N1), by 67% [95% CI = 54–80] for A(H3N2), and by 38% [95% CI = 28–49] for B). The effect was more pronounced among those receiving synthetic statin drugs (fluvastatin, atorvastatin, and rosuvastatin) relative to those receiving fermentation-derived statins (pravastatin, simvastatin, lovastatin, and Advicor) (*213*). A retrospective cohort study covering nine influenza seasons found reduced effectiveness of influenza vaccine against MAARI among statin users (*214*); however, this study did not evaluate confirmed influenza illness. Further study of the specific impact of statins on influenza vaccine effectiveness is needed.

Multiple studies indicate that vaccination might be beneficial for persons with chronic liver disease. A prospective

study of 311 persons with cirrhosis, 198 of whom received IIV3 and the remainder of whom were unvaccinated, noted reduction in the rates of ILI (14% versus 23%; p = 0.064) and of culture-positive influenza (2.3% versus 8.8%; p = 0.009) in the vaccinated group (*215*). Review of data from Taiwan's National Health Insurance program from 2000 through 2009 noted a lower hospitalization rate among persons with chronic hepatitis B infection who had been vaccinated compared with those who had not (16.29 versus 24.02 per 1,000 person-years) (*216*).

Studies of the immunogenicity and effectiveness of seasonal influenza vaccine among persons with obesity have shown conflicting results. An evaluation of immunogenicity of influenza vaccine conducted among pregnant and postpartum women reported that seroconversion rates among obese women were lower than those among normal-weight participants, but the difference was not statistically significant (*217*). Two other observational studies focused on the impact of obesity on postvaccination immune response. One study comparing 1-month and 12-month postvaccination immune response showed that obese persons mounted a vigorous initial antibody response to IIV3 (*218*). However, higher BMI was associated with a decline in influenza antibody titers after 12 months postvaccination. A second study of older adults reported that immunogenicity of IIV3 was similar in obese and normal-weight older adults, with a slight increase in seroconversion for the A/H3N2 virus but not for the other viruses (*219*). In a small study involving 51 children aged 3–14 years with varying BMI measurements (*220*), seroprotection rates at 4 weeks postvaccination were significantly higher against influenza A(H1N1)pdm09 strain in the overweight/obese group (p<0.05) when compared with the normal-weight group. This difference diminished over time, with the antibody response similar or slightly higher in overweight/obese children when measured 4 months postvaccination. A test-negative case-control study of hospitalized adult patients reported an unadjusted vaccine effectiveness against LCI hospitalizations of 79% (95% CI = -6– 96); after adjusting for obesity, the vaccine effectiveness estimate increased to 86% (95% CI = 19–97); the presence of obesity increased the odds of laboratory-confirmed influenza by 2.8 times (*221*).

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 responses (*222–224*). Among persons who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, IIV might not induce protective antibody titers (*224*,*225*); a second dose of vaccine does not improve immune response (*225*,*226*). 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 (*227*). 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 of IIV3 for prevention of culture- or RT-PCR–confirmed influenza illness was 75% (95% CI = 9–96) (*228*).

In a randomized study comparing the immunogenicity of high-dose versus standard-dose IIV3 among 195 HIV-infected adults aged ≥18 years (10% of whom had CD4 counts under 200 cells/μL), seroprotection rates were higher in the high-dose group for A(H1N1) (96% versus 87%; p = 0.029) and influenza B (91% versus 80%; p = 0.030). Both vaccines were well-tolerated (*229*). However, in a comparative study of 41 children and young adults aged 3–21 years with cancer or HIV infection, high-dose IIV3 was no more immunogenic than standard-dose IIV3 among the HIV-infected recipients (*230*).

Several observational studies suggest that immunogenicity among persons with solid organ transplants varies according to factors such as transplant type, time from transplant, and varying immunosuppressive regimen. Overall seroprotective and seroconversion responses have ranged from 15% to 93% with lower responses seen in lung transplant and greater responses several years after kidney transplant (*231*). In one study, kidney transplant recipients who were 3–10 years posttransplant had a 93% seroprotection rate to A(H1N1) antigen after vaccination (*232*). Among persons with kidney or heart transplants, seroresponse rates were similar or slightly reduced compared with healthy persons (*232–237*). However, a small study involving participants with liver transplants indicated a reduced immunologic response to influenza vaccinations (*238*). Response rates were lowest if vaccination occurred within the four months after the transplant procedure (*239*). A study of persons with a history of kidney transplant found that influenza vaccination in the first year after transplant was associated with a lower rate of transplant rejection (aHR: 0.77; 95% CI = 0.69–0.85; p<0.001) and death (0.82; 95% CI = 0.76–0.89; p<0.001) (*240*).

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 LAIV3 has been assessed in multiple studies (*241–245*).

The single LAIV licensed in the United States was originally a trivalent vaccine (FluMist; MedImmune, Gaithersburg, Maryland). FluMist Quadrivalent was licensed by FDA in 2012, and replaced the trivalent formulation beginning with the 2013–14 season. Prelicensure studies comparing LAIV4 to LAIV3 demonstrated that HAI antibody responses to LAIV4 were noninferior to responses to LAIV3 among healthy children and adults ≤49 years (*246–248*). LAIV4 might confer increased protection against seasonal influenza B by targeting more than one influenza B lineage. No comparative efficacy or effectiveness data for LAIV4 versus LAIV3 are available.

LAIV3 in Children

A large randomized, double-blind, placebo-controlled trial among 1,602 healthy children aged 15–71 months assessed the efficacy of LAIV3 against culture-confirmed influenza during two seasons (1996–98) (*249*,*250*). During the first season, when vaccine and circulating virus strains were well-matched, efficacy against culture-confirmed influenza was 94% (95% CI = 88–97) for participants who received 2 doses of LAIV3 separated by >6 weeks, and 89% (95% CI = 65–96) for those who received 1 dose (*249*). During the second season, when the A(H3N2) component in the vaccine was not well-matched with circulating virus strains, efficacy for 1 dose was 86% (95% CI = 75–92) for this virus. The overall efficacy for any influenza during the two seasons was 92% (95% CI = 88–94) (*250*). In a randomized placebo-controlled trial comparing 1 dose versus 2 doses of LAIV3 in 3,200 vaccine-naïve children aged 6–35 months in South Africa, Brazil, and Argentina during the 2001 and 2002 seasons, efficacy was 57.7% (95% CI = 44.7–67.9) after 1 dose of LAIV3 and 73.5% (95% CI = 63.6–81) after 2 doses (*251*) during the first year of the study. Other two-season, randomized, placebo-controlled trials have demonstrated similar efficacy rates of LAIV3 among young children, ranging from 85% to 89% among children in childcare (*252*) to 64% to 70% for children in eight regions in Asia (*253*). LAIV3 efficacy in preventing LCI also has been demonstrated in studies comparing the efficacy of LAIV with IIV rather than with a placebo (see Comparisons of LAIV3/4 and IIV Efficacy or Effectiveness).

Effectiveness studies have demonstrated that LAIV3 use among healthy children was associated with reduced risk of outcomes other than LCI. In one community-based, nonrandomized open-label study, reductions in MAARI were observed during the 2000–01 season among children who received 1 dose of LAIV3 during 1999–2000 or 2000–2001), even though antigenically drifted influenza A(H1N1) and B viruses were circulating during the latter season (*116*). Receipt of LAIV3 resulted in 21% fewer febrile illnesses (95% CI = 11–30) and 30% fewer febrile otitis media (95% CI = 18–45) (*249*). A meta-analysis of six placebo-controlled studies concluded that the effectiveness of LAIV3 against acute otitis media associated with culture-confirmed influenza among children aged 6–83 months was 85% (95% CI = 78–90) (*254*).

LAIV3 in Younger Adults

A randomized, double-blind, placebo-controlled trial of LAIV3 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 LAIV3 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 (*255*). Estimated efficacy of LAIV3 against influenza confirmed by either culture or RT-PCR in a randomized, placebo-controlled study among approximately 1,200-2,000 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 (*256–258*).

Comparisons of LAIV3/4 and IIV Efficacy or Effectiveness

Studies comparing the efficacy of IIV3 to that of LAIV3 among adults have been conducted in a variety of settings and populations using several different outcomes. Among adults, most comparative studies demonstrated that LAIV3 and IIV3 have similar efficacy, or that IIV3 was more efficacious (*259*). One randomized, double-blind, placebo-controlled challenge study that was conducted among 92 healthy adults aged 18–45 years assessed the efficacy of both LAIV3 and IIV3 in preventing influenza infection when artificially challenged with wild-type strains that were antigenically similar to vaccine strains (*245*). 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 LAIV3 and 71% for IIV3 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 (*245*). In a randomized, double-blind, placebo-controlled trial conducted among young adults during the 2004–05 influenza season, when the majority of circulating A(H3N2) viruses were antigenically drifted from that season's vaccine viruses, the efficacy of LAIV3 and IIV3 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 (*256*). Similar studies conducted among adults during the 2005–06 and 2007–08 influenza seasons found no significant difference in vaccine efficacy in the 2005–06 season (*257*) but did find a 50% relative efficacy of IIV3 compared with LAIV3 in the 2007–08 season (*258*). 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 IIV3 had a significantly lower incidence of health care encounters resulting in diagnostic coding for P&I compared with those who received LAIV3 (adjusted incidence rate ratio [aIRR]: 0.57 [95% CI = 0.51–0.64] for the 2004–05 season, 0.79 [95% CI = 0.72–0.87] for the 2005–06 season, and 0.80 [95% CI = 0.74–0.86] for the 2006–07 season) (*260*). However, in a retrospective cohort study comparing LAIV3 and IIV3 among 701,753 nonrecruit military personnel and 70,325 new recruits, among new recruits, incidence of ILI was lower among those who received LAIV3 than IIV3. The previous vaccination status of the recruits was not stated; it is possible that this population was relatively naïve to vaccination compared with previous service members who were more likely to have been vaccinated routinely each year (*261*).

