

Background Document for

“Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2017-18 Influenza Season”

Introduction

This document contains background material relevant to “Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2017-18 Influenza Season” (MMWR Recomm Rep 2017;66[no.RR-2]:1-20). The CDC/ACIP recommendations for use of influenza vaccines in various populations for the 2017-18 season, discussion of vaccines expected to be available, contraindications and precautions to vaccination, and relevant figures and tables may be found in the above-referenced MMWR document.

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) (1). Antibody to surface antigens, HA and NA, reduces likelihood of infection (2, 3). Antibody against one influenza virus type or subtype confers limited or no protection against another type or subtype (4). 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, can occur among influenza A viruses. Antigenic shifts occur less frequently than antigenic drift events, and generally arise through genetic reassortment. 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 (1). 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 (5, 6).

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 (7). Influenza B viruses from both lineages have co-circulated during most influenza seasons since the 1980s (8, 9). 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 (10). For 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 the precise timing of the onset, peak, and end of influenza activity varies from one season to the next, annual epidemics of 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) (11). More precise estimates of burden are provided by surveillance studies based on laboratory-confirmed influenza (12). 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 (13).

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 (14). Hospitalizations and deaths related to seasonal influenza are typically greatest among persons aged ≥65 years, children aged <5 years (particularly those aged <2 years), and persons of any age who have medical conditions that confer increased risk for complications from influenza (12, 15-23).

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 caused by exacerbations of underlying cardiac and pulmonary conditions that are associated with influenza infection (24-26). Thus, some authors use the broader category of respiratory and circulatory excess events for influenza burden estimates. During seasonal influenza epidemics from 1979–80 through 2000–01, the estimated annual overall number of influenza-associated hospitalizations in the United States ranged from approximately 55,000 to 431,000 per annual epidemic, with a mean of 226,000 (25). Between the 1976–77 and the 2006–07 season, estimated annual deaths in the United States attributable to influenza ranged from 3,349 to 48,614 each season (17). A subsequent modeling analysis of population-based surveillance data for seasons following the 2009 pandemic (2010–11 through 2012–13), which used a multiplier method developed to correct for under-detection 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 (27). Using similar methodology, estimates for the 2015-16 season were 25 million influenza illnesses, 11 million influenza-related medical visits, 310,000 influenza-related hospitalizations, and 12,000 P&I deaths (28).

Children

Influenza is an important cause of outpatient medical visits and hospitalizations among young children. In a long-term population-based retrospective cohort study conducted in three metropolitan areas (Nashville, Rochester, and Cincinnati), hospitalization rates for children aged < 5 years with acute respiratory illness or fever caused by laboratory-confirmed influenza averaged 0.9 per 1000 (range 0.4-1.5) for seasons 2000-01 through 2003-04 and 0.58 per 1000 (range 0.36 to 0.97) for the seasons 2004-05 through 2008-09 (12, 29). 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 (19). 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 (30). 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 emergency department visits ranged from 89 to 620 per 10,000 children per year (31).

Estimated rates of influenza-associated hospitalization generally are substantially higher among infants and children <5 years than among older children (12, 20, 29, 32-38). 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 (36). Estimates of influenza-related hospitalization rates for children with high-risk medical conditions are higher than for those without (20, 39, 40). In a study of children in 3 U.S. cities of children hospitalized with confirmed influenza infection, length of stay was longer for those with high-risk conditions than for healthy children of the same age (4.7 vs. 3.0 days for those aged 6 through 23 months; 5.8 vs. 3.6 days for those aged 2 through 17 years) (34). Thirty-seven percent had an ACIP-defined high risk condition; the most common high-risk conditions were asthma (45%), followed by neurological (23%), cardiovascular (21%), metabolic and immunosuppressive disorders (7% each). In another study, asthma was associated with 23% of the influenza hospitalizations and 15% of the outpatient visits (39).

Estimates of influenza mortality rates for children based on pneumonia and influenza diagnoses, respiratory and circulatory diagnoses, or confirmed influenza have generally been low, <1 per 100,000 person-years (24, 34, 41, 42). However, the absolute number of pediatric deaths varies from season to season (43). Moreover, it is important to note that these deaths often occur in children with no other risk factors for severe influenza illness. In one study of the 2003-04 season, nearly half occurred in previously healthy children (42). In the United States, death associated with laboratory-confirmed influenza (LCI) among children aged <18 years has been a nationally reportable condition since October 2004 (41). Since reporting began, the annual number of reported influenza-associated pediatric deaths during regular influenza seasons has ranged from 37 deaths in the 2011-12 season to a high of 171 in 2012-13 (43). 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 (44).

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, 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 5.2 million illnesses, 2.4 million outpatient visits, 31,800 hospitalizations, and 684 deaths (45). Studies of worker vaccination have reported lower rates of ILI (46, 47), lost work time (46-49), and health care visits (47, 49) 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 (50) 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 crude rates of LCI-related hospitalization for the Emerging Infections Program (EIP; 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 (51). 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 (52).

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 1996–97 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) (22). In a retrospective study of adults hospitalized with laboratory-confirmed influenza during the 2014–15 season, when compared with patients under 80 years of age, patients aged 80 years or older had a lower glomerular filtration rate (mean: 49.7 mL/min vs. 62.2 mL/min; $p=0.006$), a greater need for non-invasive mechanical ventilation (22% vs 9%; $p=0.02$), greater co-morbidity due to cardiac insufficiency (40% vs. 16%; $p<0.001$) and/or chronic renal disease (32.9 vs. 20%, $p=0.03$), and elevated mortality (19% vs. 3%; $p<0.001$) (53).

Deaths associated with influenza are most frequent among older adults. From the 1976–77 through 2006–07 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 (17). 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 (27).

Pregnant Women and Neonates

Pregnant women are vulnerable to severe symptoms and illness attributable to influenza. Physiologic changes associated with pregnancy, such as altered cardiopulmonary mechanics and changes in cell mediated immunity, might contribute to enhanced susceptibility (54). 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 non-influenza acute respiratory illness (55). Case reports and some observational studies suggest that pregnancy increases the risk for hospitalization and serious maternal medical complications (56-58). 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 (58).

Increased severity of influenza among pregnant women was reported during the pandemics of 1918–19, 1957–58, and 2009–10 (59-64). During the 2009(H1N1) pandemic, severe infections among postpartum (delivered within previous 2 weeks) women also were observed (60, 63, 65). In a case series conducted during the 2009(H1N1) pandemic, 56 deaths were reported among 280 pregnant women admitted to intensive care units. Among U.S. deaths due to pandemic influenza reported to CDC, five percent of all US deaths from pandemic influenza involved pregnant women, even though they represented <1% of the population (66, 67). Among the deaths, 36 (64%) occurred in the third trimester. Pregnant women who were treated with neuraminidase inhibitor 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 publically available hospital discharge database; 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 (68). 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) (69). 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 (70). However, other studies of infants born to women with LCI during pregnancy have not shown higher rates of prematurity, preterm labor,

low birth weight, or lower Apgar scores compared with infants born to uninfected women (71-73).

Influenza symptoms often include fever, which during pregnancy might be associated with neural tube defects and other adverse outcomes (74). 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) (75). A 2005 meta-analysis of fifteen observational studies noted an association between maternal fever and neural tube defects (76). Associations between maternal fever and congenital heart defects (77) and orofacial cleft (78) have been reported in some studies; in one study of congenital anomalies such as orofacial clefts, congenital heart defects, and omphalocele, the association with maternal fever was ameliorated among those mothers who had taken multivitamins (79).

Persons with Increased Risk for Severe Influenza Illness and Complications

In the first U.S. recommendations for annual influenza vaccination of the civilian population, 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 (80). 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 and immunosuppression (81). 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. While some observational studies (mostly conducted prior to the widespread use of highly effective antiretroviral therapy) noted increased likelihood of severe influenza illness among persons with HIV infection, more recent studies indicate that there may be no increased risk of severe disease among persons in for whom HIV is well-controlled (82-90).

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 (91-93). In a case-cohort study, among persons aged ≥ 20 years, hospitalization with illness attributable to laboratory confirmed 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) (94). 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) (95). 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 (96).

