# Background Document for Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2019-20 Influenza Season

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## Abbreviations

| | |
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| ACIP | Advisory Committee on Immunization Practices |
| AE | Adverse event |
| aIIV3 | Adjuvanted trivalent inactivated influenza vaccine |
| ARI | Acute respiratory illness |
| ccIIV4 | Mammalian cell culture-based quadrivalent inactivated influenza vaccine |
| CDC | U.S. Centers for Disease Control and Prevention |
| CI | Confidence Interval |
| CMS | U.S. Centers for Medicare and Medicaid Services |
| FDA | U.S. Food and Drug Administration |
| GMT | Geometric mean titer |
| HA | Hemagglutinin |
| HD-IIV3 | Trivalent high-dose inactivated influenza vaccine |
| ICU | Intensive care unit |
| IIV | Inactivated Influenza Vaccine (trivalent or quadrivalent) |
| IIV3 | Trivalent inactivated influenza vaccine |
| IIV4 | Quadrivalent inactivated influenza vaccine |
| ILI | Influenza-like illness |
| LAIV | Live attenuated influenza vaccine (trivalent or quadrivalent) |
| LAIV3 | Trivalent live attenuated influenza vaccine |
| LAIV4 | Quadrivalent live attenuated influenza vaccine |
| LCI | Laboratory-confirmed influenza |
| MAARI | Medically-attended acute respiratory illness |
| MI | Myocardial infarction |
| mos | Months |
| NA | Neuraminidase |
| P&I | Pneumonia and influenza |

| | |
|---|---|
| RIV | Recombinant influenza vaccine (trivalent or quadrivalent) |
| RIV3 | Trivalent recombinant influenza vaccine |
| RIV4 | Quadrivalent recombinant influenza vaccine |
| SAE | Serious adverse event |
| SD-IIV | Standard-dose inactivated influenza vaccine (generally used when necessary to distinguish from high-dose inactivated influenza vaccine). |
| TND | Test-negative design |
| VAERS | Vaccine Adverse Event Reporting System |
| VSD | Vaccine Safety Datalink |
| yrs | years |

# Background Document for Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2019-20 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, 2019-20 Influenza Season" (MMWR Recomm Rep 2019;68[No.RR-3]). The above-referenced document contains the CDC/ACIP recommendations for use of influenza vaccines in various populations for the 2019-20 season, methods for the development of recommendations, discussion of vaccines expected to be available, contraindications and precautions to vaccination, and relevant figures and tables. This document contains additional background relevant to these topics.

## Background and Epidemiology

### Influenza Viruses and Vaccine Composition

Among humans, annual epidemic influenza illness is caused by two types of influenza viruses, influenza A and influenza B (1). Influenza virus types A and B are further subclassified through serologic and genetic testing. For influenza A viruses, differences in two viral surfaces glycoproteins, hemagglutinin (HA) and neuraminidase (NA), permit categorization into different subtypes. In the nomenclature of influenza A viruses, these different HA and NA proteins are represented by the letters "H" and "N", respectively. Since the late 1970s, influenza A(H1N1) and influenza A(H3N2) have been the common influenza A viral subtypes circulating among humans (2). Influenza B viruses are separated into two distinct genetic lineages (Yamagata and Victoria) on the basis of differences in the HA glycoprotein. Influenza B viruses from both lineages have co-circulated during most influenza seasons since the 1980s (3, 4).

Influenza viruses undergo constant genetic change, which has substantial impact on induced immunity and considerations for vaccine composition. Two main types of changes are recognized. Point mutations and recombination events occur in the viral genome, resulting in constant emergence of new virus variants. This phenomenon is termed "antigenic drift" (1, 2). While it occurs among both influenza A and B viruses, influenza A viruses undergo antigenic drift more rapidly than influenza B viruses (5). Frequent emergence of antigenic variants through antigenic drift is the virologic basis for seasonal influenza epidemics, and necessitates consideration of adjustment of vaccine viruses each season.