Several studies comparing LAIV3 with IIV3 prior to the 2009 pandemic demonstrated superior efficacy of LAIV3 among young children (*259*). A randomized controlled trial conducted among 7,852 children aged 6–59 months during the 2004–05 influenza season demonstrated a 55% reduction in cases of culture-confirmed influenza among children who received LAIV3 compared with those who received IIV3 (*262*). In this study, LAIV3 efficacy was higher compared with IIV3 against antigenically drifted viruses and well-matched viruses. An open-label, nonrandomized, community-based influenza vaccine trial conducted among 7,609 children aged 5–18 years during an influenza season when circulating A(H3N2) strains were poorly matched with strains contained in the vaccine also indicated that LAIV3, but not IIV3, was effective against antigenically drifted A(H3N2) viruses. In this study, children who received LAIV3 had significant protection against LCI (37%) and P&I events (50%) (*263*). LAIV3 provided 32% increased protection in preventing culture-confirmed influenza compared with IIV3 in one study conducted among children aged ≥6 years and adolescents with asthma (*264*) and 52% increased protection compared with IIV3 among children aged 6–71 months with recurrent respiratory tract infections (*265*).

On the basis of these data, in June 2014, ACIP recommended that when immediately available, LAIV should be used for healthy children aged 2 through 8 years who have no contraindications or precautions. However, analysis of data from three observational studies of LAIV4 vaccine effectiveness for the 2013–14 season (the first season in which LAIV4 was available) revealed low effectiveness of LAIV4 against influenza A(H1N1)pdm09 among children aged 2 through 17 years (*266*,*267*). Analysis of data from the U.S. Influenza Vaccine Effectiveness Network for the 2010–11 through 2013–14 seasons noted that children aged 2 through 17 years who received LAIV had similar odds of influenza regardless of receipt of LAIV3 or IIV3 during 2010–11 through 2012–13; however, during the 2013–14 season odds of influenza were significantly higher for those who received LAIV4 (OR: 5.36; 95% CI = 2.37–12.13 for children aged 2 through 8 years; OR: 2.88; 95% CI = 1.62–5.12 for children aged 2 through 17 years) (*268*). During this season, the H1N1pdm09 virus predominated for the first time since the 2009 pandemic. The diminished effectiveness against H1N1pdm09 was hypothesized to be attributable to reduced stability and infectivity of the A/California/2009/(H1N1) vaccine virus, conferred by a single amino acid mutation in the stalk region of the HA protein (*269*). Moreover, although one large randomized trial observed superior relative efficacy of LAIV3 compared with IIV3 against antigenically drifted H3N2 influenza viruses during the 2004–05 season (*262*), analysis of observational data from the U.S. Influenza Vaccine Effectiveness Network for the early 2014–15 season (in which antigenically drifted H3N2 viruses were predominant) indicated that neither LAIV4 nor IIV provided significant protection in children aged 2 through 17 years; LAIV4 did not offer greater protection than IIV for these viruses (*270*). Based on these influenza vaccine effectiveness data for the 2013–14 and 2014–15 seasons, ACIP concluded that a preference of LAIV4 over IIV was no longer warranted (*6*).

For the 2015–16 season, to address stability concerns surrounding the A/California/7/2009(H1N1) HA, HA from a different influenza A(H1N1) virus was included in LAIV4 (A/Bolivia/559/2013(H1N1). In June 2016, ACIP reviewed data pertaining to effectiveness of LAIV4 and IIV in the United States for the 2015–16 season (*271*). During this season, in which A(H1N1)pdm09 viruses were predominant, analysis of data from the U.S. Influenza Vaccine Effectiveness Network

showed no significant vaccine effectiveness among children aged 2 through 17 years for LAIV4 for all influenza A and B viruses combined (3%; 95% CI = -49–37) or for influenza A(H1N1)pdm09 (-21%; 95% CI = -108–30). A Department of Defense analysis similarly noted no statistically significant vaccine effectiveness of LAIV4 against influenza A(H1N1) in this age group for the 2015–16 season. Data presented by MedImmune to ACIP on June 22, 2016 included a somewhat higher point estimate for LAIV4 effectiveness against influenza A(H1N1) (50%), but this value was not statistically significant. Conversely, estimated effectiveness of IIV against these viruses among children aged 2 through 17 years was significant across all three studies. Following review of this information in June 2016, ACIP made the interim recommendation that LAIV4 should not be used for the 2016–17 influenza season.

Immunogenicity, Efficacy, and Effectiveness of RIV

RIV, available as a trivalent vaccine, Flublok (RIV3; Protein Sciences, Meriden, Connecticut) was licensed by FDA in 2013. This vaccine contains 135 μg of purified HA proteins (45 μg for each virus). The HA proteins are produced in an insect cell line; this process uses neither live influenza viruses nor eggs.

As a relatively new product, fewer postmarketing effectiveness data are available for RIV3 than IIVs. Initial licensure was for persons aged 18 through 49 years. In prelicensure studies comparing RIV3 versus placebo among persons aged 18 through 49 years, serum antibody responses were induced to all three vaccine components (*272*). In a randomized placebo-controlled study conducted among healthy persons aged 18 through 49 years during the 2007–08 influenza season (*273*,*274*), 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 (*273*). Estimated vaccine effectiveness without regard to match was 44.6% (95% CI = 18.8–62.6) (*274*).

Although RIV3 was licensed initially for use in persons aged 18 through 49 years, in October 2014, the approved age indication was expanded to ≥18 years on the basis of data from randomized trials demonstrating adequate immunogenicity among persons aged ≥50 years (*275*,*276*); effectiveness data are not yet available for this age group.

Safety of Influenza Vaccines

Safety of 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 6–23 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 IIV administration compared with control periods 2–4 weeks before and after vaccination (*277*). In a retrospective cohort study using VSD data from 45,356 children aged 6–23 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 or prevent these conditions (*278*). A subsequent VSD study of 66,283 children aged 24–59 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 was associated with complications (*279*).

In a study of 791 healthy children aged 1 through 15 years, postvaccination fever was noted among 12% of those aged 1 through5 years, 5% among those aged 6 through10 years, and 5% among those aged 11 through 15 years (*103*). Fever, malaise, myalgia, and other systemic symptoms that can occur after vaccination with IIV3 most often affect persons who have had no previous exposure to the influenza virus antigens in the vaccine (e.g., young children) (*280*). These reactions are generally self-limited and subside after 1–2 days.

Studies conducted during the 1970s of monovalent and bivalent whole-virus influenza vaccines demonstrated greater reactogenicity among young children as compared with older

children and adults (*133*,*281–283*). These findings were the basis for the recommendation that children aged 6 through 35 months receive half the dose of IIV (0.25 cc) compared with older children and adults. Whole virus IIVs are no longer available in the United States, having been replaced with split-virus and subunit IIVs. As a group, the newer IIVs are less reactogenic than the previous whole-virus products (*284*). A multisite randomized controlled trial comparing full-dose (0.5 mL) IIV3 with half-dose (0.25 mL) IIV3 in children aged 6 through35 months reported no significant differences in local or systemic reactions (*285*).

Febrile seizures are not uncommon in young children. At least one febrile seizure is experienced by 2%–5% of children aged 6–60 months; nearly all children who have a febrile seizure recover quickly and are healthy afterward (*286*). Prior to the 2010–11 influenza season, an increased risk for febrile seizures following receipt of IIV3 had not been observed in the United States (*278*,*287*). During the 2010–11 influenza season, CDC and FDA conducted enhanced monitoring for febrile seizures following receipt of influenza vaccines after reports of an increased risk for fever and febrile seizures (up to nine febrile seizures per 1,000 vaccine doses) in young children in Australia associated with a 2010 Southern Hemisphere IIV3 produced by CSL Biotherapies (now Seqirus) (*288*). Because of the findings in Australia, ACIP does not recommend the U.S.-licensed Seqirus 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 receipt of IIV3 (*289*,*290*). Further assessment through a VSD study determined that risk for febrile seizures was increased in children aged 6 months–4 years from the day of vaccination until the day after (risk window: day 0–1). The risk was higher when children received concomitant PCV13 (i.e., when the two vaccines are administered at the same health care visit) and peaked at approximately age 16 months (*290*). The magnitude of the increased risk for febrile seizures in children aged 6–23 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 (*288*). Findings from surveillance for febrile seizures in young children following influenza vaccine for the 2011–12 season, which had the same formulation as that of the 2010–11 season, were consistent with the 2010–11 season. An observational clinical study also showed that risk for fever in the 0–1 days after vaccination was higher when young children received 2011–12 IIV3 and PCV13 concomitantly versus receipt of IIV3 or PCV13 without the other product (*291*). An increased risk for febrile seizures following receipt of IIV3 was not observed during the 2012–13 season (CDC, unpublished data, 2013) (*292*). After evaluating the data on febrile seizures from the 2010–11 season and taking into consideration benefits and risks of vaccination, ACIP recommended no policy change for use of IIV (*293*,*294*). A subsequently published analysis of data from the 2010–11 season reported that there was no association between receipt of IIV3 (adjusted for concomitant PCV13 or DTaP) and febrile seizures (IRR adjusted for age and seasonality: 1.36; 95% CI = 0.78–2.39) (*295*). Same-day IIV3 and PCV13 vaccination was not associated with more febrile seizures compared with separate-day vaccination (1.08 fewer febrile seizures per 100,000 with same day administration; 95% CI = -5.68–6.09). However, a VSD study of data from the 2013–14 and 2014–15 seasons found an elevated risk for febrile seizures among 6- through 23 month-olds 0–1 days after concomitant receipt of IIV3 and PCV13 (RR: 5.30; 95% CI = 1.87–14.75). There was no significant increased risk following administration of IIV3 without PCV13 (*296*). Surveillance for febrile seizures following receipt of IIVs is ongoing through the Vaccine Adverse Event Reporting System (VAERS; https://vaers.hhs.gov/index), and VSD conducts near real-time sequential monitoring for seizures following receipt of IIV during the influenza season.

Since the 2013–14 season, in addition to previously available IIV3s, several IIV4 formulations have been licensed. IIV4s include products licensed for children as young as age 6 months. In prelicensure studies of IIV4s, overall frequencies of most solicited adverse events were similar to the corresponding comparator IIV3s (*297–299*). Most local and general adverse events are temporary and mild to moderate in severity. Among children, the most common safety complaint was a modest increase in injection-site pain (*124*,*126*,*128*,*300*). The first postlicensure review of VAERS reports covering the 2013–14 and 2014–15 seasons noted that the most common adverse events reported following receipt of IIV4 among children aged 6 months through 17 years were injection-site reactions and fever. No specific safety concerns were identified; the safety profile was similar to that of IIV3 (*301*).