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 (97–102). 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 (101, 103). 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 (104).

Immunogenicity, Efficacy, and Effectiveness of Influenza Vaccines

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 estimates 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 (105).

Randomized controlled trials that measure LCI virus infections (by viral culture or reverse transcription polymerase chain reaction [RT-PCR]) as the outcome provide the best and most persuasive evidence of vaccine efficacy, but such data are not available for all populations. Such studies are difficult to perform in populations for which influenza vaccination is already recommended. Observational studies, particularly those that compare non-influenza-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 (106, 107). Bias due to frailty (a characteristic which can be

associated with both a lower likelihood of vaccination and increased likelihood of severe illness) is also a concern in observational studies. 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 (108).

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% in classic case-control studies (109). In a simulation study which evaluated the effects of different values of influenza diagnostic test sensitivity and specificity on vaccine effectiveness estimates from cohort, classic case-control, and test-negative designs, it was concluded that misclassification resulted in slightly more biased VE estimates for test-negative studies than for other designs. However, the degree of bias was not thought to be meaningful when realistic combinations of attack rates, sensitivity, and specificity were considered (110).

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 of 295,000 hospitalizations associated with P&I of (95% CI = 139,000–451,000) and a 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 (111). 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 against hemagglutinin are considered to be correlates of vaccine-induced protection for inactivated influenza vaccines (IIVs) (2). 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 (3, 112-114). Most healthy children and adults have high titers of strain-specific antibody after IIV vaccination (113, 115). 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 (HAI) titer of 32 or 40) might not predict protection from infection on the individual level.

Compared with IIV, live attenuated influenza vaccine (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 (116).

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 (117).

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 (118). 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 (119), ILI in younger working adults (47), and LCI (120) 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 (121, 122). In addition to antigenic drift of circulating influenza viruses, vaccine viruses might undergo adaptive mutations during propagation in eggs that also can contribute to antigenic differences between vaccine virus and circulating viruses, which in some cases, has been suggested to contribute to reduced vaccine effectiveness (123).

Immunogenicity, Efficacy, and Effectiveness of Inactivated Influenza Vaccines (IIVs)

Inactivated influenza vaccines (IIVs) comprise the largest category of vaccines currently available. 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 (IIV4) in the United States during the 2013–14 season, both trivalent (IIV3) and quadrivalent 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.

In general, prelicensure studies of immunogenicity of the currently licensed IIV4s compared with corresponding IIV3 products from the same manufacturer have demonstrated superior immunogenicity for IIV4 for the added influenza B virus without interfering with immune responses to the remaining three vaccine viruses (124-132). Effectiveness studies conducted during some seasons have demonstrated that IIV3 provided similar protection against circulating influenza B viruses of both lineages. For example, 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 (133). Similarly, in an observational study conducted during the 2011-12 season, in which both B lineages co-circulated, effectiveness was similar for both (52%, 95%CI 8 to 75% for B/Victoria; and 66%, 95%CI 38 to 81% for B/Yamagata) (134). Cross-lineage protection was observed for IIV3 and ccIIV3 in a randomized trial (135); in another randomized trial of IIV3 there was no cross lineage protection (136).

Children

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 $p = 0.001$ for influenza B) (137). 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 (138). 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 (139). 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) (140). 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) (141). 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 (113). 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 (142); 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) (143).

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 (144, 145). 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 (143). 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

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 (146). 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 (47, 49). 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 (147).

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 (80). 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 (HD-IIV3), adjuvanted IIV3 (aIIV3), and quadrivalent recombinant influenza vaccine (RIV4) in this age group occurs below.

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 (148). 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). 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 (149). 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 (3), 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 (150). Limited or no increase in antibody response is reported among elderly adults when a second dose is administered during the same season (151–153).

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 (154). 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 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 (118).

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 laboratory-confirmed influenza (LCI) or influenza like illness (ILI) (155). 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) (156). 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 viruses matched circulating viruses. Vaccine was effective during sporadic activity, but only when vaccine matched (OR: 0.69; 95% CI = 0.48–0.99) (157).

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 (158-163). 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 (106, 107, 164-167). Several studies that have used methods to account for unmeasured confounding have reported effectiveness estimates for nonspecific serious outcomes such as P&I hospitalizations or all-cause mortality among community-dwelling older persons of $\sim 10\%$ or less, which is more plausible than higher estimates from earlier studies (168-170). 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) (171). In a study covering the 2007-08 through 2010-11 seasons, among outpatients aged ≥ 65 years presenting with ARI with RT-PCR-confirmed influenza, self-rated symptom severity was less for those who had been vaccinated than for those who had not (172). An analysis of data from the Influenza Hospitalization Surveillance Network (FluSurv-NET) for the 2012-13 season found no difference in symptom severity in vaccinated vs unvaccinated adults, but length of ICU stay was shorter for those aged 50 through 64 years who had been vaccinated (173). A subsequent study from the same network for 2013-14 found vaccination to be associated with reduced length of hospital and ICU stay among persons aged 50-64 years ≥ 65 years, as well as lower odds of in-hospital death in these age groups (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 specifically for this age group, in addition to standard-dose unadjuvanted IIVs and RIVs. Specific discussion of HD-IIV3, aIIV3, and RIV4 for older adults is discussed below (see *HD-IIV3, aIIV3, and RIV4 for Older Adults*).

Pregnant Women and Neonates

Passive transfer of anti-influenza antibodies from vaccinated women to neonates has been documented (180-182). Protection of infants through maternal vaccination has been observed in several studies. 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 to 85) in preventing LCI in their breastfed infants during the first 6 months of life (183). 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 to 71.2) among the HIV-uninfected mothers and 48.8% (95% CI = 11.6 to 70.4) among their infants (184). In a study conducted in Mali in which pregnant women were randomized to receive either IIV3 or quadrivalent meningococcal vaccine during the third trimester and infants were followed to detect LCI through 6 months of age, vaccine effectiveness against LCI among the infants was

67.9% (95%CI 35.2 to 85.3) through 4 months and 57.3% (95%CI 30.6 to 74.4) through 5 months; by six months of follow up effectiveness was 33.1% (95%CI 3.7 to 53.9) (185). A randomized placebo-controlled trial of year-round influenza vaccination in Nepal (where influenza circulates throughout the year, rather than seasonally), vaccine effectiveness against LCI among infants 0--6 months of age was 30% (95%CI = 5 to 48) for the full study period. Vaccines with two different compositions were used during this period; vaccine effectiveness for the vaccine used during the first period was 16% (95%CI -19 to 41) while that for the latter was 60% (95%CI = 26 to 88) (186).

Among observational studies, 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 to 98.1) (187). 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 to 0.93) and a 39% reduction in risk for ILI-associated hospitalization (RR: 0.61; 95% CI = 0.45 to 0.84) (188). 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 to 0.95) (189). In a case control study covering the 2010-11 and 2011-12 influenza seasons, vaccination of pregnant women reduced their risk of laboratory-confirmed influenza by approximately half (190).

Persons with Chronic Medical Conditions

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 (191). 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 to 75; $p = 0.01$), but no association was noted among children aged 6 through 12 years (192).

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 (193). 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 to 0.84) in oral steroid use in the 12 months before the survey (194). Other studies have failed to show any benefit against asthma exacerbation (195, 196).

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 (197).

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 to 66) compared with 60% (95% CI = 43 to 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 to 63) whereas it was 90% (95% CI = 68 to 97) among healthy adults (198).

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%. (199). 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 (200). 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 (106, 107).

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 to 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 (201). A systematic review of studies of influenza vaccine among COPD patients identified evidence of reduced risk for exacerbation from vaccination (202). 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 (203).

Evidence suggests that acute respiratory infections might trigger atherosclerosis-related acute vascular events (204). 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 (205, 206). 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) (207). 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) (208). 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 to 58), cardiovascular deaths (pooled effectiveness: 60%; 95% CI = 29 to 78); and hospitalization (pooled effectiveness 51%; 95% CI = 16 to 72) in vaccinated participants at one-year follow up (209). 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 (210).