In addition to antigenic drift, larger genetic change events, termed “antigenic shift”, can occur among influenza A viruses. Antigenic shift occurs less frequently than antigenic drift, and generally arises though genetic reassortment among different viruses. These events can lead to new or substantially different influenza A viruses, for which there is little pre-existing immunity in the population. Such viruses can be associated with widespread pandemic influenza illness, if they exhibit efficient and sustained transmission among humans (1). In April 2009, a novel influenza A(H1N1) virus caused the most recent worldwide pandemic. This virus was antigenically distinct from human influenza A(H1N1) viruses in circulation from 1977 through spring 2009 (6, 7).

Each season, viruses belonging to influenza A subtypes A(H1N1) and A(H3N2) and to both B lineages co-circulate (1, 2). Natural infection and vaccination induce the production of antibodies to influenza HA and NA surface glycoproteins, which reduce likelihood of infection (8). However, antibodies produced against one influenza virus type or subtype confer limited or no protection against another type or subtype (9).

Currently available seasonal influenza vaccines are either trivalent or quadrivalent in composition. Trivalent vaccines contain HA derived from one A(H1N1) virus, one A(H3N2) virus, and one B virus (representing one influenza B lineage). Quadrivalent vaccines have the same HA composition as trivalent vaccines, with the addition of HA from a second influenza B virus (such that both influenza B lineages are represented).

## Seasonality and Burden of Influenza Illness

The exact timing of the onset, peak, and end of influenza activity vary, and cannot be predicted precisely from one season to the next. In general, however, annual epidemics of influenza typically occur in the United States during the fall and winter. Influenza activity often begins to increase in the U.S. during October, and can extend as late as May. Peak activity most commonly occurs during the winter. During the 36 seasons from 1982-83 through 2017-18, peak activity occurred most commonly during February (in 15 [42%] seasons); however peak activity was observed during December (7 [19%]), January (6 [17%]), and March (6 [17%]) during other seasons (10).

Surveillance systems and research studies use different case definitions to characterize influenza activity and illness. Some outcomes (e.g., influenza illness confirmed by viral culture or polymerase chain reaction [PCR]) are more specific than others (e.g., influenza-like illness defined by a clinical case definition, without confirmatory diagnostic testing). Studies that report rates of clinically-defined 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 specific burden estimates are provided by surveillance studies based on laboratory-confirmed influenza (LCI). However, less specific

outcomes are useful in national surveillance of influenza activity, and are used in some components of routine U.S. influenza surveillance. 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 and describing the seasonal and geographic occurrence of influenza each year (12).

Persons of all ages are susceptible to influenza. Influenza incidence is difficult to quantify precisely, as many or most of those infected may not seek medical attention and are therefore not diagnosed. An estimated incidence of approximately 8% (varying from 3% to 11%) was derived through statistical extrapolation of U.S. hospitalization data and a meta-analysis of published literature (13). In a systematic review of randomized controlled trials which examined LCI events in the control (unvaccinated or placebo) arms of the included studies, an estimated 1 in 5 unvaccinated children and 1 in 10 unvaccinated adults were infected, with approximately half of these cases being symptomatic (14).

Burden of severe outcomes associated with influenza illness, such as hospitalization and death, may be estimated in several ways, such as through assessing rates of these events during influenza seasons, though mathematical modelling methods, and through studies that examine LCI. In typical influenza seasons, increases in deaths and hospitalizations are observed during periods when influenza viruses are circulating. Although not all excess events occurring during these periods are attributable to influenza, surveillance of these events is useful for monitoring season-to-season trends in influenza-associated outcomes. Estimates based on hospitalizations or deaths associated with pneumonia and influenza (P&I) diagnoses 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. Thus, some authors have used the broader category of respiratory and circulatory excess events for influenza burden estimates. A modeling analysis of population-based surveillance data for seasons following the 2009 pandemic (2010–11 through 2012–13) 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 (15). An estimated 54%–70% of hospitalizations and 71%–85% of deaths occurred among adults aged ≥65 years. This model used a multiplier method to correct for under-detection in hospitalizations attributable to cases for which influenza testing was not performed and for suboptimal test sensitivity. Using similar methodology, for seven seasons from 2010-11 through 2015-16 it has been estimated that between 9.2—35.6 million illnesses, 4.3—16.7 million outpatient medical visits, 139,000—708,000 hospitalizations were attributable to influenza each season (16) Excess deaths were estimated to be 4,000-20,000 per season for P&I deaths and 12,000-56,000 for respiratory and circulatory deaths.