Adults

In placebo-controlled studies of IIV3 among older adults, the most frequent side effect of vaccination was soreness at the vaccination site (affecting 10%–64% of patients) that lasted <2 days (*302*,*303*). 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 proportions of systemic symptoms (e.g., fever, malaise, myalgia, and headache) when compared with placebo injections (*302–304*). Adverse

TABLE 1. Influenza vaccines — United States, 2016–17 influenza season*

Trade name	Manufacturer	Presentation	Age indication	Mercury (from thimerosal), µg/0.5mL	Latex	Route
Inactivated Influenza Vaccine, quadrivalent (IIV4), standard dose†						
Fluarix Quadrivalent	GlaxoSmithKline	0.5 mL single-dose prefilled syringe	≥3 yrs	NR	No	IM§
Flulaval Quadrivalent	ID Biomedical Corp. of Quebec (distributed by GlaxoSmithKline)	0.5 mL single-dose prefilled syringe	≥3 yrs	NR	No	IM
		5.0 mL multi-dose vial	≥3 yrs	<25	No	IM
Fluzone Quadrivalent	Sanofi Pasteur	0.25 mL single-dose prefilled syringe	6 through 35 mos	NR	No	IM
		0.5 mL single-dose prefilled syringe	≥36 mos	NR	No	IM
		0.5 mL single-dose vial	≥36 mos	NR	No	IM
		5.0 mL multi-dose vial	≥6 mos	25	No	IM
Fluzone Intradermal Quadrivalent¶	Sanofi Pasteur	0.1 mL single-dose prefilled microinjection system	18 through 64 yrs	NR	No	ID**
Inactivated Influenza Vaccine, quadrivalent, cell culture-based (ccIIV4), standard dose†						
Flucelvax Quadrivalent	Seqirus	0.5 mL single-dose prefilled syringe	≥4 yrs	NR	No	IM
Inactivated Influenza Vaccine, trivalent (IIV3), standard dose†						
Afluria	Seqirus	0.5 mL single-dose prefilled syringe	≥9 yrs††	NR	No	IM
		5.0 mL multi-dose vial	≥9 yrs†† (needle and syringe) 18 through 64 years (jet injector)	24.5	No	IM
Fluvirin	Seqirus	0.5 mL single-dose prefilled syringe	≥4 yrs	≤1	Yes§§	IM
		5.0 mL multi-dose vial	≥4 yrs	25	No	IM
Adjuvanted Inactivated Influenza Vaccine, trivalent (aIIV3), standard dose†						
Fluad	Seqirus	0.5 mL single-dose prefilled syringe	≥65 yrs	NR	Yes§§	IM
Inactivated Influenza Vaccine, trivalent (IIV3), High Dose¶¶						
Fluzone High-Dose	Sanofi Pasteur	0.5 mL single-dose prefilled syringe	≥65 yrs	NR	No	IM
Recombinant Influenza Vaccine, trivalent (RIV3)* **						
Flublok	Protein Sciences	0.5 mL single-dose vial	≥18 yrs	NR	No	IM
**Live Attenuated Influenza Vaccine, quadrivalent (LAIV4) ††† **						
FluMist Quadrivalent	MedImmune	0.2 mL single-dose prefilled intranasal sprayer	2 through 49 yrs	NR	No	NAS

Abbreviations: ACIP = Advisory Committee on Immunization Practices; ID = intradermal; IM = intramuscular; NAS = intranasal; NR = not relevant (does not contain thimerosal).

* Immunization providers should check Food and Drug Administration–approved prescribing information for 2016–17 influenza vaccines for the most complete and updated information, including (but not limited to) indications, contraindications, warnings, and precautions. Package inserts for U.S.-licensed vaccines are available at http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm. Availability of specific products and presentations might change and differ from what is described in this table.

† Standard dose intramuscular IIVs contain 15 µg of each vaccine HA antigen (45 µg total for trivalents and 60 µg total for quadrivalents) per 0.5mL dose.

§ For adults and older children, the recommended site for intramuscular influenza 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, available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm.

¶ Quadrivalent inactivated influenza vaccine, intradermal: a 0.1-mL dose contains 9 µg of each vaccine HA antigen (36µg total).

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

†† 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 Seqirus' 2010 Southern Hemisphere IIV3. 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 benefits and risks of influenza vaccination with Afluria before administering this vaccine. Afluria may be used in persons aged ≥9 years. Afluria is licensed for administration by jet injector for persons aged 18 through 64 years only.

§§ Syringe tip cap might contain natural rubber latex.

¶¶ High-dose IIV3 contains 60 µg of each vaccine antigen (180 µg total) per 0.5mL dose.

*** RIV3 contains 45 µg of each vaccine HA antigen (135 µg total) per 0.5mL dose.

††† ACIP recommends that Flumist (LAIV4) not be used during the 2016–17 season.

events in adults aged ≥18 years reported to VAERS during 1990–2005 were analyzed (*305*). 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) (*306*), 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) (see Guillain-Barré Syndrome and IIV). However, VAERS cannot assess whether a vaccine caused an event to occur.

Injection-site reactions and systemic adverse events were more frequent after vaccination with high-dose IIV3 (Fluzone High-Dose; Sanofi Pasteur, Swiftwater, Pennsylvania), which contains 180 μg of HA antigen (60 for each vaccine virus) than after vaccination with standard dose IIV3 (45 μg) (Fluzone; Sanofi Pasteur, Swiftwater, Pennsylvania), 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 1,262 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) (*181*). 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) (*307*). 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 events were nonserious (*308*). CDC and FDA will continue to monitor the safety of high-dose vaccine through VAERS.

Fewer postmarketing safety data have thus far accumulated for IIV4, which first became available during the 2013–14 season, compared with IIV3. Among adults the most common safety complaints were injection-site pain and systemic reactions, such as myalgia, headaches, and fatigue (*123*,*125*,*127*,*129*,*130*,*309*). The first postlicensure safety assessment of VAERS reports covering the 2013–14 and 2014–15 seasons noted a safety profile similar to that of IIV3. The most common adverse event reported following receipt of IIV4 among adults aged 18 through 64 years was injection-site pain. No specific safety concerns were identified (*301*).

Intradermal IIV, which was available as an IIV3 for the 2011–12 through 2014–15 seasons and as an IIV4 since 2015–16, has been observed to be associated with increased frequency of some injection-site reactions as compared with intramuscularly administered IIV. In a randomized study of intradermal IIV3 versus intramuscular IIV3 among approximately 4,200 adults aged 18–64 years, erythema, induration, swelling, and pruritus occurred with greater frequency following receipt of intradermal vaccine compared with intramuscular vaccine (*310*); frequency of injection-site pain was not significantly different. A review of studies comparing intradermal and intramuscular IIV3 similarly noted higher rates of erythema, induration, swelling, and pruritus among adults aged 18–60 years within the first 7 days after receiving intradermal vaccine; local pain and ecchymosis and systemic reactions occurred with similar frequency (*311*). A review of VAERS reports covering the 2011–12 and 2012–13 seasons, the first two seasons that the intradermal IIV3 was available, revealed no new safety concerns (*312*). A randomized study comparing safety of the newer IIV4 with that of IIV3 revealed a similar adverse event profile (*130*).

Cell culture-based IIV3 (ccIIV3), licensed by FDA in 2013, appears to have a similar safety profile to other, previously licensed IIVs. A review of 629 VAERS reports related to ccIIV3 during the 2013–14 and 2014–15 seasons noted that injection-site and systemic symptoms were the most commonly reported adverse effects; no concerning pattern of adverse effects was identified (*313*). ACIP will continue to review safety data pertaining to cell culture based vaccines.

An MF59-adjuvanted IIV3 (aIIV3), Fluad (Seqirus, Holly Springs, North Carolina), approved in November 2015 for use in persons aged ≥65 years, will be available during the 2016–17 season. In clinical trials among persons in this age group, some local and systemic adverse events were observed to occur more frequently following aIIV3 compared with unadjuvanted IIV; most were mild in severity. The safety profile of MF59-adjuvanted IIV3 compares favorably to that of unadjuvanted IIV (*314*).

Pregnant Women and Neonates

Currently available IIVs are classified as either Pregnancy Category B or Category C[†] medications, depending on 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 (*315*). A matched case-control study of 252 pregnant women who received IIV3 within the 6 months before delivery determined that no serious adverse events occurred after vaccination and that no difference in pregnancy outcomes was identified among these pregnant women compared with 826 pregnant women who were not vaccinated (*316*). A case-control analysis of data from six health care organizations participating in VSD found no significant increase in the risk for pregnancy loss in the 4 weeks following seasonal influenza vaccination during the 2005–06

[†] 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) 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 might warrant use of the drug in pregnant women despite potential risks. Additional information about pregnancy categories is available at https://www.gpo.gov/fdsys/pkg/FR-2008-05-29/pdf/E8-11806.pdf.

and 2006–07 seasons (*317*). A review of health registry data in Norway noted an increased risk for fetal death associated with influenza A(H1N1) pdm09 infection, but no increased risk for fetal mortality associated with vaccination (*68*). During 1990–2009, VAERS reports of pregnant women after receipt of IIV3 did not find any new, unusual, or unexpected pattern of adverse pregnancy events or fetal outcomes (*318*).

Background rates of spontaneous abortion vary from 10.4% in women aged <25 years to 22.4% in women aged >34 years (*319*); considering the number of pregnant women vaccinated, miscarriage following (but not attributable to) influenza vaccination would not be an unexpected event. Preliminary (as yet unpublished) results of a VSD study suggested an increased risk for spontaneous abortion in some pregnant women in the 1 to 28 days after receiving IIV3 during either the 2010–11 or the 2011–12 seasons; the increased risk was seen primarily in women who had also received a H1N1pdm09-containing vaccine in the previous season (*320*). A systematic review and meta-analysis of seven published observational studies (four involving unadjuvanted A[H1N1]pdm09 monovalent vaccine, two involving adjuvanted A[H1N1]pdm09 monovalent vaccine, and one involving A/New Jersey/8/76 monovalent vaccine) found decreased risk for stillbirth among women who were vaccinated (for all studies, RR: 0.73; 95% CI = 0.55–0.96; for studies of influenza A(H1N1)pdm09 vaccines RR: 0.69; 95% CI = 0.52–0.90); there was no significant difference in risk for spontaneous abortion between vaccinated and unvaccinated women (RR: 0.91; 95% CI = 0.68–1.22) (*321*). Several reviews of studies involving seasonal and 2009(H1N1) IIV in pregnancy concluded that no evidence exists to suggest harm to the fetus from maternal vaccination (*322–324*).