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 to 50] for A(H1N1), by 67% [95% CI = 54 to 80] for A(H3N2), and by 38% [95% CI = 28 to 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) (211). A retrospective cohort study covering nine influenza seasons found reduced effectiveness of influenza vaccine against MAARI among statin users (212); however, this study did not evaluate confirmed influenza illness. In a population-based study of 3,285 adults aged 45 years and over covering the 2004-5 through 2014-15 influenza seasons, statin use was associated with lower vaccine effectiveness against LCI due to H3N2 viruses (vaccine effectiveness 45% [95%CI 27 to 59] for statin nonusers vs. -21% [95%CI -84 to 20] for statin users); statin use was not associated with lower vaccine effectiveness against H1N1pdm09 or B viruses (213).

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 (214). 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) (215).

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 (216). 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 (217). 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 among those who were obese, but not for the other viruses (218). In a small study involving 51 children aged 3–14 years with varying BMI measurements (219), 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 (220).

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 (221–223). Among persons who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, IIV might not induce protective antibody titers (223, 224); a second dose of vaccine does not improve immune response (224, 225). 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 (226). 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) (227). In a randomized study of a two-dose regimen of IIV3 vs. placebo conducted among 410 children aged 6–59 months (92% of whom were receiving antiretroviral therapy) in South Africa during 2009, vaccine efficacy was 17.7% (95% CI = 0 to 62.4). It was suggested that poor immunogenicity and drift of the circulating H3N2 virus contributed to the poor efficacy (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). It should be noted that high-dose IIV3 is currently licensed only for adults aged ≥ 65 years.

Observational studies suggest that immunogenicity among persons with solid organ transplants varies according to factors such as transplant type, time from transplant, and immunosuppressive regimen. In one review, overall seroprotective and seroconversion responses ranged from 15% to 93%, with lower responses seen in lung transplant and greater responses several years after kidney transplant (231). Among persons who have undergone kidney transplantation, seroresponse rates have been observed that were similar or slightly reduced compared with healthy persons (232–236). Response may be dependent upon time post-transplant. Antibody response among persons who were 6 months post kidney transplant were lower than observed for healthy controls in one prospective study (232). In another study, among kidney transplant recipients who were 3–10 years posttransplant, a 93% seroprotection rate to A(H1N1) antigen after vaccination was noted (233). In 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; $p < 0.001$) (237). A small study involving participants with liver transplants indicated a reduced immunologic response to influenza vaccinations (238); another study noted rates were lowest if vaccination occurred within the four months after the transplant procedure (239). In a randomized controlled trial among persons who had received various solid organ transplants (kidney, liver, heart, and lung) comparing one dose of IIV3 with two doses spaced 5 weeks apart, seroprotection rates were higher at 10 weeks postvaccination among those who received two doses; there was no significant difference at one year postvaccination. Prevalence of microbiologically diagnosed influenza was similar in the two groups (2/252, or 0.8%, in the one-dose group compared with 3/247, or 1.2%, in the two-dose group) (240).

Immunogenicity, Efficacy, and Effectiveness of Recombinant Influenza Vaccine (RIV)

RIV was initially licensed as the trivalent vaccine, Flublok (RIV3, Protein Sciences, Meriden, Connecticut), A quadrivalent formulation, Flublok Quadrivalent (RIV4; Protein Sciences, Meriden, Connecticut) was licensed in 2016. For the 2017–18 season, it is anticipated that both RIV3 and RIV4 will be available.

RIVs contain 45 μg of purified HA protein per virus (135 μg total for RIV3; 180 μg total for RIV4). The HA proteins are produced via the introduction of the genetic sequence for the HA into an

insect cell line (*Spodoptera frugiperda*) via a *Baculovirus* viral vector. This process uses neither live influenza viruses nor eggs (241, 242).

As a relatively new type of influenza vaccine, fewer postmarketing effectiveness data are available for RIVs than IIVs. Initial licensure of RIV3 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 (243). In a randomized placebo-controlled study conducted among healthy persons aged 18 through 49 years during the 2007–08 influenza season (242, 244), 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. Of note, more precise estimation of vaccine effectiveness against matched strains was not possible because 96% of isolates in this study did not antigenically match the strains represented in the vaccine (242). Estimated vaccine effectiveness without regard to match was 44.6% (95% CI = 18.8–62.6) (244).

In October 2014, the approved age indication for Flublok was expanded to ≥ 18 years on the basis of data from randomized trials demonstrating adequate immunogenicity among persons aged ≥ 50 years (245, 246). More recently, a pre-licensure randomized controlled trial of Flublok Quadrivalent vs. a licensed comparator IIV4 was performed among persons aged ≥ 50 years during the 2014-15 season (247, 248). This study is discussed in a later section (see *HD-IIV3, aIIV3, and RIV4 for Older Adults*). When evaluated in children 6 through 59 months of age, Flublok was found to be safe but less immunogenic than comparable volumes of IIV3, particularly amongst children < 36 months of age (249). Flublok is not licensed for children < 18 years of age.

HD-IIV3, aIIV3, and RIV4 for Older Adults

Given the high risk of severe influenza illness for older adults, and the lesser benefit of vaccination in this age group noted in many studies, substantial efforts have gone toward the development and study of new influenza vaccines intended to provide better immunity in this age group. Vaccines recently licensed specifically for persons aged ≥ 65 years include high-dose IIV3 (HD-IIV3) and adjuvanted IIV3 (aIIV3). In recent years, studies have been conducted comparing the benefits for older adults of these vaccines, as well as for RIV4, with those conferred by standard-dose, unadjuvanted IIVs (SD-IIVs); a few have been studies of LCI-related outcomes (Table 3 in Recommendations document). For each of these vaccines, there is at least some evidence of benefit as compared with SD-IIVs. However, no studies directly comparing these three vaccines to one another have been reported.

HD-IIV3 (Fluzone High-Dose)

The only 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 (180 µg total), compared with 15 µg of each vaccine virus per dose in standard-dose IIVs (250). 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 (251-253). Prespecified criteria for superiority in one clinical trial study were 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)(252, 254).

The largest study to date documenting benefit of high-dose vaccine for older adults is a randomized comparative efficacy trial of high-dose versus standard-dose IIV3 conducted among nearly 32,000 persons aged ≥65 years over the 2011–12 and 2012–13 influenza seasons. The primary endpoint of this study was efficacy of HD-IIV3 relative to SD-IIV3 in preventing culture- or RT-PCR-confirmed influenza caused by any influenza viral types or subtypes, and associated with protocol-defined ILI. Protocol-defined ILI was specified as occurrence of at least one respiratory symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing) concurrent with at least one systemic symptom (temperature >99.0°F, chills, tiredness, headaches or myalgia). For this outcome, the study reported 24.2% (95%CI 9.7 to 36.5) greater relative efficacy of the high-dose IIV3 compared to standard-dose IIV3 for protection against LCI caused by any viral type or subtype (255). In this study, superior efficacy of Fluzone High-Dose compared to SD-IIV3 was demonstrated. The pre-specified statistical superiority criterion for the primary endpoint (lower limit of the 2-sided 95% CI of vaccine efficacy of Fluzone High-Dose relative to Fluzone >9.1%) was met (250). For a secondary outcome, prevention of culture-confirmed influenza caused by viral types/subtypes similar to those contained in the vaccine and associated with modified CDC-defined ILI (temperature >99°F with cough or sore throat), the relative efficacy of HD-IIV3 vs. SD-IIV3 was 51.1% (95%CI 16.8 to 72.0). While this study did not examine health care utilization, pneumonia, and deaths confirmed to be due to influenza, all-cause hospitalizations, deaths, and pneumonia cases were examined. A subsequent analysis of data from this trial, in which SAEs were evaluated for possible relatedness to influenza by blinded physician reviewers, reported that compared to SD-IIV3, HD-IIV3 was associated with a relative vaccine efficacy of 39.8% (95%CI 19.3 to 55.1) for serious pneumonia and 17.7% (95%CI 6.6 to 27.4) for serious cardiopulmonary events possibly related to influenza; relative efficacy against all-cause hospitalizations was lower (6.9%; 95%CI 0.5 to 12.8) (256).