### *Children*

Influenza is an important cause of outpatient medical visits and hospitalizations among young children. In a population-based retrospective cohort study, hospitalization rates for children aged <5 years with acute respiratory illness (ARI) or LCI-associated fever 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 (17, 18). 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). 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 influenza-related emergency department visits ranged from 89 to 620 per 10,000 children per year (20).

Estimated rates of influenza-associated hospitalization generally are substantially higher among infants and children <5 years than among older children (17, 18, 21-26). 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 (23). Estimated hospitalization rates for children with high-risk medical conditions are generally higher than for those without (26-28). In a study 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) (21). 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 (27).

Estimates of influenza mortality rates for children based on pneumonia and influenza diagnoses, respiratory and circulatory diagnoses, or laboratory confirmed influenza have generally been low, <1 per 100,000 person-years (29, 30). However, the absolute number of pediatric deaths varies from season to season (31). 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 (30). In the United States, death associated with LCI among children aged <18 years has been a nationally reportable condition since October 2004 (32). 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 187 in 2017-18 (31). A larger number of deaths were reported during the 2009 influenza A(H1N1)pdm09 pandemic, for which 358 pediatric deaths were reported to CDC from April 15, 2009 through October 2, 2010 (33). In a review of pediatric mortality surveillance data covering the 2010-11 through 2015-16 seasons, death rates were inversely associated with age, with the highest rates occurring among those aged < 6 months. Among

children aged ≥6 months, only 31% had received at least one dose of influenza vaccine in the season that death occurred (34).

### *Younger Adults*

In typical seasons, influenza-associated hospitalization occurs less frequently among younger adults as compared with children aged <5 years and adults aged ≥65 years. However, some authors have reported that 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 (35). Studies of worker vaccination have reported lower rates of ILI (36, 37), lost work time (36-39), and health care visits (37, 39) in association with vaccination as compared with no vaccine or placebo. Influenza may be associated with greater workplace productivity losses among working adults than acute respiratory infections caused by other pathogens (40).

During the 2009 influenza A(H1N1)pdm09 pandemic adults aged <65 years appeared to be at higher risk for influenza-related hospitalizations and deaths (41) as compared with typical influenza seasons. During the 2009 influenza A (H1N1) pandemic period (April 2009 through May 1, 2010), the cumulative crude rates of LCI-related hospitalization for the Emerging Infections Program 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 (42). 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 (43).

### *Older Adults*

Hospitalization rates during typical influenza seasons are generally highest for adults aged ≥65 years (12). Risk of hospitalization may be greater among older adults with high-risk underlying medical conditions than for those without such conditions. 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 for 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) (44).

Deaths associated with influenza are most frequent among older adults. From the 2010-11 through 2015-16 seasons, an estimated 9,000-43,000 influenza-related deaths occurred among adults aged ≥65 years, corresponding to >75% of estimated annual average deaths across all age groups (16). In comparison, the average annual mortality was estimated to be 200-1,300 deaths among persons aged <18 years and 2,700-11,000 deaths among persons aged 18–64 years.

Some studies have examined potential associations between acute respiratory illnesses and acute vascular events such as myocardial infarction and ischemic stroke (45-48). A self-controlled case series analysis of 364 hospitalizations for myocardial infarction found an increased risk for myocardial infarction within 7 days of laboratory detection of influenza (incidence ratio [IRR]=6.05, 95%CI 3.86—9.50 for all influenza; IRR=10.11, 95%CI 4.37—23.38 for influenza B, and IRR=5.17, 95%CI 3.02—8.84 for influenza A) (45). A self-controlled case series analysis of the United Kingdom Myocardial Ischaemia National Audit Project and the General Practice Research Database found that the risk of acute myocardial infarction was significantly higher 1-3 days after the onset of an acute respiratory infection (IRR=4.19, 95%CI 3.18—5.53). This effect was greatest among those aged ≥80 years (46). In an analysis of hospitalization data, admissions for myocardial infarction and stroke among persons aged ≥75 years were correlated with circulation of influenza (47). A retrospective analysis of medical record data reported that persons hospitalized for an ischemic stroke had increased odds of having had a recent previous hospitalization for ILI. In this study, the association between ILI and stroke was greatest for younger adults (those under 43 years of age), and decreased with increasing age (though it remained statistically significant) (48).