A systematic review and meta-analysis of studies of congenital anomalies after vaccination including data from 15 studies (14 cohort studies and one case-control study), eight of which reported data on first-trimester immunization showed that risk for congenital malformations was similar for vaccinated and unvaccinated mothers: in the cohort studies, events per vaccinated versus unvaccinated were 2.6% versus 3.1% (5.4% versus 3.3% for the subanalysis involving first-trimester vaccination); in the case-control study, the percentage vaccinated among cases versus controls was 37.3% versus 41.7% (*325*). There was no association between congenital defects and influenza vaccination in any trimester (OR: 0.96; 95% CI = 0.86–1.07) or specifically in the first trimester (OR: 1.03; 95% CI = 0.91–1.18). With respect to major malformations, there was no increased risk after immunization in any trimester (OR: 0.99; 95% CI = 0.88–1.11) or in the first trimester (OR: 0.98; 95% CI = 0.83–1.16). In a retrospective cohort study of 57,554 women, influenza vaccination was not associated with increased or decreased risk for preterm birth or small for gestational age birth (*326*).

Ocular and Respiratory Symptoms After Receipt of IIV

Oculorespiratory syndrome (ORS), an acute, self-limited reaction to IIV, was first described during the 2000–01 influenza season in Canada (*327*,*328*). The initial case-definition for ORS was the onset of one or more of the following within 2–24 hours after receiving IIV3, and resolving within 48 hours of onset: red eyes, cough, wheeze, chest tightness, difficulty breathing, sore throat, or facial swelling (*327*,*329*). ORS was initially noted to be associated with one vaccine preparation (Fluviral S/F; Shire Biologics, Quebec, Canada) not available in the United States during the 2000–01 influenza season (*327*). 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 (*330*).

The cause of ORS has not been established; however, studies suggest that the reaction is not IgE-mediated (*331*). 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 Reactions After Receipt of 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 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 (*332*,*333*).

Guillain-Barré Syndrome and IIV

Guillain-Barré Syndrome (GBS) is an autoimmune disease associated with rapid-onset muscle weakness. Evidence exists that multiple infectious illnesses, most notably *Campylobacter jejuni* gastrointestinal infections and upper respiratory tract infections, are associated with GBS (*334–336*). The annual incidence of GBS is 10–20 cases per 1 million adults (*337*). An analysis of 405 patients admitted to a single facility identified an association between serologically confirmed influenza virus infection and GBS, with time from onset of influenza illness to GBS of 3–30 days (*338*).

The 1976 swine influenza vaccine was associated with an increased frequency of GBS, estimated at one additional case of GBS per 100,000 vaccinated persons. The risk for influenza vaccine–associated GBS was higher among persons aged ≥25 years than among persons aged <25 years (*339*). 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 (*340*,*341*).

During three of four influenza seasons studied during 1977–1991, the overall relative risk estimates for GBS after influenza vaccination were not statistically significant (*342*–*344*). 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 (*341*). 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 (*345*). Published data from the United Kingdom's General Practice Research Database (GPRD) found influenza vaccination to be associated with a non-statistically significant decreased risk for GBS (OR: 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 (i.e., healthier persons might be more likely to be vaccinated and also be at lower risk for GBS) is unclear (*346*). 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 (*347*). A third GPRD analysis found that GBS was associated with recent ILI, but not influenza vaccination (*348*). A meta-analysis of 39 observational studies of seasonal and 2009 pandemic influenza vaccines published between 1981 and 2014 found an overall relative risk for GBS of 1.41 (95% CI = 1.20–1.66); the risk was higher for pandemic vaccines (RR: 1.84; 95% CI = 1.36–2.50) than for seasonal vaccines (RR: 1.22; 95% CI = 1.01–1.48) (*349*).

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 (*341*). In addition, data from the systems monitoring influenza A(H1N1) 2009 monovalent vaccines suggest that the increased risk for GBS is approximately one or two additional cases per 1 million persons vaccinated, which is similar to that observed in some years for seasonal IIV (*350*–*356*). Studies have also shown an increased risk for GBS following influenza infection, of higher magnitude than the risk observed following influenza vaccination (*338*,*357*).

Persons with a history of GBS have a substantially greater likelihood of subsequently experiencing GBS than persons without such a history (*337*). 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 (*358*). In a Kaiser Permanente Northern California database study among >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 (*359*).

As a precaution, persons who are not at high risk for severe influenza complications (see Persons at Risk for Medical Complications Attributable to Severe Influenza) and who are known to have experienced GBS within 6 weeks of influenza vaccination generally should not be vaccinated. As an alternative to vaccination, 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

Thimerosal, an ethyl mercury-containing antimicrobial compound, is used in multidose vial preparations of IIV to reduce the likelihood of microbial growth that might occur if organisms are introduced via the needle and syringe. Although accumulating evidence shows no increased risks from exposure to vaccines containing thimerosal (*360*–*370*), 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 (*360*,*361*). LAIV, RIV, and most single-dose vial or syringe preparations of IIV do not contain thimerosal. Persons recommended to receive IIV may receive any age- and risk factor–appropriate vaccine preparation, depending on availability.

Persons at Higher Risk for Influenza-Related Complications

Overall, safety data pertaining to persons with specific underlying conditions are more limited that pertaining to healthy populations. A study of 52 children aged 6 months through 4 years with chronic lung disease or congenital heart disease reported fever among 27% and irritability and insomnia among 25% (*131*); and a study among 33 children aged 6–18 months with bronchopulmonary dysplasia or congenital heart disease reported that one child had irritability and one had a fever and seizure after vaccination (*284*). 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 were aged either ≥65 years or 18–64 years and who had one or more chronic medical conditions compared with outpatients; injection-site soreness was the most common complaint (*371*).

Several randomized clinical trials comparing IIV to placebo among persons with COPD reported safety outcomes. A study of 125 COPD patients at a Thai hospital clinic reported that significantly more patients in the vaccine group had local reactions (27% versus 6% placebo; p = 0.002) (*372*). The most common local reactions among vaccinated patients were swelling, itching and pain when touched. The duration was usually <48 hours and did not require specific treatment. There were no significant differences between the two groups in systemic reactions, such as headache, myalgia, fever, skin rash, nor in lung function, dyspneic symptoms, and exercise capacity at one week and at 4 weeks.

IIV is safe and well tolerated in asthmatic children (*373*) and adults (*205*). A multicenter, randomized, double-blind, placebo-controlled crossover trial involving 2,032 asthmatic subjects aged 3–64 years found a similarly high frequency of asthma exacerbations during the 2 weeks following either vaccination or placebo injection (28.8% versus 27.7%). Only myalgia was reported more frequently following IIV3 (25% versus 21% placebo; p<0.001) (*374*). A randomized study of IIV3 versus placebo among 262 asthmatic adults noted that vaccination was associated with a decline in peak expiratory flow; however, this effect was no longer significant when adjusted for the presence of concomitant symptomatic cold symptoms (*375*). A randomized crossover design study of IIV3 versus saline placebo showed no significant difference in the occurrence of asthma exacerbations during the 14 days postvaccination (*376*).

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. Although 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 (*224*,*377*,*378*), better-designed studies have not documented a substantial increase in replication (*379–382*). 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 (*383*). Limited information is available about the effect of antiretroviral therapy on increases in HIV RNA levels after either influenza virus infection or influenza vaccination (*384*,*385*).

IIV generally has been shown to be well-tolerated in both adult and pediatric solid organ transplant recipients (*231*). In small studies, IIV vaccination did not affect allograft function or cause acute rejection episodes in recipients of kidney (*232*,*233*,*386*), heart (*234*), lung (*386*) or liver transplants (*238*,*239*,*387*) A literature review concluded that there is no convincing epidemiologic link between vaccination and allograft dysfunction (*231*). A single case of Guillain-Barré syndrome in a liver transplant recipient and another case of rhabdomyolysis leading to acute allograft dysfunction after IIV vaccination have been reported (*388*,*389*). Several case reports of corneal graft rejection have been reported following receipt of IIV (*390–392*), but no studies demonstrating an association have been conducted.

Safety of LAIV

Shedding, Transmission, and Phenotypic Stability of LAIV Viruses

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. 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 participants aged 5–49 years who received LAIV3 and for whom shedding was assessed by viral culture of nasal swabs (daily for days 1–7 postvaccination, every other day for days 9 through 25, and on day 28) 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 (*393*). Other smaller studies have reported similar findings (*394*,*395*). In an open-label study of

200 children aged 6–59 months who received a single dose of LAIV3, 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 6–23 months compared with 69% of children aged 24–59 months) (*396*). The incidence of shedding was highest on the second day postvaccination. Mean duration of shedding was 2.8 days (3.0 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 6–23 months (an age group for which LAIV is not licensed). Titers of shed virus were low (*396*). Vaccine virus was detected from nasal secretions in one (2%) of 57 HIV-infected adults who received LAIV3 compared with none of 54 HIV-negative participants (*397*), and in three (13%) of 24 HIV-infected children compared with seven (28%) of 25 children who were not HIV-infected (*398*).

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 9–36 months in a child care center assessed the potential for transmission of LAIV3 vaccine viruses from 98 vaccinated children to 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 transmission of vaccine virus within a contact group with a single LAIV recipient in this population was 0.58% (95% CI = 0–1.7) (*399*).

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 LAIV3 genotype after replication in the human host, and all retained the cold-adapted and temperature-sensitive phenotypes (*400*).

Children

In a randomized trial published in 2007, LAIV3 and IIV3 were compared among children aged 6–59 months (*262*). 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 24–59 months who received LAIV3, the proportion of children who experienced medically significant wheezing was not greater than among those who received IIV3. Wheezing was observed more frequently following the first dose among previously unvaccinated younger LAIV3 recipients, primarily those aged <12 months; LAIV3 is not licensed for this age group. In a previous randomized placebo-controlled safety trial among children without a history of asthma, an increased risk for asthma events (RR: 4.1; 95% CI = 1.3–17.9) was documented among the 728 children aged 18–35 months who received LAIV3. 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 was not observed in other age groups (*401*).