In addition to the clinical outcomes evaluated in the study described above, healthcare-consumption data derived from this trial were used to perform a cost-effectiveness analysis (257). Mean participant medical costs in the study were lower among those who received HD-IIV3 (\$1376.52) than those who received SD-IIV3 (\$1492.64; difference=-115.62, 95%CI -264.18 to 35.48). Mean societal costs were also lower among the HD-IIV3 participants (\$1506.48 vs.

\$1634.50; difference=-128.02, 95%CI -286.89 to 33.30). A probabilistic sensitivity analysis indicated that the HD-IIV3 is 93% likely to be cost saving.

A cluster-randomized trial conducted during the 2013-14 season among residents of 823 U.S. nursing homes (409 facilities in which residents received HD-IIV3 and 414 in which they received SD-IIV3) evaluated risk of hospital admissions related to pulmonary or influenza-like illnesses (258). The included facilities included 75,917 residents aged 65 years and older, 53,008 of whom were considered long-stay residents. Outcomes were identified via Medicare hospital claims data, which were matched to 38,256 residents. The incidence of respiratory-related admissions was significantly lower among the facilities randomized to HD-IIV3 (adjusted relative risk [aRR] 0.873, 95%CI 0.776 to 0.982). Also significantly lower were rates for pneumonia admissions (aRR 0.791, 95%CI 0.267 to 0.953), and all-cause hospital admissions (aRR 0.915, 95%CI 0.863 to 0.970).

An observational study conducted during the 2010-11 season among patients aged ≥ 65 years receiving primary care at Veterans Health Administration medical centers noted no significant differences in effectiveness of HD-IIV3 vs. SD-IIV3 for hospitalizations with a discharge diagnosis for influenza or pneumonia. Receipt of HD-IIV3 was also not associated with lower rates of all-cause hospitalization. However, for the subset of participants aged ≥ 85 years, receipt of HD-IIV3 was associated with lower risk of hospitalization for pneumonia and influenza (risk ratio 0.52; 95%CI 0.29 to 0.9) (259).

HD-IIV3 has also been evaluated through analysis of Medicare data. Among 929,730 recipients aged ≥ 65 years of HD-IIV3 and 1,615,545 recipients of SD-IIV3 during the 2012-13 season, receipt of HD-IIVs was associated with fewer non-laboratory confirmed but probable influenza infections (defined as receipt of a rapid influenza diagnostic test followed by a prescription for oseltamivir, relative VE 22%, 95%CI 15 to 29) and hospital admissions with a billing code for influenza (relative VE 22%, 95%CI 16 to 27) (260). In an analysis of Medicare data from the 2012-13 and 2013-14 seasons (including 1,039,645 recipients of HD-IIV and 1,683,264 recipients of SD-IIV during 2012-13, and 1,508,176 HD-IIV and 1,877,327 SD-IIV recipients during 2013-14), receipt of HD-IIV3 was associated with reduced risk of death relative to SD-IIV3 during the 2012-13 season (36.4%; 95% CI, 9.0% to 56%), when A(H3N2) viruses predominated; but not during the 2013-14 season (2.5%; 95% CI, -47% to 35%), in which A(H1N1) viruses predominated (261).

aIIV3 (Fluad)

The only adjuvanted influenza vaccine in the U.S., Fluad (Seqirus, Holly Springs, North Carolina), was initially licensed in the U.S. in November 2015. It contains the oil-in-water adjuvant, MF59. Similarly to HD-IIV3, it is licensed specifically for persons aged ≥ 65 years. Several studies have compared aIIV3 with SD-IIV3; however, fewer data are available than for HD-IIV3, and there have been no randomized trials of relative efficacy against LCI among older adults. 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;

criteria for superiority were not met (262, 263). In a Canadian observational study of 282 persons aged ≥ 65 years (165 of whom received aIIV3, 62 of whom received SD-IIV3, and 55 of whom were unvaccinated) conducted during the 2011–12 season that compared Fluad with unadjuvanted IIV3, the relative effectiveness of Fluad against LCI among the 227 vaccinated participants was reported to be 63% (95% CI = 4 to 86) (264). Some differences in the populations receiving each vaccine were described (in two of three health authorities participating, persons aged 75 years and older and those in long-term care facilities were preferentially given aIIV3; in the third, those in long term care facilities received aIIV3 and all others received SD-IIV3). A prospective study of 107,661 medical records covering 170,988 person-seasons during the 2006-07 through 2008-09 influenza seasons reported lower relative risk of hospitalizations coded for influenza and pneumonia among persons aged 65 years and older who received aIIV3 as compared with IIV3 (relative risk 0.75, 95%CI=0.57 to 0.98) (265). An observational study conducted in Italy during the 2010-11 and 2011-12 seasons, in which unadjuvanted SD-IIV3 was used during the first season and aIIV3 during the second season, reported that aIIV3 was more effective in preventing hospitalizations coded for pneumonia and influenza (not LCI) among recipients aged ≥ 75 years (adjusted VE 53%, 95%CI=33 to 68 for aIIV3 vs. adjusted VE 46%, 95%CI=24 to 62 for IIV3), while unadjuvanted SD-IIV3 was more protective than aIIV3 for recipients aged 65 through 74 years (adjusted VE 53%; 95%CI 3 to 78 for IIV3 vs. adjusted VE 34%, 95%CI=24 to 65) (266). That the two vaccines were not compared during the same season may be a limitation of this study.

RIV4 (Flublok Quadrivalent)

Two RIVs are currently licensed in the U.S.: Flublok (RIV3) and Flublok Quadrivalent (RIV4; Protein Sciences, Meriden, Connecticut). Both are licensed for persons aged 18 years and older. Fewer data are available concerning the relative effectiveness of RIV4 compared with other licensed vaccines for this age group than is currently the case for HD-IIV3. In prelicensure studies comparing RIV3 versus placebo among persons aged 18 through 49 years, serum antibody responses were induced to all three vaccine components (243). In a study comparing RIV3 with IIV3 among persons aged ≥ 65 years, seroconversion rates against influenza A(H1N1) and A(H3N2) were higher in the RIV3 group. Response was inferior for influenza B; however, this result is difficult to interpret as the B antigens were different in the two vaccines (245). In a pre-licensure randomized controlled trial of Flublok Quadrivalent vs. IIV4 among 8,604 persons aged ≥ 50 years during the 2014-15 season, RIV4 was more effective in prevention of LCI than IIV4, with a relative efficacy of 30% (95%CI 10 to 47). This season was characterized by a predominance of drifted A(H3N2) viruses, and consequent poor match between vaccine and circulating viruses (247, 248). While the study was not powered for statistical significance for relative efficacy by influenza virus type or subtype, results showed a trend towards non-inferior relative efficacy for Flublok Quadrivalent against influenza A, but not against influenza B (for which there were fewer cases). Relative efficacy for all A(H3N2) was 36% (95% CI: 14 to 53) and for influenza B was 4% (95% CI: -72 to 46). The RIV4 Influenza B antigens were well matched to circulating strains. In a subanalysis of data from those aged ≥ 65 years against all influenza A and B, RIV4 was not

significantly more effective than IIV4 against RT-PCR-confirmed protocol-defined ILI (relative efficacy 17%, 95%CI=-20 to 43), but was more effective than IIV4 against culture-confirmed protocol-defined ILI (relative efficacy 42%, 95%CI=9 to 65).

Immunogenicity, Efficacy, and Effectiveness of Live Attenuated Influenza Vaccine (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 (267-269).

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 (270, 271).

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 (1996-97 and 1997-98) (272, 273). 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 (272). 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) (273). 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 (274) 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 (275) to 64% to 70% for children in eight regions in Asia (276).

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 (277). Receipt of LAIV3

resulted in 21% fewer febrile illnesses (95% CI = 11–30) and 30% fewer febrile otitis media diagnoses (95% CI = 18–45) (272). 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) (278).

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 (279). 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 (280–282).

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 (280–285). 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 (286).

Several studies comparing LAIV3 with IIV3 prior to the 2009 pandemic demonstrated superior efficacy of LAIV3 among young children (283, 287–290). 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 (288). 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%) (290). 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 (289) and 52% increased protection compared with IIV3 among children aged 6–71 months with recurrent respiratory tract infections (287).