### *Pregnant Women and Pregnancy Outcomes*

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 (49). 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. The rate ratio for hospital admissions was significantly increased during all trimesters of pregnancy, and increased with successive stages (for the third trimester, relative risk [RR] 7.9 [95%CI 5.0–12.5] among women with comorbidities and 5.1 [95%CI 3.6–7.3] among those without comorbidities) (50). A cohort study conducted in New Zealand found increased risk of LCI-associated hospitalizations among pregnant women compared with women who were not pregnant. Risk was increased for all trimesters and increased with successive stages of pregnancy (RR=2.5, 95%CI 1.2—5.4 for first trimester; RR=3.9, 95%CI 2.4—6.3 for second trimester; and RR=4.8, 95%CI 3.0—7.7 for third trimester) (51). A systematic review and meta-analysis of observational studies concluded that influenza infection during

pregnancy was associated with an increased risk for hospitalization relative to infection in non-pregnant individuals (OR=2.44, 95%CI 1.22—4.87), but not for death (52).

Increased severity of influenza among pregnant women was reported during the pandemics of 1918–19, 1957–58, and 2009–10 (53-58). During the 2009(H1N1) pandemic, severe infections among postpartum (delivered within previous 2 weeks) women also were observed (54, 57, 59). In a case series conducted during the 2009(H1N1) pandemic, 56 (20%) 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 (60, 61). 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 (61).

Some studies of pregnancy outcomes have suggested increased risk for pregnancy complications attributable to maternal influenza illness; others have not. A review of data from the National Inpatient Sample (a publicly available hospital discharge database; *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 (62). 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) (63). 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 (64). In a retrospective cohort study of 86,779 pregnancies in which 192 cases of LCI were identified during the 2012-14 and 2013-14 seasons, women infected during the first trimester had a significantly lower mean length of gestation than uninfected women (38 vs. 39 weeks). The infants of those infected with influenza B had a 4% lower mean percent of optimal weight (65). 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 (66-68).

Influenza symptoms often include fever, which during pregnancy might be associated with neural tube defects and other adverse outcomes (69). 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 (70). However, many of the included studies were conducted during the 1950s through 1970s, and a nonspecific definition of influenza was used (any reported influenza, ILI, or fever with influenza, with or without serological or clinical confirmation). A 2005 meta-analysis of fifteen observational studies noted an association between maternal fever and neural tube defects (71). Associations between maternal fever and

congenital heart defects (72) and orofacial cleft (73) 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 (74).

### *Persons with Increased Risk for Severe Influenza Illness and Complications*

Persons with "chronic debilitating diseases" (specifically those with cardiovascular disease, pulmonary disease, diabetes and Addison's disease), were included (along with persons aged ≥65 years and pregnant women) among those recommended to receive vaccine as early as 1960. These groups had been noted to have contributed most to the excess deaths observed during the 1957 influenza pandemic (75). Since that time, the list of conditions potentially conferring increased risk of severe illness attributable to influenza has expanded to include persons with chronic medical conditions of most body systems, immunocompromised persons, those who are extremely obese, and American Indian/Alaska Native populations (76). In general, risk groups have been added as a result of increased observed risk of hospitalization or other severe outcomes during some influenza seasons. For any given group, the degree of increased risk may not be the same in all seasons. However, the potential for increased risk of severe illness cannot be predicted in any given season. Moreover, most risk categories comprise a heterogeneous group of conditions, the severity of which varies among different individuals, as well as with the presence or absence of medical treatment for the underlying condition. It is possible that these factors may alter illness risk for any given individual.

In a study of 4,756 adults hospitalized with influenza from October 2005 through April 2008, characteristics significantly associated with pneumonia (a potential severe complication of influenza) included underlying chronic lung disease and immunosuppression (77). 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. In a case control study of children 6 through 59 months of age during the 2005-06 through 2008-09 seasons, hospitalization for influenza was significantly associated with pulmonary, hematologic/oncologic, and neurologic conditions (78). In a systematic review of studies of risk factors for influenza-related complications among children, hospitalization was most strongly associated with neurologic disorders, prematurity, sickle-cell disease, immunosuppression, and diabetes (79).