In a subset of healthy children aged 60–71 months from one clinical trial, certain signs and symptoms were reported more often after the first dose among LAIV3 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) (*402*). However, these differences were not statistically significant. In other trials, signs and symptoms reported after LAIV3 administration have included runny nose or nasal congestion (18%–82%), headache (3%–46%), fever (0–32%), vomiting (3%–17%), abdominal pain (2%), and myalgia (0–21%) (*242*,*243*,*252*,*401*,*403*–*406*). 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 prespecified medically attended outcomes during the 42 days after vaccination, LAIV3 was associated with increased risk for asthma, upper respiratory infection, musculoskeletal pain, otitis media with effusion, and adenitis/adenopathy. In this study, the proportion of serious adverse events was 0.2% in LAIV3 and placebo recipients; none of the serious adverse events was judged to be related to the vaccine by the study investigators (*401*).

An open-label field trial was conducted among approximately 11,000 children aged 18 months–18 years in which 18,780 doses of LAIV3 were administered between 1998–2002. For children aged 18 months–4 years, no increase was reported in asthma visits 0–15 days after vaccination compared with the prevaccination period. A significant increase in asthma events was reported 15–42 days after vaccination, but only in vaccine year 1 (*407*). This trial later assessed LAIV3 safety among 2,196 children aged 18 months–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 receipt of LAIV3 compared with the pre- and postvaccination reference periods (*408*).

A review of 460 reports (including persons aged 2 through 70 years) to VAERS following distribution of approximately 2.5 million doses of LAIV3 during the 2003–04 and 2004–05 influenza seasons did not indicate any new safety concerns (*409*). Few (9%) of the LAIV3 VAERS reports concerned serious adverse events; respiratory events were the most common conditions reported. During 2005–2012, VAERS received 2,619 reports in children aged 2–18 years after receipt of LAIV3 (*410*). Consistent with the earlier VAERS study, few (7.5%) of these reports were serious and no new adverse event patterns were identified. During 2013–2014, after approximately 12.7 million doses of LAIV4 were distributed, VAERS received 770 reports (599 in children aged 2–17 years); the safety profile of LAIV4 was consistent with prelicensure clinical trials and data from postlicensure assessment of LAIV3 (*411*).

Adults

In one clinical trial among a subset of healthy adults aged 18–49 years, signs and symptoms reported significantly more often ($p<0.05$; Fisher exact test) among LAIV3 recipients (n = 2,548) than placebo recipients (n = 1,290) within 7 days after each dose included cough (14% versus 10%), runny nose (44% versus 27%), sore throat (27% versus 16%), chills (89% versus 6%), and tiredness/weakness (25% versus 21%) (*402*). A review of 460 reports to VAERS after distribution of approximately 2.5 million doses of LAIV3 during the 2003–04 and 2004–05 influenza seasons did not indicate any new safety concerns (*409*). Few (9%) of the VAERS reports described 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. LAIV3 was well-tolerated among adults aged ≥65 years with chronic medical conditions (*412*). In a study of 57 HIV-infected persons aged 18–58 years with CD4+ counts >200 cells/μL who received LAIV3, no serious adverse events attributable to vaccines were reported during a 1-month follow-up period (*397*). Similarly, another study demonstrated no significant difference in the frequency of adverse events or viral shedding among 24 HIV-infected children aged 1–8 years on effective antiretroviral therapy who were administered LAIV3 compared with 25 HIV-uninfected children receiving LAIV3 (*398*). In a study comparing immunogenicity and shedding of LAIV4 among 46 HIV-infected (CD4+ counts >200 cells/μL) and 56 uninfected persons aged 2 through 25 years, adverse events were similar between the two groups. Shedding of vaccine virus was somewhat more prevalent among the HIV-infected participants, 67% of whom shed any vaccine virus up to 14–21 days postvaccination, compared with 50% of uninfected participants ($p = 0.14$) (*413*).

Among 27 reports to VAERS involving inadvertent administration of LAIV3 to pregnant women during 1990–2009, no unusual patterns of maternal or fetal outcomes were observed (*318*); among 138 reports noted in a health insurance claims database, all outcomes occurred at similar rates to those observed in unvaccinated women (*414*). 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.

Data on the relative safety of LAIV and IIV are limited for children and adults with chronic medical conditions conferring a higher risk for influenza complications. Safety data were collected from 1,940 children aged 2–5 years with asthma or prior wheezing from two randomized, multinational trials of LAIV3 and IIV3 (*415*). The results showed that wheezing, lower respiratory illness, and hospitalization were not significantly increased among children receiving LAIV3 relative to IIV3; however, increased prevalence of rhinorrhea (8.1% LAIV versus 3.1% IIV3; $p=0.002$) and irritability (2.0% versus 0.3%; $p = 0.04$) were observed among LAIV3 recipients. A study of LAIV and IIV3 among children aged 6–17 years with asthma noted no significant difference in wheezing events after receipt of LAIV3 (*264*). Available data are insufficient to determine the level of severity of asthma for which administration of LAIV would be inadvisable.

Safety of RIV

RIV, currently available as a trivalent vaccine (RIV3) has been available in the United States since the 2013–14 season. In prelicensure studies, the most frequently reported injection-site reaction (reported in ≥10% of recipients) was pain (37% among those aged 18 through 49 years; 32% among those aged 50 through 64 years, and 19% among those aged ≥65 years); the most common solicited systemic reactions were headache (15%, 17%, and 10%, respectively), fatigue (15%, 13%, and 13%, respectively), and myalgia (11% among persons aged 18 through 49 years and 11% among those aged 50 through 64 years) (*273*). Local pain and tenderness were reported significantly more frequently with RIV3 than placebo; however, most reports of pain following RIV3 were rated as mild. As a relatively new vaccine, fewer postmarketing safety data have accumulated for RIV3.

Immediate Hypersensitivity Reactions After Receipt of 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 (*416*). 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 (*416*,*417*).

Allergic reactions might be caused by the vaccine antigen, residual animal protein, antimicrobial agents, preservatives, stabilizers, or other vaccine components (*8*,*418*). Manufacturers use a variety of compounds to inactivate influenza viruses and add may 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 (*8*). The Clinical Immunization Safety Assessment (CISA) Project (http://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa), 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 (*416*).

Anaphylaxis after receipt of influenza vaccines is rare. A VSD study conducted during 2009–2011 observed that the incidence of anaphylaxis in the 0–2 days after any vaccine was 1.31 (95% CI = 0.90–1.84) cases per million vaccine doses in all ages. The incidence of anaphylaxis in the 0–2 days after IIV3 (without other vaccines) was 1.35 (95% CI = 0.65–2.47) per million IIV3 doses administered in all ages (*419*). Anaphylaxis occurring after receipt of IIV and LAIV rarely has been reported to VAERS (*305*,*409*,*420*,*421*). A VSD study of children aged <18 years in four health maintenance organizations during 1991–1997 estimated the overall risk for postvaccination anaphylaxis after any type of childhood vaccine to be approximately 1.5 cases per 1 million doses administered. In this study, no cases were identified in IIV3 recipients (*422*).

Recommendations for the Use of Influenza Vaccines, 2016–17 Season

Groups Recommended for Vaccination

Routine annual influenza vaccination is recommended for all persons aged ≥6 months who do not have contraindications. Recommendations regarding timing of vaccination, considerations for specific populations, the use of specific vaccines, and contraindications and precautions, are summarized in the sections that follow.

Timing of Vaccination

Optimally, vaccination should occur before onset of influenza activity in the community. Health care providers should offer vaccination by the end of October, if possible. Children aged 6 months through 8 years who require 2 doses (see Children Aged 6 Months Through 8 Years) should receive their first dose as soon as possible after vaccine becomes available, and the second dose ≥4 weeks later. The majority of adults have a protective antibody response within 2 weeks after vaccination (*423*,*424*). Vaccination should continue to be offered as long as influenza viruses are circulating and unexpired vaccine is available. To avoid missed opportunities for vaccination, providers should offer vaccination during routine health care visits and hospitalizations when 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 season, the optimal time to vaccinate cannot be predicted precisely because influenza seasons vary in timing and duration. Moreover, more than one outbreak might occur in a given 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 74% of influenza seasons since 1982, 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 59% of seasons, the peak was in February or later (*425*).

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. In particular, some recent studies raise the possibility that very early vaccination of adults, particularly the elderly, might contribute to reduced protection later in the season. Protective antibody levels decline over time postvaccination (*426*–*428*). However, one study of HA and

neuraminidase antibody levels following vaccination of adults noted a slow decline, with a 2-fold decrease in titer taking >600 days (*429*). A review of studies reporting postvaccination seroprotection rates among adults aged ≥60 years noted that seroprotection levels meeting Committee of Proprietary Medicinal Products standards were maintained for ≥4 months for the H3N2 component in all 8 studies and for the H1N1 and B components in 5 of 7 studies (*430*).

Several observational studies of influenza vaccine effectiveness have reported decreased vaccine protection within a single season, particularly against influenza A(H3N2) (*118*–*121*). Some have noted a more pronounced decline in protection among older adults. However, this effect has not been observed consistently across age groups and seasons, and the observed decline in protection could be attributable to other factors, such as increased circulation of antigenically drifted variants over the course of the influenza season. A test negative case-control study of children and adults conducted in Navarre, Spain during the 2011–12 season noted a decline in vaccine effectiveness, from 61% (95% CI = 5–84) in the first 100 days after vaccination to 42% (95% CI = -39–75) between days 100–119 and then to -35% (95% CI = -211–41) after ≥120 days. Persons vaccinated ≥120 days before diagnosis were at an increased risk for contracting influenza, when compared with those vaccinated <100 days (OR: 3.45; 95% CI = 1.10–10.85; p = 0.034) (*119*). This decline primarily affected persons aged ≥65 years, among whom the OR for influenza was 20.81 (95% CI = 2.14–202.71; p = 0.009) for persons vaccinated >120 days before diagnosis versus those vaccinated <100 days before diagnosis. A similar study conducted in the United Kingdom, also during the 2011–12 season, estimated an overall vaccine effectiveness against A(H3N2) of 53% (95% CI = 0–78) among those vaccinated <3 months prior, and 12% (95% CI = -31–41) for those vaccinated ≥3 months prior. The proportion of older participants was too small to detect a substantial difference in vaccine effectiveness in this age group (*121*). An additional case-control analysis from the 2007–08 season revealed a modest but significant increase in the OR for A(H3N2) influenza every 14 days after vaccination among young children (OR for influenza increasing 1.2 for each 14-day interval for children aged 2 years) and older adults (1.3 for each 14-day interval for adults aged 75 years); the same pattern was not observed among older children and younger adults (*118*). The inconsistent evidence for intraseason waning of influenza vaccine protection makes drawing conclusions difficult, and further evaluation of this effect in larger studies and different seasons is needed.