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 (291). However, subsequent 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 no statistically significant effectiveness of LAIV4 against influenza A(H1N1)pdm09 among children aged 2 through 17 years (292–294). 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) (295). During this season, the H1N1pdm09 virus predominated for the first time since the 2009 pandemic. During the 2014–15 season, when antigenically drifted H3N2 viruses predominated, neither LAIV4 nor IIV provided significant protection among U.S. children aged 2 through 17 years; LAIV4 did not offer greater protection than IIV for these viruses (296–298), in contrast to earlier studies in which LAIV3 provided better protection than LAIV against drifted H3N2 viruses (288, 290). LAIV4 exhibited significant effectiveness against circulating influenza B viruses in these U.S. studies. 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 (299).

The diminished effectiveness against H1N1pdm09 during the 2013–14 season 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 (300), and possibly associated with exposure of some LAIV lots to temperatures above those recommended for storage during U.S. distribution (301). For the 2015–16 season, to address stability concerns surrounding the A/California/7/2009(H1N1) HA, a different influenza A(H1N1) virus was included in LAIV4 (A/Bolivia/559/2013[H1N1]) (302). During the 2015–16 season, in which A(H1N1)pdm09 viruses were again predominant, data from the U.S. Influenza Vaccine Effectiveness Network, U.S. Department of Defense, and MedImmune demonstrated no statistically significant effectiveness of LAIV4 among children aged 2 through 17 years against H1N1pdm09, although point estimates varied (303). 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 (304).

Estimates of effectiveness of LAIV against H1N1pdm09 have not been consistent in all studies and all countries. Point estimates of vaccine effectiveness have varied. In the United Kingdom, where a phased rollout of routine use of LAIV for healthy children began during the 2013-14 season, effectiveness of LAIV4 among 2 through 17 year olds during the 2015-16 season was estimated to be 57.6% (95%CI 25.1—76.0) for all influenza, 41.5% (95%CI -8.5—68.5) for H1N1pdm09, and 81.4% (95%CI 39.6—94.3) against influenza B (305). In Finland during the 2015-16 season, effectiveness of LAIV4 against H1N1pdm09 among 2-year-olds was 50.7% (95%CI 28.4—66.1) against all influenza, 47.9% (95%CI 21.6—65.4) for influenza A (presumably predominantly H1N1pdm09), and 57.2% (95%CI 0.0—81.7) for influenza B (306). In addition to the different age group under study (2 year olds vs. 2 through 17 year olds), these results contrast with those of the U.S. and the United Kingdom, in that the estimate for H1N1 is statistically significant, whereas that for influenza B is not (and has a lower point estimate). In both the United Kingdom and Finland, as in the U.S., the point estimates for effectiveness of LAIV against H1N1pdm09 were lower for LAIV than for IIV. In Canada, data collected with the Sentinel Provider Site Surveillance Network (SPSN) for both 2013-14 and 2015-16 showed similar point estimates for effectiveness against H1N1pdm09 for LAIV (LAIV3 in 2013-14 and LAIV4 in 2015-16) and IIV; however, the estimate for LAIV in each case was not statistically significant (likely due to the small sample size in these analyses) (307). The Canadian National Advisory Committee on Immunization (NACI) concluded that for the 2016-17 season, the Canadian preference of the use of LAIV for 2 through 17 year olds was no longer supported by the available data.

The cause(s) of the low effectiveness of LAIV observed against H1N1pdm09, and for the differences in reported effectiveness among the various populations and countries studied, are not completely understood. Multiple factors may be involved. In addition to the reduced replicative fitness of the A/California/7/2009 and A/Bolivia/559/2013 H1N1 viral constructs (currently believed to be the root cause (308)), a potential contributory factor might be interference associated with the introduction of the second influenza B strain in LAIV4 (which was introduced in the U.S. in 2013-14). However, reduced effectiveness of LAIV against influenza A(H1N1)pdm09 was also observed with LAIV3 in the U.S. during the 2010-11 season (295). It has also been hypothesized that differences in prior vaccine coverage among children may contribute to differences in replicative fitness in different populations, leading to differences in effectiveness. However, analyses of U.S. data from the US Flu VE Network revealed no significant effect of prior vaccination (303). ACIP will continue to review data relevant to LAIV as it becomes available.

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.

Even in seasons in which vaccine composition does not change, annual vaccination has been recommended because of decline in protective antibodies over time postvaccination (309-311); however, the rate and degree of decline observed has varied. One study of HA and neuraminidase antibody levels following vaccination of adults noted a slow decline, with a 2-fold decrease in titer estimated to take >600 days (312). 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 (313).

Nonetheless, concerns have arisen regarding waning of protection within the course of a single influenza season, particularly among adults. 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 (314-317). 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; $p = 0.034$) (315). 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 (317). 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 (314). A recent multiseason analysis from the U.S. Influenza Vaccine Effectiveness (U.S. Flu VE) Network found that VE declined by about 7% per month for H3N2 and influenza B, and 6–11% per month for H1N1pdm09 (318). VE remained greater than zero for at least five to six months after vaccination. Similar waning effects have not been observed consistently across age groups and virus subtypes in different populations, and the observed decline in protection could be attributable to bias, unmeasured confounding, or the late season emergence of antigenic drift variants that are less well-matched to the vaccine strain.

Repeated Vaccination

Observations of a potential negative effect of repeat vaccination on vaccine effectiveness were initially made during the 1970s (319-322). A number of recent studies have indicated that response to, and effectiveness of, influenza vaccine during any given season may be modified by receipt of vaccine in prior seasons. In a study conducted among healthy 30- through 60-year olds during the 1983-84 through 1987-88 seasons during which whole-virus seasonal trivalent inactivated vaccines were used (the one exception being the addition of a monovalent split-virus A(H1N1) recommended to supplement the trivalent vaccine in 1986), moderate reductions in serum antibody response were associated with increased prior exposure to influenza vaccine during the last seasons of the study, but no decrease in protection against infection was noted (323).

Some more recent studies have noted decreased effectiveness associated with vaccination in the prior season. In a community-based study in Michigan conducted in 2010-11 (during which H3N2 viruses predominated), overall vaccine effectiveness was low and not significant (31%, 95% CI -7 to 55%). When stratified by whether vaccine had been received the previous season, substantially lower effectiveness was noted among those who had been vaccinated during both 2010-11 and 2009-10 (-45%, 95% CI -226 to 35), as compared with those who received vaccine during only the latter season (62%, 95%CI 17 to 82%) (324). In a similarly designed study in the same community conducted during the 2013-14 season, when H1N1pdm09 predominated, no negative effect of prior season vaccination was observed (325). A study in Australia conducted over the 2010-11 through 2014-15 seasons noted no significant difference in effectiveness of hospitalization for influenza illness between those vaccinated in the current season only (35%, 95%CI 21 to 46) vs the prior season only (33%, 95%CI 17 to 47); effectiveness was highest among those who had received vaccine during both seasons (51%, 95%CI 45 to 57) (326).

Other studies have evaluated vaccination history over more than one prior season. In a case-control study conducted in a healthcare system in Wisconsin, covering eight seasons between 2004-05 and 2012-13, which examined effectiveness against (H3N2) and B viruses, and in which participants were classified as frequent vaccinees (had received IIV during 4 or 5 of the previous 5 seasons), infrequent vaccinees (received IIV during 1 to 3 of the previous 5 seasons) or nonvaccinees (received no IIV during the previous 5 seasons), current season vaccination was effective regardless of previous vaccination history. Considering vaccination history for only current and prior seasons, effectiveness was similar for those who were vaccinated during the current season only, the previous season only, or both seasons. However, in an analysis using 5 seasons of vaccination history, there were significant differences in vaccine effectiveness among frequent vaccinees as compared with nonvaccinees (327). In a Spanish study which evaluated the effectiveness of vaccination against H1N1pdm09 from the 2010-11 through 2015-16 seasons, compared with those who had never been vaccinated, effectiveness was not reduced among those who were vaccinated in the current season only, or among those who were unvaccinated in the current season but had previously received >2 doses of H1N1pdm09-containing vaccine.