Some early studies suggested increased severity of influenza among HIV-infected persons (80, 81). Studies conducted since the widespread availability of effective HIV antiretroviral therapy indicate that there may be no increased risk of severe disease among persons for whom HIV is well-controlled (82-87). However, influenza may be associated with secondary bacterial pneumonia, particularly *Streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus,* which may be more severe among HIV-infected persons (88).

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 (89-91). 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) (92). 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) (93). A retrospective cohort study of Australian national health insurance data between 2006 and 2015 found that compared to adults with a healthy BMI, those with a BMI of 30 to <40 had a higher risk of influenza-associated hospital admission (aHR=1.57, 95%CI 1.22--2.01); those with a BMI of ≥40 had an even higher risk (aHR=4.81, 95%CI 3.23—7.17) (94). Conversely, a two-season prospective cohort study (2007–09) in the United States found no association between obesity and medically attended LCI, including both seasonal and pandemic virus circulation (95). In a four-season (2010-11 through 2013-14) cohort study conducted in Mexico of children and adults with viral ILI, influenza infection was significantly associated with increased risk of hospitalization among adults who were either underweight or morbidly obese. Among children in this study, influenza was not analyzed separately; obesity was associated with increased risk for hospitalization for ILI due to any viral pathogen (96).

Also during the 2009 pandemic, racial and ethnic disparities in the risk for influenza-related complications among adults were noted, 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). 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(107). Observational studies that use a test-negative design (TND, 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 of case/control status 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).

The CDC U.S. Influenza Vaccine Effectiveness (U.S. Flu VE) Network, a collaboration of 5 U.S. sites, produces annual estimates of vaccine effectiveness against outpatient MAARI, using a test-negative

case-control design. Results are stratified by age group and vaccine type (when there is sufficient use of a specific vaccine to permit a VE estimate). VE estimates from this network for selected recent seasons are summarized in some of the sections that follow. Further information concerning methods, summaries of additional results, and links to reports are available at CDC's Influenza Vaccine Effectiveness Networks | Flu Vaccines Work | CDC.

## Immune Response Following Vaccination

Serum antibodies against hemagglutinin are considered to be correlates of vaccine-induced protection for inactivated influenza vaccines (IIVs)(8). Higher 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 (9, 111-113). Most healthy children and adults have high titers of strain-specific antibody after IIV vaccination (112, 114). 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 increases in these parameters were noted among adults following receipt of either vaccine (115).

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 (116).

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 (117). 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.

## 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 (118), ILI in younger working adults (37), and LCI (119) 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 (120, 121).

In addition to antigenic drift of circulating influenza viruses, vaccine viruses might undergo adaptive mutations during propagation in eggs. In some instances, these mutations may result in antigenic differences between vaccine viruses and circulating viruses, which may in turn result in reduced vaccine effectiveness (122). While the majority of influenza vaccines licensed in the United States are egg-based, two which use non-egg based technologies have been licensed in recent seasons. These include a cell culture-based IIV4 Flucelvax Quadrivalent (ccIIV4, Seqirus) and a recombinant quadrivalent vaccine, Flublok (RIV4, Sanofi Pasteur). Flucelvax Quadrivalent is produced via propagation of vaccine viruses in canine kidney cells instead of eggs (123). Flublok Quadrivalent contains HA produced via recombinant methods in an insect cell line, and uses neither influenza viruses nor eggs in its production (124). In a retrospective cohort analysis of Centers for Medicare and Medicaid (CMS) data including >13 million beneficiaries aged ≥65 years during the 2017-18 season, effectiveness of ccIIV4 was somewhat better than that of egg based vaccines (relative VE=11%, 95%CI 8—14% compared with standard-dose egg based quadrivalent inactivated vaccines); use of RIV4 was insufficient for analysis (125). The authors concluded the modest relative benefit of ccIIV4 indicated that changes in egg propagated vaccine viruses were probably not sufficient to fully account for the relatively low VE observed during 2017-18. More comparative studies are needed to elucidate potential benefits of non-egg based vaccines.