Although delaying vaccination until later in the season might result in greater immunity later in the season, such deferral might also 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 onset of influenza circulation occurs. Revaccination later in the season of persons who have already been fully vaccinated is not recommended. ACIP will continue to evaluate additional data as they become available.

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. Although vaccination by the end of October is recommended, vaccine administered in December or later, even if influenza activity has already begun, is likely to be beneficial in the majority of influenza seasons.

Guidance for Use in Specific Populations

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 who do not have contraindications (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–18 years) who are receiving long-term aspirin therapy and who might be at risk for experiencing Reye syndrome after influenza virus infection;
- residents of nursing homes and other long-term care facilities;
- American Indians/Alaska Natives; and
- persons who are extremely obese (BMI ≥40).

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

All persons aged ≥6 months without contraindications should be vaccinated annually; however, 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, including 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.
- household contacts (including children) and caregivers of children aged ≤59 months (i.e., aged <5 years) and adults aged ≥50 years, particularly 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.

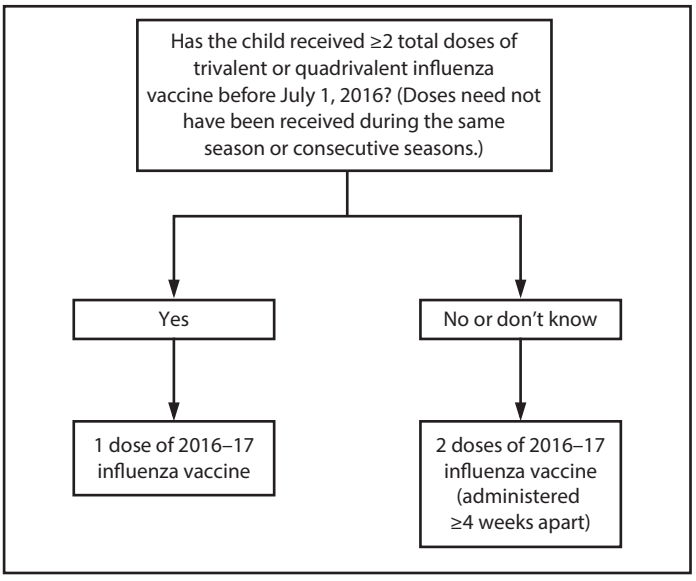
ACIP recommends that LAIV4 not be used during the 2016–17 season for any population. Should LAIV be available, providers who elect to use it should consider previous guidance for use of LAIV4 for persons who care for or have contact with immunocompromised persons. Health care personnel and persons who are contacts of persons in these groups and who are contacts of severely immunocompromised persons (those living in a protected environment) may receive any IIV or RIV influenza vaccine that is otherwise indicated. ACIP and HICPAC have previously recommended that health care personnel who receive LAIV4 should avoid providing care for severely immunosuppressed patients requiring a protected environment for 7 days after vaccination, and that hospital visitors who have received LAIV4 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 (*431*).

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 for optimal protection (*138–141*). Several studies using serologic endpoints have indicated that intervals between two initial doses from 4 weeks to 1 year produce similar immune responses when the antigens in the 2 doses are the same (*432–434*). Because of the change in vaccine composition for the 2016–17 season, children aged 6 months through 8 years will need to have received ≥2 doses of influenza vaccine previously to require only 1 dose for the 2016–17 season.

For 2016–17, ACIP recommends that children aged 6 months through 8 years who have previously received ≥2 total doses of trivalent or quadrivalent influenza vaccine before July 1, 2016 require only 1 dose for 2016–17. The two previous doses need not have been given during the same season or consecutive seasons. Children in this age group who have not previously received a total of ≥2 doses of trivalent or quadrivalent influenza vaccine before July 1, 2016 require 2 doses for the 2016–17 season. The interval between the 2 doses should be at least 4 weeks (Figure).

FIGURE. Influenza vaccine dosing algorithm for children aged 6 months through 8 years — Advisory Committee on Immunization Practices, United States, 2016–17 influenza season



Influenza Vaccination of Pregnant Women

Because pregnant and postpartum women are at higher risk for severe illness and complications from influenza than women who are not pregnant, the ACIP recommends that all women who are pregnant or who might be pregnant in the upcoming influenza season receive IIV. Influenza vaccination can be administered at any time during pregnancy, before and during the influenza season. The ACIP recommends that LAIV4 not be used in any population for the 2016–17 season; providers considering its use should note that LAIV4 should not be used during pregnancy.

Vaccination of Older Adults

For persons aged ≥65 years, any age-appropriate IIV formulation (standard-dose or high-dose, trivalent or quadrivalent, unadjuvanted or adjuvanted) or RIV3 is an acceptable option. No preference is expressed for any one of these vaccines over another for this age group. High-dose IIV3 (available as Fluzone High-Dose) is licensed 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. 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 (*180*–*183*). In a randomized controlled trial comparing high-dose versus standard-dose IIV3, conducted among over 30,000 community-dwelling persons aged ≥65 years, high-dose IIV3 was 24.2% more effective in preventing LCI associated with protocol-defined ILI (*184*).

In addition to standard-dose IIV3 and IIV4 and high-dose IIV3, aIIV3 (licensed for persons aged ≥65 years) is expected to be available for the 2016–17 season. No data directly comparing high-dose IIV3 and aIIV3 are available. ACIP will continue to review data related to the relative effectiveness of these vaccines in older adults.

Vaccination of Immunocompromised Persons

Immunocompromised states are caused by a heterogeneous range of conditions. In many instances, limited data are available regarding the use of influenza vaccines in the setting of specific immunocompromised states. The ACIP recommends that LAIV4 not be used in any population for the 2016–17 season; providers considering its use should note that live virus vaccines should not be used for persons with most forms of altered immunocompetence (*8*), given the uncertain but biologically plausible risk for disease attributable to the vaccine virus. In addition to potential safety issues, immune response to live or inactivated vaccines might be blunted in some clinical situations, such as for persons with congenital immune deficiencies, persons receiving cancer chemotherapy, and persons receiving immunosuppressive medications. For this reason, timing of vaccination might be a consideration (e.g., vaccinating during some period either before or after an immunocompromising intervention).

The Infectious Diseases Society of America (IDSA) has published detailed guidance for the selection and timing of vaccines for persons with specific immunocompromising conditions, including congenital immune disorders, stem cell and solid organ transplant, anatomic and functional asplenia, and therapeutic drug-induced immunosuppression, as well as for persons with cochlear implants or other conditions leading to persistent cerebrospinal fluid-oropharyngeal communication (*435*). ACIP will continue to review accumulating data on use of influenza vaccines in these contexts.

Influenza Vaccination of Persons with a History of Egg Allergy

Severe allergic reactions, including anaphylaxis, can occur in response to various components of all types of vaccines. Such reactions are fortunately rare. A VSD study of over 25.1 million doses of vaccine of various types (i.e., not exclusively influenza vaccines) administered to children and adults revealed a total of 33 cases of reactions consistent with anaphylaxis, giving a rate of 1.31 (95% CI = 0.90–1.84) per 1 million vaccine doses. In eight cases, symptoms began within 30 minutes of vaccination; however, in 21 cases, symptom onset was >30 minutes postvaccination, including one case in which symptoms began the following day. Among more than 7.4 million doses of IIV3 given without other vaccines, there were 10 cases of anaphylaxis (1.35; 95% CI = 0.65–2.47 per 1 million doses) (*419*).

As is the case for other vaccines, influenza vaccines contain various different components that might cause allergic and anaphylactic reactions. Not all such reactions are related to egg proteins; however, the possibility of reactions to influenza vaccines in egg-allergic persons might be of concern to these persons and vaccine providers. With the exceptions of RIV3 and ccIIV4, currently available influenza vaccines are prepared by propagation of virus in embryonated eggs. Not all manufacturers disclose ovalbumin content in their package inserts. Among influenza vaccines for which ovalbumin content was disclosed during the 2011–12 through 2014–15 seasons, reported maximum amounts were ≤1 μg/0.5 mL dose for IIVs and <0.24 μg/0.2 mL dose for LAIV4. Of the two vaccines

produced using nonegg based technologies, RIV3 (Flublok; Protein Sciences, Meriden, Connecticut) and ccIIV4 (Flucelvax Quadrivalent; Seqirus, Holly Springs, North Carolina), only Flublok is considered egg-free. 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 (Seqirus, unpublished data, 2016).

Reviews of studies of experience with use of IIV, and more recently LAIV, indicate that severe allergic reactions to the currently available egg-based influenza vaccines in persons with egg allergy are unlikely. In a 2012 review of published data, including 4,172 egg-allergic patients (513 reporting a history of severe allergic reaction) there were no noted occurrences of anaphylaxis following administration of IIV3, though some milder reactions did occur (*436*). Subsequently, several evaluations of LAIV use in persons with egg allergy have been published. In a prospective cohort study of children aged 2 through 16 years (68 with egg allergy and 55 without), all of whom received LAIV, none of the egg-allergic subjects developed signs or symptoms of an allergic reaction during the one hour of postvaccination observation, and none reported adverse reactions that were suggestive of allergic reaction or that required medical attention after 24 hours (*437*). In a larger study of 282 egg-allergic children aged 2 through 17 years (115 of whom had experienced anaphylactic reactions to egg previously), no systemic allergic reactions were observed after LAIV administration (*438*). Eight children experienced milder, self-limited symptoms that might have been caused by an IgE-mediated reaction. In another study of 779 egg-allergic children aged 2 through 18 years (270 of whom had previous anaphylactic reactions to egg), no systemic allergic reactions occurred. Nine children (1.2%) experienced milder symptoms, possibly allergic in nature within 30 minutes of vaccination (four rhinitis, four localized/contact urticaria, and one oropharyngeal itching) (*439*). A study that compared adverse reactions in eight egg-allergic and five nonegg-allergic children when given increasing doses of egg protein (*440*) showed only mild symptoms of rhinitis after exposure to 10–100 μg. This is substantially more than the concentration of ovalbumin reported on the LAIV package insert (<0.24 μg per 0.2 mL dose). All eight egg-allergic children tolerated LAIV doses without any allergic symptoms. These data indicate that LAIV4 may be administered safely to persons with a history of egg allergy. However, ACIP recommends that LAIV4 not be used in any population during the 2016–17 season because of concerns regarding effectiveness against influenza A(H1N1)pdm09.