However, effectiveness was lower among those vaccinated in the current season after >2 prior doses, and among those currently unvaccinated who had 1-2 prior doses (328).

The effects of prior vaccination have not been observed consistently across all studies and seasons, and may differ by influenza virus type or subtype. A better understanding of these effects is needed in order to guide recommendations. Importantly, most studies in which a negative effect of prior vaccination was observed, vaccination during the current season (with or without prior season vaccination) was more protective than being unvaccinated in the current season.

Safety of Influenza Vaccines

Safety of Inactivated Influenza Vaccines (IIVs)

Children

Currently available IIVs are generally well-tolerated by 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; 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 (329). 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 (330). 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 (331).

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) (332). These reactions are generally self-limited and subside after 1–2 days. In a study of 791 healthy children aged 1 through 15 years, postvaccination fever was noted among 12% of those aged 1 through 5 years, 5% among those aged 6 through 10 years, and 5% among those aged 11 through 15 years (113). An observational study assessed post-vaccination fever frequency in 314 children aged 24–59 months receiving IIV during the 2013–14 influenza season. On the vaccination day to 2 days after vaccination (risk window 0–2 days), 7.1% and 6.0% of children had fever after IIV4 and IIV3, respectively (333).

Febrile Seizures: 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 (334). Febrile seizures may occur in the context of febrile illnesses, including influenza. In an observational study of 143 children aged 6 months through 5 years who presented with febrile seizures to an emergency department, at least

one virus was isolated from nasal or rectal specimens obtained from 102 children (71%); influenza was isolated from 19 (13%) (335). Seizures occurred within 14 days of administration of a vaccine in 16 (11%) children, none of whom had received an influenza vaccine within this period.

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 (330, 336). During the 2010–11 influenza season, CDC and FDA conducted enhanced monitoring for febrile seizures (primarily among children under 9 years of age) and febrile reactions 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) (337).

Following these events in Australia, from July 2010 through the 2016-17 season, ACIP did not recommend use of the U.S.-licensed CSL IIV3, Afluria, for children aged <9 years (304, 338). Subsequent laboratory investigation by CSL into the potential etiology of these reactions concluded that the 2010 Southern Hemisphere formulation induced a stronger inflammatory cytokine response than that associated with previous formulations of the vaccine, or with other IIVs. This was hypothesized to be related to the introduction of the viruses B/Brisbane/60/2006 and A/California/7/2009 to the vaccine, and believed to be mediated by higher concentrations of residual lipid and RNA remaining in the vaccine following splitting of the B, and to a lesser extent, the H1N1 components (339). At the time, lower concentrations of the detergent splitting agent taurodeoxycholate (TDOC) were used for the H1N1 and B viruses (0.9% and 0.5%, respectively) than for the H3N2 component (1.5%). Increasing the concentration of TDOC to 1.5% for all three viruses resulted in attenuation of the cytokine response in an *in vitro* model (340). In a study comparing fever rates among 402 children aged 5 through 9 years, 302 of whom received a trivalent Afluria produced using 1.5% TDOC for the B viruses and 100 of whom who received a licensed comparator (non-CSL) IIV4, prevalence of fever was similar in both groups (8.2% for Afluria IIV3 vs. 9.2% for the comparator IIV4) (341). In a randomized trial of 5- through 17-year-olds comparing Afluria IIV4 (manufactured using 1.5% TDOC for all four viruses) with a licensed comparator IIV4, higher prevalence of fever was observed with Afluria IIV4 (4.5% vs. 3.6% for 5- through 8-year-olds and 2.1% vs. 0.8% for 9- through 17-year-olds); this difference was not statistically significant (342)

Subsequent to the events in Australia during 2010, surveillance among children receiving U.S.-licensed influenza vaccines in two different surveillance systems (VAERS and VSD) during the 2010–11 influenza season detected safety concerns for febrile seizures in young children following receipt of IIV3 (343, 344). Further assessment of this signal through the VSD 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 were administered at the same health care visit) and peaked at approximately age 16 months (344), but the effect of other concomitant vaccines was not evaluated. 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 (337). 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 (345, 346).

A follow-up VSD study assessed the risk for febrile seizure on days 0-1 with the concomitant administration of IIV3 and all other routine childhood vaccines in children aged 6-23 months during 5 influenza seasons (2006-2007 through 2010-11) (347). This study found that there was an increased risk for febrile seizure when IIV3 was administered simultaneously with either PCV or DTaP-containing vaccines, but no increased risk when IIV3 was administered alone. The increased risk with these vaccine combinations was observed to have been present in seasons prior to 2010-11. Another study done in the US to follow-up the 2010–11 season findings, using the separate FDA-sponsored PRISM (Post-licensure Rapid Immunization Safety Monitoring) system population, found no association between receipt of IIV3 (adjusted for concomitant PCV13 or DTaP) and febrile seizures among children 6-59 months of age during 2010-11 (IRR adjusted for age and seasonality: 1.36; 95% CI = 0.78–2.39) (348). 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, surveillance findings in subsequent seasons for febrile seizures in young children following influenza vaccine have been consistent with the original findings of an increased risk in 2010-11. During the 2011–12 season (for which had the influenza vaccine composition was the same as that of the 2010–11 season), an observational clinical study showed that risk for fever in the 0–1 days after vaccination was higher when children 6 to 23 months old received IIV3 and PCV13 concomitantly versus receipt of IIV3 or PCV13 without the other product (349). The viral composition of U.S. influenza vaccines was changed for the 2013-14 season, and this same composition was used for the 2014-15 season. VSD surveillance for 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 (350). Similarly, analysis of 2013-14 data from the PRISM system revealed no increased risk for seizure following either IIV3 or LAIV when an individual-level, self-controlled risk interval comparison method was used, but did reveal increased risk for IIV3 and PCV13 administered concomitantly (but not alone) when using a method comparing current and historical rates (351). 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.

Quadrivalent IIVs (IIV4s): 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 (352-355). 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 (125, 127, 129, 356). 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 (357).

Safety of Full-Dose IIV4 for children aged 6 through 35 months: The dose of IIV given to persons aged ≥ 3 years is 0.5 mL. During the last several seasons prior to November 2016, the only influenza vaccines licensed for children 6 through 35 months of age were Fluzone (IIV3) and Fluzone Quadrivalent (IIV4, Sanofi Pasteur, Swiftwater, Pennsylvania), given in a 0.25mL dose (half the dose given to persons aged ≥ 3 years). The rationale for this reduced dose was greater frequency of fever and other reactogenicity events noted in studies conducted during the 1970s among children in this age group, primarily with older, whole-virus vaccines (358-362). 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 generally less reactogenic than the previous whole-virus products (363). More recently, evaluations of some currently available split-virion IIVs have revealed comparable safety of the 0.5mL dose for children in this age group (364, 365). The safety of 0.5mL FluLaval Quadrivalent (IIV4, ID Biomedical Corporation of Quebec, Quebec, Canada) was compared with 0.25mL of Fluzone Quadrivalent in a randomized controlled trial conducted among 2,424 children aged 6 through 35 months; safety and reactogenicity (including prevalence of fever) were comparable between the two groups, with no significant differences in local or systemic adverse reactions.

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 (366, 367). These injection site 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 (366-368). Adverse events in adults aged ≥ 18 years reported to VAERS during 1990–2005 were analyzed (369). 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) (370), 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 per vaccine virus) than after vaccination with standard dose IIV3 (15 µg per virus; 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) (252). 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) (371). 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 (372). A survey of adults aged ≥65 years in the Minneapolis Veteran Affairs Health Care System who received influenza vaccines (547 high-dose and 541 standard dose) during October 2015 showed that local and systemic side effects were more common after high-dose influenza vaccine than after standard dose vaccine during the week after vaccination; there was no significant difference in prevalence of severe side effects or healthcare visits between groups (373). 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 (124, 126, 128, 130, 131, 374). 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 (375).

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 (376); 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; injection site pain and ecchymosis and systemic reactions occurred with similar frequency (377). 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 (378). A randomized study

comparing safety of the newer intradermal IIV4 with that of intradermal IIV3 revealed a similar adverse event profile (131).

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 (379). ACIP will continue to review safety data pertaining to cell culture based vaccines.

An MF59-adjuvanted IIV3 (aIIV3), Fluad (Seqirus, Holly Springs, North Carolina) was approved in November 2015 for use in persons aged ≥ 65 years. In clinical trials among persons in this age group, some injection site and systemic adverse events were observed to occur more frequently following aIIV3 compared with unadjuvanted SD-IIV3; most were mild in severity. The prevalence of SAEs was similar between the two groups (263).

Persons at Higher Risk of Influenza-Related Complications

Overall, safety data pertaining to persons with specific underlying conditions are more limited relative to data from healthy populations, and studies directly comparing persons with high risk conditions with healthy populations are few. 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% (380); 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 (363). 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 (381).

Several randomized clinical trials comparing IIV to placebo among persons with chronic obstructive pulmonary disease (COPD) and asthma have reported safety outcomes. A study of 125 COPD patients at a Thai hospital clinic reported that significantly more patients in the vaccine group had injection site reactions (27% versus 6% placebo; $p = 0.002$) (382). The most common injection site 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 well tolerated in asthmatic children (383) and adults (384). 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; $p < 0.001$) (385). 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 (386). 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 (387).

Immunocompromised Persons

Transient increases in replication of HIV-1 in the plasma or peripheral blood mononuclear cells of HIV-infected persons after vaccine administration have been observed in some, but not all studies (20, 388-392). However, IIV does not appear to have a clinically important impact on HIV infection or immunocompetence in HIV-infected persons. 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 (393). Limited information is available about the effect of antiretroviral therapy on increases in HIV RNA levels after either influenza virus infection or influenza vaccination (394, 395).

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 (233, 234, 396), heart (397), lung (396) or liver transplants (238, 239, 398). A literature review concluded that there is no convincing epidemiologic link between vaccination and allograft dysfunction (231). Guillain-Barré syndrome in a liver transplant recipient and another case of rhabdomyolysis leading to acute renal allograft dysfunction after IIV vaccination have been reported (399, 400). Several case reports of corneal graft rejection have been reported following receipt of IIV (401-404), but no studies demonstrating an association have been conducted.

Guillain-Barré Syndrome and IIVs

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 (405-407). The annual incidence of GBS is 10–20 cases per 1 million adults (408). 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 (409).

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 (410). Data on the risk of GBS following IIV since the 1976 swine influenza vaccination program

have been variable and inconsistent across influenza seasons, but have not demonstrated an increase in GBS associated with influenza vaccines on the order of magnitude seen in the 1976–77 season (411, 412).

During three of four influenza seasons studied during 1977–1991, the overall relative risk estimates for GBS after influenza vaccination were not statistically significant (413–415). 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 (412). 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 (416). 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 (417). 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 (418). A third GPRD analysis found that GBS was associated with recent ILI, but not influenza vaccination (419). 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) (420).

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 (412). 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 (421–427). Studies have also shown an increased risk for GBS following influenza infection; that is, of higher magnitude than the risk observed following influenza vaccination (409, 428).

Persons with a history of GBS have a substantially greater likelihood of subsequently experiencing GBS than persons without such a history (408). 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 (429). 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 (430).

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 (431, 432). 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 (431, 433). 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 (431). 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 (434).

The cause of ORS has not been established; however, studies suggest that the reaction is not IgE-mediated (435). 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 (436, 437).

Thimerosal

Thimerosal, an ethyl mercury-containing antimicrobial compound, is primarily used in multidose vial preparations of IIV as a preservative to inhibit microbial growth. For these preparations, the mercury content from thimerosal is ≤ 25 μg of mercury per 0.5 mL dose. For one single-dose IIV preparation (Fluvirin, Seqirus, Holly Springs, North Carolina), thimerosal is used in the manufacturing process, and trace amounts remain in the finished vaccine (yielding a mercury content of ≤ 1 μg per 0.5 mL dose) (Table 1).

Although accumulating evidence is reassuring regarding health risks associated with exposure to vaccines containing thimerosal (438-450), 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 (438, 442). LAIV, RIV, and most single-dose vial or syringe preparations of IIV do not contain thimerosal.

Safety of Recombinant Influenza Vaccines (RIVs)

RIV was initially available in the U.S. during the 2013-14 season as RIV3. RIV4 was licensed in late 2016, and is anticipated to be available for the 2017-18 season. In prelicensure studies of RIV3, the most frequently reported injection site reaction (reported in $\geq 10\%$ 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) (354). Injection site pain and tenderness were reported significantly more frequently with RIV3 than placebo; however, most reports of pain following RIV3 were rated as mild. In studies comparing RIV3 to licensed comparator IIV3s among persons aged 50 years and older (246, 451, 452), safety profiles were generally similar to the comparator inactivated vaccines. In pre-licensure studies comparing safety of RIV4 with licensed comparator IIV4s among persons aged 18 through 49 years and ≥ 50 years, the frequency of injection site and systemic solicited adverse events was generally similar between the two treatment groups (247).

As a relatively new category of vaccine, fewer postmarketing safety data have accumulated for RIVs. 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 (453). All were considered to be consistent with possible anaphylaxis; 3 cases appeared to meet Brighton Collaboration criteria (454) 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. In a randomized study conducted among adults 50 years of age and older in which incidence of rash, urticaria, swelling, non-pitting edema, or other potential hypersensitivity reactions were actively solicited for 30 days following vaccination, 2.4% of Flublok recipients and 1.6% of IIV3 recipients reported such events within the 30 day follow-up period. A total of 1.9% and 0.9% of Flublok and IIV3 recipients, respectively, reported these events within 7 days following vaccination. Of these solicited events, rash was most frequently reported (Flublok 1.3%; IIV3 0.8%) over the 30 day follow-up period (451).

Safety of Live Attenuated Influenza Vaccine (LAIV)

Shedding, Transmission, and Phenotypic Stability of LAIV Viruses

Children and adults can shed vaccine viruses after receipt of LAIV; this shedding is less than that typical of shedding of wild-type influenza viruses during influenza infection. Measurements of 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 (455). Other smaller studies have reported similar findings (456, 457). In an open-label study of 200 children aged 6–59 months who received a single dose of LAIV3, shedding of low titers 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). 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) (458). 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 (459), and in three (13%) of 24 HIV-infected children compared with seven (28%) of 25 children who were not HIV-infected (460).

Transmission of shed LAIV vaccine viruses from vaccine recipients to unvaccinated persons has been documented. However, serious illnesses have not been reported among unvaccinated persons 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) (461).

In a study of genotypic and phenotypic stability of LAIV vaccine viruses, 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 (462). In a more recent study, serial passage of the LAIV H1N1pdm09 monovalent

vaccine virus in Madin-Darby canine kidney (MDCK) cells at increasing temperatures resulted in a variant that reproduced at higher temperatures and produced severe disease in mice (463).

Children

Among healthy children aged 60–71 months enrolled in one clinical trial, some 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). However, these differences were not statistically significant (464). 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%) (268, 269, 275, 465–469). 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 which 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 (465)

In a randomized trial published in 2007, LAIV3 and IIV3 were compared among children aged 6–59 months (288). 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 (465).

An open-label field trial was conducted between 1990 and 2002 among approximately 11,000 children aged 18 months–18 years in which 18,780 doses of LAIV3 were administered. 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 (470). 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

MAARI, including acute asthma exacerbation, during the 0–14 or 0–42 days after receipt of LAIV3 compared with the pre- and postvaccination reference periods (471).

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 (472). 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 (473). 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 (357). An analysis of health maintenance organization data for the 2013-14 season including persons aged 2 through 49 years noted a slightly higher risk of wheezing events among children aged 2 through 4 years who received LAIV4 relative to unvaccinated controls (hazard ratio 1.50, 95%CI 1.03–2.20). Of the 66 LAIV4 recipients who experienced these events, 5 were evaluated in an emergency department, but none were hospitalized (474).

Adults

Among healthy adults aged 18–49 years in one clinical trial, 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%) (464). A review of 460 reports (involving persons aged 2 through 70 years) 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. Few (9%) of the VAERS reports described serious adverse events; respiratory events were the most common conditions reported (472).