Occasional cases of anaphylaxis in egg-allergic persons have been reported to the Vaccine Adverse Event Reporting System (VAERS) after administration of influenza vaccines (*420*,*421*). ACIP will continue to review available data regarding anaphylaxis cases following influenza vaccines.

Persons 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. 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 directed against egg proteins (*441*).

Although RIV does not contain egg protein, it has been associated with anaphylactic and other, less severe reactions reported in VAERS. A review of VAERS reports from January 2013 through June 2014 noted 12 reports that included signs and symptoms consistent with acute hypersensitivity reactions following administration of RIV3 (*442*). All were considered to be consistent with possible anaphylaxis; 3 cases appeared to meet Brighton Collaboration criteria (426) for level 2 anaphylaxis. Although it is not possible to infer causality from these data, they illustrate that allergic reactions following influenza vaccination are not necessarily related to egg proteins. A randomized safety study of RIV3 versus a licensed comparator IIV3 among adults aged ≥50 years found RIV to be noninferior to IIV3 with regard to the occurrence of expert-adjudicated events of likely hypersensitivity (*443*).

For the 2016–17 influenza season, ACIP recommends the following:

1. Persons with a history of egg allergy who have experienced only hives after exposure to egg should receive influenza vaccine. Any licensed and recommended influenza vaccine (i.e., any age-appropriate IIV or RIV3) that is otherwise appropriate for the recipient's age and health status may be used.
2. Persons who report having had reactions to egg involving symptoms other than hives, such as angioedema, respiratory distress, lightheadedness, or recurrent emesis; or who required epinephrine or another emergency medical intervention, may similarly receive any licensed and recommended influenza vaccine (i.e., any age-appropriate IIV or RIV3) that is otherwise appropriate for the recipient's age and health status. The selected vaccine should be administered in an inpatient or outpatient medical setting (including but not necessarily limited to hospitals, clinics, health departments, and physician offices). Vaccine administration should be supervised by a health care provider who is able to recognize and manage severe allergic conditions.
3. A previous severe allergic reaction to influenza vaccine, regardless of the component suspected of being responsible for the reaction, is a contraindication to future receipt of the vaccine.

Use of Influenza Antiviral Medications

Administration of IIV to persons receiving influenza antiviral drugs for treatment or chemoprophylaxis is acceptable. ACIP recommends that LAIV4 should not be used during the 2016–17 season. However, if used, LAIV4 should not be administered until 48 hours after cessation of influenza antiviral therapy, because antiviral drugs reduce replication of influenza viruses (*444*). If influenza antiviral medications are administered within 2 weeks after receipt of LAIV4, the LAIV4 dose should be repeated ≥48 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 LAIV4 may be revaccinated with another appropriate vaccine formulation (e.g., IIV or RIV).

Vaccination Issues for Travelers

In temperate climate regions of the Northern and Southern hemispheres, influenza activity is seasonal, occurring approximately from October through May in the Northern Hemisphere and April through September in the Southern Hemisphere. In the tropics, influenza occurs throughout the year. Travelers can be exposed to influenza when travelling to an area where influenza is circulating, or when traveling as part of large tourist groups (e.g., cruise ships) that include persons from areas of the world in which influenza viruses are circulating (*445*,*446*). In a survey among Swiss travelers to tropical and subtropical countries, influenza was the most frequently acquired vaccine-preventable disease (*447*). Among 109 travelers returning to Australia from travel in Asia who reported acute respiratory infection symptoms, 4 had evidence of influenza A infection (evidenced by fourfold rise in antibody titer) (*448*).

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

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

No information is available indicating a benefit to revaccinating persons before summer travel who already were vaccinated during the preceding fall. Revaccination is not recommended. Persons at high risk who receive the previous season's vaccine before travel should receive the current vaccine the following fall or winter. Persons at higher risk for influenza complications should consult with their health care practitioner to discuss the risk for influenza or other travel-related diseases before embarking on travel during the summer.

Influenza vaccine formulated for the Southern Hemisphere might differ in viral composition from the Northern Hemisphere vaccine. However, Southern Hemisphere formulation seasonal influenza vaccines generally are not licensed or commercially available in the United States. More information on influenza vaccines and travel is available at http://www.cdc.gov/flu/travelers/travelersfacts.htm.

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 (*449*) 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 (*450*).

In the absence of specific data indicating interference, following ACIP's general recommendations for vaccination is prudent (*8*). Inactivated vaccines do not interfere with the immune response to other inactivated vaccines or to live vaccines. LAIV4 is not recommended for use in 2016–17. Providers considering its use should note that although inactivated or live vaccines can be administered simultaneously with LAIV4, after administration of a live vaccine (such as LAIV4), at least 4 weeks should pass before another live vaccine is administered.

Influenza Vaccine Composition and Available Products

Influenza Vaccine Composition for the 2016–17 Season

All influenza vaccines licensed in the United States will contain HA derived from influenza viruses antigenically identical to those recommended by FDA (*451*). Both trivalent and quadrivalent influenza vaccines will be available in the United States (Table 1).

The 2016–17 U.S. influenza vaccines will contain HA derived from the following:

- an A/California/7/2009 (H1N1)–like virus,
- an A/Hong Kong/ 4801/2014 (H3N2)–like virus, and
- a B/Brisbane/60/2008–like virus (Victoria lineage).

The 2016–17 U.S. quadrivalent vaccines will contain the same three antigens, and an additional influenza B virus HA, derived from a B/Phuket/3073/2013–like virus (Yamagata lineage). The composition for 2016–17 represents a change in the influenza A(H3N2) virus and a switch in lineage for the influenza B viruses.

Vaccine Products for the 2016–17 Season

A variety of influenza vaccine products are licensed (Table 1) and available from several different manufacturers. For many vaccine recipients, more than one type or brand of vaccine might be appropriate within indications and ACIP recommendations. A licensed, age-appropriate influenza vaccine product should be used. 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, fewer postmarketing safety and effectiveness data are available, 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. Vaccination should not be delayed in order to obtain a specific product when an appropriate one is already available. Moreover, these recommendations apply to all licensed influenza vaccines used within Food and Drug Administration–licensed indications, including changes in FDA-approved labeling that might occur after publication of this document. Differences between ACIP recommendations and labeled indications are noted (Table 1).

Recently Licensed Influenza Vaccine Products

Fluad (MF59-Adjuvanted Standard-dose IIV3 [aIIV3])

In November 2015, FDA licensed Fluad (Seqirus, Holly Springs, North Carolina), a trivalent, MF59-adjuvanted inactivated influenza vaccine, for persons aged ≥65 years. Fluad is the first adjuvanted influenza vaccine marketed in the United States. It is a standard-dose vaccine, containing 15 μg of HA per vaccine virus per dose. Contraindications and precautions are similar to those for other inactivated influenza vaccines (see Contraindications and Precautions for the Use of IIV) (Table 2) (*314*).

In clinical studies comparing Fluad with the nonadjuvanted IIV3 among persons aged 65 years and over, the solicited adverse reactions reported by ≥10% of participants who received Fluad included injection site pain, (25.0% versus 12.2%), tenderness (21.1% versus 11.2%), myalgia (14.7% versus 9.7%), headache (13.2% versus 11.2%) and fatigue (13.3% versus 10.4%). In a comparison of immunogenicity of the two vaccines, Fluad met criteria for noninferiority for all three vaccine viruses based on predefined thresholds for seroconversion rate differences and GMT ratios (*314*). In a Canadian observational study of 282 persons aged ≥65 years conducted during the 2011–12 season that compared Fluad with unadjuvanted IIV3, the relative effectiveness of Fluad against LCI was 63% (95% CI = 4–86) (*452*). To date, there have been no randomized studies comparing Fluad with Fluzone High-Dose, which is also indicated for this age group and has demonstrated improved efficacy over standard-dose IIV3 in a randomized controlled trial (*184*).

Flucelvax Quadrivalent (Cell Culture-Based IIV4 [ccIIV4])

In May 2016, FDA licensed Flucelvax Quadrivalent (Seqirus, Holly Springs, North Carolina), a cell culture-based IIV4, for persons aged ≥4 years. Similarly to the previously licensed trivalent formulation of Flucelvax, Flucelvax Quadrivalent is prepared from virus propagated in Madin-Darby canine kidney cells rather than in eggs. Prelicensure data included two separate immunogenicity and safety studies conducted among persons aged ≥18 years and 4 through 17 years, respectively. Each study compared ccIIV4 with two licensed comparator ccIIV3s (the trivalent formulation of Flucelvax), each containing one of the two influenza B viruses included in the IIV4. Flucelvax Quadrivalent met criteria for immunogenic noninferiority in both studies (*453*,*454*). Among adults aged 18 through 64 years, solicited adverse reactions reported by ≥10% of participants who received Flucelvax Quadrivalent were injection-site pain (45.4%) headache (18.7%), fatigue (17.8%) myalgia (15.4%), injection-site erythema (13.4%), and induration (11.6%); among persons aged ≥65 years these were injection-site pain (21.6%) and injection-site erythema (11.9%). Among children, solicited adverse reactions reported by ≥10% of participants who received Flucelvax Quadrivalent were as follows: among children aged 4 through 5 years, tenderness at the injection site (46%), injection-site erythema (18%), sleepiness (19%), irritability (16%), injection-site induration (13%) and change in eating habits (10%); among children aged 6 through 8 years pain at the injection site (54%), injection-site erythema (22%), injection-site induration (16%), headache (14%), fatigue (13%) and myalgia (12%); and among children aged 9 through 17 years pain at the injection site (58%), headache (22%), injection-site erythema (19%), fatigue (18%) myalgia (16%), and injection-site induration (15%). In general, prevalences of these events were similar to those observed with the comparator trivalent vaccines.

TABLE 2. Contraindications and precautions to the use of influenza vaccines — United States, 2016–17 influenza season*

Vaccine	Contraindications	Precautions
IIV	History of severe allergic reaction to any component of the vaccine† 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	**For the 2016–17 season, ACIP recommends that LAIV not be used. Content below is provided for information.**	
	History of severe allergic reaction to any component of the vaccine† or after a previous dose of any influenza vaccine Concomitant aspirin or salicylate-containing therapy in children and adolescents Children aged 2 through 4 years who have received a diagnosis of asthma or whose parents or caregivers report that a health care provider has told them during the preceding 12 months that their child had wheezing or asthma or whose medical record indicates a wheezing episode has occurred during the preceding 12 months Children and adults who have immunosuppression (including immunosuppression caused by medications or by HIV) Close contacts and caregivers of severely immunosuppressed persons who require a protected environment Pregnancy Receipt of influenza antiviral medication within the previous 48 hours	Moderate to severe illness with or without fever History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine Asthma in persons aged ≥5 years Other underlying medical conditions that might predispose to complications after wild-type influenza infection (e.g., chronic pulmonary, cardiovascular [except isolated hypertension], renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus)

Abbreviations: ACIP = Advisory Committee on Immunization Practices; IIV = Inactivated Influenza Vaccine; LAIV = Live-Attenuated Influenza Vaccine; RIV = Recombinant Influenza Vaccine.

* Immunization providers should check Food and Drug Administration–approved prescribing information for 2016–17 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.

† History of severe allergic reaction (e.g., anaphylaxis) to egg is a labeled contraindication to the use of IIV and LAIV. However, ACIP recommends that any licensed, recommended, and appropriate IIV or RIV may be administered to persons with egg allergy of any severity (see Influenza Vaccination of Persons with a History of Egg Allergy).

In addition to the new licensure of Flucelvax Quadrivalent, the trivalent formulation of Flucelvax, which was previously licensed for persons aged ≥18 years, is now licensed for persons aged ≥4 years. Licensure was based upon evaluation of immunogenicity of Flucelvax versus Fluvirin (egg-based standard-dose IIV3; Seqirus, Holly Springs, North Carolina) in children 4 through 17 years of age (*455*). In this analysis, prespecified criteria for noninferiority of Flucelvax were not met for the A(H3N2) component for children 4 through 8 years of age; however, other immunogenicity endpoints for A(H3N2) were met. It is anticipated that the trivalent formulation of Flucelvax will not be available for 2016–17, and will instead be replaced by the new quadrivalent formulation.

Storage of Influenza Vaccines

In all instances, approved manufacturer packaging information should be consulted for authoritative guidance concerning storage of all influenza vaccines. Vaccines should be protected from light and stored at recommended temperatures. In general, influenza vaccines should be refrigerated between 2° to 8° C (36° to 46° F) and should not be frozen; vaccine that has frozen should be discarded. Single-dose vials should not be accessed for more than 1 dose. Multi-dose vials should be returned to recommended storage conditions between uses, and once accessed should not be kept beyond the recommended period of time. In addition, the cold chain must be maintained when LAIV4 is transported. For information on permissible temperature excursions and other departures from recommended storage conditions that are not discussed in the package insert, contact the manufacturer. Vaccine should not be used after the expiration date on the label.

Inactivated Influenza Vaccines (IIVs)

Available products: IIVs comprise a large group of products. For the 2016–17 season, both IIV4 and IIV3 products are expected to be available. All IIVs are manufactured through propagation of virus in eggs, with the exception of the cell culture-based vaccine Flucelvax Quadrivalent (Seqirus, Holly Springs, North Carolina), for which (similarly to the previous trivalent formulation of Flucelvax) vaccine viruses are propagated in Madin-Darby canine kidney cells. All IIVs licensed in the United States contain no adjuvant, with the exception of the recently approved MF59-adjuvanted trivalent inactivated influenza vaccine, Fluad (Seqirus, Holly Springs, North Carolina).

As a class, IIVs include products that can 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 (Seqirus, Parkville, Victoria, Australia) 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 Seqirus's 2010 Southern Hemisphere IIV3 (*288*). 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.

Dosage and administration: All IIV preparations contain 15 μg of HA per vaccine virus strain (45 μg total for IIV3s and 60 μg total for IIV4s) per 0.5 mL dose, with two exceptions. Fluzone High Dose (Sanofi Pasteur, Swiftwater, Pennsylvania), an IIV3 licensed for persons aged ≥65 years, contains 60 μg of each HA per vaccine virus strain (180 μg total) (*456*). Fluzone Intradermal Quadrivalent (Sanofi Pasteur, Swiftwater, Pennsylvania), an intradermally administered IIV4 licensed for persons aged 18 through 64 years, contains 9 μg of each HA per vaccine virus strain (36 μg total) (*457*).

The one IIV product currently licensed by FDA for children aged 6 through 35 months contains 0.25 mL/dose, containing 7.5 μg of HA per vaccine virus strain (Fluzone Quadrivalent; Sanofi Pasteur, Swiftwater, Pennsylvania). 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 (containing 15 μg of HA per vaccine virus strain). 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.

With the exception of Fluzone Intradermal Quadrivalent (Sanofi Pasteur, Swiftwater, Pennsylvania), IIVs are 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 (*8*). Fluzone Intradermal Quadrivalent is administered intradermally, preferably over the deltoid muscle, using the included delivery system (*457*). One IIV3, Afluria (Seqirus, Parkville, Victoria, Australia) is licensed for intramuscular administration via jet injector (Stratis; Pharmajet, Golden, Colorado) for persons aged 18 through 64 years (*458*).

Trivalent versus quadrivalent IIVs: Both trivalent and quadrivalent IIVs will be available during the 2016–17 season. Quadrivalent vaccines contain one virus from each of the two influenza B lineages (one B/Victoria virus and one B/Yamagata virus), whereas trivalent vaccines contain one influenza B virus from one lineage. Quadrivalent vaccines are thus designed to provide broader protection against circulating influenza B viruses. However, no preference is expressed for either IIV3 or IIV4.

IIVs and persons aged ≥65 years: In addition to various formulations of standard-dose IIV3 and IIV4, both high-dose IIV3 (HD-IIV3, available as Fluzone High-Dose) and adjuvanted IIV3 (aIIV3, available as Fluad) are 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 (*180–183*,*456*). Subsequently, a randomized trial comparing high-dose IIV3 with standard-dose IIV3 among >31,000 persons aged ≥65 years during the 2011–12 and 2012–13 seasons found 24.2% greater relative efficacy of high-dose vaccine in prevention of LCI associated with a protocol-defined ILI (*184*). 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 (*180–183*,*456*).

An MF59-adjuvanted trivalent inactivated influenza vaccine (aIIV3; Fluad, Seqirus, Holly Springs, North Carolina) was initially approved in the United States in November 2015. In prelicensure trials, aIIV3 elicited significantly greater antibody responses compared with nonadjuvanted IIV3, although predefined superiority criteria were not met (*459*). Reactogenicity, particularly pain, swelling, myalgia, headache, and fatigue, were reported more frequently among persons who received aIIV3; most of these reactions were mild in severity and were transient in nature (*459*).

No preferential recommendation is made for aIIV3, standard-dose IIV, or high-dose IIV3 for persons aged ≥65 years. Any age-appropriate vaccine may be used.

Contraindications and precautions for the 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, history of severe allergic reaction to the vaccine or any of its components (including egg) is a labeled contraindication to the receipt of IIV (Table 2). However, ACIP makes specific recommendations for the use of influenza

vaccine in persons with egg allergy (see Influenza Vaccination of Persons with a History of Egg Allergy). Influenza vaccine is not recommended for persons with a history of severe allergic reaction to the vaccine or to components other than egg. Information about vaccine components is located in package inserts from each manufacturer. Prophylactic use of antiviral agents is an option for preventing influenza among persons who cannot receive vaccine.

Moderate or severe acute illness with or without fever is a general precaution for vaccination (*8*). 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 (RIV3)

Available products: One RIV product, Flublok, a trivalent recombinant HA vaccine, is available for the 2016–17 influenza season. RIV3 is indicated for persons aged ≥18 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 RIV3 versus IIV within specified indications.

Dosage and administration: RIV3 is administered by intramuscular injection. A 0.5 mL dose contains 45 μg of HA derived from each vaccine virus (135 μg total).

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 (*8*). 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.

Live Attenuated Influenza Vaccine (LAIV4)

For the 2016–17 season, ACIP recommends that LAIV4 not be used. As it is a licensed vaccine and might be available during 2016–17, the material in this section is provided for information.

Dosage and administration: LAIV4 is administered intranasally using the supplied 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. 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.

Contraindications and precautions: ACIP recommends that LAIV4 not be used during the 2016–17 season. Previously issued guidance regarding contraindications and precautions is provided for informational purposes (Table 2).

Additional Sources for Information Regarding Influenza

Influenza 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 (VAERS)

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 (https://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 https://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 (NVICP)

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/vaccineinjurytable.pdf) lists the vaccines covered by VICP and the associated injuries and conditions (including death) that might 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 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 might be eligible to file a claim. Additional information is available at http://www.hrsa.gov/vaccinecompensation or by calling 1-800-338-2382.

Additional Resources

ACIP Statements

- ACIP General Recommendations on Immunization, 2011. MMWR Recomm Rep2011;60(No. RR-2). http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm.
- ACIP Immunization of Healthcare Personnel. 2011. MMWR Recomm Rep 2011;60(No. RR-7). http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6007a1.htm.
- ACIP Adult Immunization Schedule, 2016: http://www.cdc.gov/vaccines/schedules/hcp/adult.html.
- ACIP Birth-18 Years and "Catch-Up" Immunization Schedules, 2016: http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html.

Vaccine Information Sheets (VISs)

- Provider Information: http://www.cdc.gov/vaccines/hcp/vis/vis-statements/flu-hcp-info.pdf.
- VIS for LAIV: http://www.cdc.gov/vaccines/hcp/vis/vis-statements/flulive.pdf.
- VIS for IIV and RIV: http://www.cdc.gov/vaccines/hcp/vis/vis-statements/flu.pdf.

Influenza Vaccine Package Inserts

- Trivalent Vaccines: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094045.htm.
- Quadrivalent Vaccines: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm295057.htm.

American Academy of Pediatrics (AAP) Guidance

- AAP Recommendations for Prevention and Control of Influenza in Children, 2016–17: http://redbook.solutions.aap.org/ss/influenza-resources.aspx.

Infectious Diseases Society of America (IDSA) Guidance

- 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host: http://cid.oxfordjournals.org/content/early/2013/11/26/cid.cit684.full

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8. CDC. General recommendations on immunization—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011;60(No. RR-2).
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