Persons at Higher Risk of 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 (475). 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 (459). 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 (460). In a study comparing

immunogenicity and shedding of LAIV4 among 46 HIV-infected (CD4+ counts >200 cells/ μ L) 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 ($p = 0.14$) (476).

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. 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 (477). 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 (289). A VSD study, conducted among children aged ≥ 2 years with a history of asthma between 2007 and 2014, found no increased risk of exacerbation during 2 weeks following LAIV or IIV, and a decreased risk following LAIV, compared with IIV (478). Another VSD study assessed the safety of LAIV in persons with asthma during 3 influenza seasons (2008-2009 through 2010-2011). This study found that LAIV was not associated with an increased risk of medically attended respiratory adverse events (479). Available data are insufficient to determine the level of severity of asthma for which administration of LAIV would be inadvisable.

Pregnant Women and Neonates

IIVs: Substantial data have accumulated which do not indicate fetal harm associated with inactivated influenza vaccines administered during pregnancy. However, data specifically concerning administration of these vaccines during the first trimester are limited (480). This can contribute to imprecision in estimates for risk of outcomes such as fetal death, spontaneous abortion and congenital malformations (481).

A matched case-control study of 225 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 (482). A review of health registry data in Norway noted an increased risk for fetal death associated with clinically diagnosed (not laboratory-confirmed) influenza A(H1N1) pdm09 infection, but no increased risk for fetal mortality associated with vaccination (69). Reviews of VAERS reports during 1990–2009 (483) and 2010–2016 (484), concerning pregnant women after receipt of IIV3 did not find any new or unexpected pattern of adverse pregnancy events or fetal outcomes

Background rates of spontaneous abortion vary from 10.4% in women aged <25 years to 22.4% in women aged >34 years (485). Considering the number of pregnant women vaccinated, miscarriage following (but not attributable to) influenza vaccination would therefore not be an unexpected event. However, data on the use of influenza vaccines are more limited during the early first trimester, when spontaneous abortions are more likely to occur. Among 7 observational studies summarized in a 2015 systematic review, none reported an increased risk of spontaneous abortion associated with influenza vaccination (481). A cohort study from the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) of vaccine exposure during the 2010-11 through 2013-14 seasons found no significant association of spontaneous abortion with influenza vaccine exposure in the first trimester or within the first 20 weeks of gestation (486). 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 and 2006–07 seasons (487). However, results of a later VSD study using similar methods 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 (488).

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) (489). 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 (490-492).

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% (493). 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). A case-control analysis from VAMPSS of data from the 2011-12 through 2013-14 seasons noted an elevated OR for omphalocele (5.16, 95%CI 1.44–18.7) during the 2011-12 season; no other significant associations were found (494).

Assessments of any association with influenza vaccination and preterm birth and small for gestational age infants have yielded inconsistent results, with most studies reporting no association or a protective effect against these outcomes (495-500). Protective effects observed in some studies may be due to biases arising from temporal variability in access to vaccine, timing of exposure to vaccination in pregnancy, and confounding due to differences in the study populations at baseline (501). A VSD study of 46,549 pregnancies during the 2009-2010 season found a strong protective effect against preterm birth of monovalent H1N1pdm09 vaccination when these potential effects were ignored, but no effect with adjustment for them (502). 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 (497).

Few studies have assessed infant health outcomes outside the neonatal period, among infants born to mothers receiving IIV during pregnancy. A retrospective cohort study of electronic medical record data including nearly 197,000 women noted no association between receipt of IIV in any trimester and diagnosis of an autism spectrum disorder (ASD) in the child. When data were analyzed by trimester, an increased risk was noted following vaccination during the first trimester (adjusted hazard ratio 1.20, 95%CI 1.04—1.39) (503). This association was no longer statistically significant after adjusting for multiple comparisons.

RIVs: Experience with the use of RIVs in pregnancy is limited, as these vaccines have been available only since the 2013-14 influenza season. In two pre-licensure studies of RIV3, 23 pregnancies occurred among participants who received RIV3. Complete follow-up was available for 18 pregnancies. Outcomes included 11 pregnancies which ended in uneventful, normal, term births; two in which the recipients experienced pregnancy-related AEs but delivered healthy infants; four elective terminations, and one spontaneous abortion (452). VAERS has received 3 RIV3 reports involving pregnant women. A pregnancy registry has been established for RIV3 and RIV4 (241, 354).

LAIV: As a live virus vaccine, LAIV has not been recommended for use during pregnancy. However, occasional reports of its use for pregnant women are reported to VAERS. 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 (483). Of 127 reports of administration of LAIV3/4 to pregnant women submitted to VAERS from July 2010 through May 2016, no adverse event was reported in 112 instances; the remaining 15 included two reports each of spontaneous abortion, elective termination, and nasal congestion and one report each of transverse myelitis, abdominal pain, preterm delivery, chest pain with dyspnea secondary to trauma, pure cell aplasia, headache, common cold, pulmonary hypertension in a newborn infant, and one unspecified pregnancy complication. Only the instance of pulmonary hypertension in the infant was reported as a serious event (484). Among 138 reports noted in a health insurance claims database, all outcomes occurred at similar rates to those observed in unvaccinated women (504).

Under the previous FDA labeling regulations, influenza vaccines were classified as either Pregnancy Category B or Category C on the basis of risk of reproductive and developmental adverse effects and on the basis of such risk weighed against potential benefit. In 2014, new regulations updated the format and content requirements of labeling for human prescription drugs and biological products, including vaccines. Under the new regulations, the previous pregnancy risk categories are replaced with a narrative summary of risk based on human and animal data for the specific product. In accordance with a defined implementation plan, many influenza vaccines are now labeled using the new format.

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 (505). 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 (454, 505).

Allergic reactions might be caused by the vaccine antigen, residual animal proteins, antimicrobial agents, preservatives, stabilizers, or other vaccine components. Manufacturers use a variety of compounds to inactivate influenza viruses and may add antibiotics to prevent bacterial growth. Package inserts for specific vaccines of interest should be consulted for additional information. ACIP has recommended that all vaccine providers should be familiar with the office emergency plan and be certified in cardiopulmonary resuscitation (506). The Clinical Immunization Safety Assessment (CISA) Project (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 (505).

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 (507). Anaphylaxis occurring after receipt of IIV and LAIV rarely has been reported to VAERS (369, 472, 508, 509). 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 (510). Some studies have noted higher rates of anaphylaxis following AS03-adjuvanted monovalent H1N1pdm09 vaccines

as compared with other vaccines (511, 512); no influenza vaccines containing this adjuvant are marketed in the United States.

Influenza Vaccination and Egg Allergy

Most currently available influenza vaccines (with the exceptions of RIVs and ccIIV4) are prepared by propagation of influenza viruses in embryonated eggs, and therefore may contain egg proteins such as ovalbumin. Among influenza vaccines for which ovalbumin content was disclosed during the 2011–12 through 2016–17 seasons, reported maximum amounts were $\leq 1 \mu\text{g}/0.5 \text{ mL}$ dose for IIVs and $<0.24 \mu\text{g}/0.2 \text{ mL}$ dose for LAIV4. Of the three vaccines produced using nonegg based technologies, currently only RIV3 and RIV4 (Flublok and Flublok Quadrivalent; Protein Sciences, Meriden, Connecticut) are considered egg-free. For ccIIV4 (Flucelvax Quadrivalent; Seqirus, Holly Springs, North Carolina), ovalbumin is not directly measured. Influenza viruses for ccIIV4 are propagated in mammalian cells rather than in eggs; however, egg proteins are potentially introduced at the start of manufacture, because some of the original viruses received from the WHO are egg-derived. From that point forward, no eggs are used, and dilutions at various steps during the manufacturing process result in a theoretical maximum of $5 \times 10^{-8} \mu\text{g}/0.5 \text{ mL}$ dose of total egg protein (Seqirus, data on file, 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 (513). 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 (514). 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 (515). 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) (516). A study that compared adverse reactions in eight egg-allergic and five nonegg-allergic children when given increasing doses of egg protein (517) 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 ($<0.24 \mu\text{g}$ 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 2017–18 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 (508, 509). ACIP will continue to review available data regarding anaphylaxis cases following influenza vaccines.

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