## 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 injection. They are manufactured using influenza viruses which have been inactivated, so no viral replication occurs after administration. Immunogenicity, effectiveness, and efficacy have been evaluated in children and adults. However, in general, fewer data from randomized studies of efficacy against LCI outcomes are available for certain age groups (e.g., persons aged ≥65 years as compared with younger age groups). Product-specific efficacy data

from randomized trials are generally limited for some of the more recently licensed quadrivalent vaccines, many of which were licensed primarily on the basis of immunogenicity studies which demonstrated non-inferior immune response as compared with their earlier trivalent counterparts. Efficacy and effectiveness studies in which different individual IIVs are compared are also limited, with the exception of some specific comparisons that are discussed in the sections that follow.

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 influenza A(H1N1) virus, an influenza A(H3N2) virus, and an influenza B virus (selected from one of the two influenza B virus lineages). IIV4s contain the viruses selected for IIV3s, and in addition contain a fourth virus, which is an influenza B virus selected from the second influenza B virus lineage (i.e., the lineage not contained in the trivalent vaccine). In general, pre-licensure 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 that is not included in IIV3, without interfering with immune responses to the remaining three vaccine viruses (126-133).

IIV4s were developed to provide better protection in seasons in which the predominant circulating influenza B lineage is not included in IIV3s. However, effectiveness studies conducted during some seasons have demonstrated that IIV3 provided similar protection against circulating influenza B viruses of both lineages. For example, the U.S. Flu VE Network found that IIV3 provided statistically significant protection against both the included B lineage (66%; 95%CI 58, 73) and the non-included B lineage (51%; 95%CI 36, 63) during the 2012– 13 season, when both lineages co-circulated (134). 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, 75% for B/Victoria; and 66%, 95%CI 38, 81% for B/Yamagata) (135). Cross-lineage protection was observed for IIV3 and ccIIV3 in a randomized trial (136); in another randomized trial of IIV3 there was no cross lineage protection (137).

### *Children*

Several 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 putatively 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) (138). Vaccine effectiveness is lower among children aged <5 years who have never received influenza vaccine previously or who received only 1 dose in their first year of vaccination than it is among children who received 2 doses in their first year of being vaccinated. A retrospective study of billing and registry data among children aged 6–21 months conducted during the 2003–04 season found that although receipt of 2 doses of IIV3 was protective against office visits for ILI, receipt of 1 dose was not (139). Another retrospective cohort study of children aged 6 months

through 8 years, the majority of whom received IIV3 (0.8% received LAIV3), also conducted during the 2003–04 season, found no effectiveness against ILI or P&I among children who had received only 1 dose (140); children who received 2 doses were protected against P&I. In a case-control study of approximately 2,500 children aged 6–59 months conducted during the 2003–04 and 2004–05 seasons, being fully vaccinated (having received the recommended number of doses) was associated with 57% effectiveness (95%CI 28, 74) against LCI for the 2004–05 season; a single dose was not significantly effective (too few children in the study population were fully vaccinated during the 2003–04 season to draw conclusions) (141). In a three-season (2015-16 through 2017-18) test-negative case-control study conducted among children aged 6 months through 8 years in Israel, IIV3 was effective for those who were fully vaccinated (VE=53.9%; 95%CI 38.6, 68.3), but not for those who were only partially vaccinated (VE=25.6%; 95%CI -3, 47) (142). 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 randomized controlled trials that used culture- or RT-PCR–confirmed influenza virus infections as the primary outcome. 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 (112). 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 1999–00. However, vaccination did not reduce culture-confirmed influenza illness significantly during 2000–01, when influenza attack rates were lower (3% versus 16% during 1999–20 season) (143). More recently, in a multinational randomized trial which included over 12,000 children aged 6 through 25 months over 5 influenza seasons between 2011 and 2014 and compared IIV4 to non-influenza control vaccines, VE was 50% (95%CI 42, 57) against LCI of any severity and 63.2% (95%CI 49, 69) against moderate-to-severe influenza (defined as LCI with any of the following features: fever >39$^{o}$C, otitis media, lower respiratory infection, serious extrapulmonary complications, intensive care unit admission, or need for supplemental oxygen for >8 hours) (144).

In observational studies for recent influenza seasons, vaccine effectiveness among children has varied by season. In the U.S. Flu VE Network (within which the majority of vaccine used in recent seasons has been IIV3 or IIV4), estimated effectiveness against medically-attended influenza illness due to all types and subtypes during the 2016-17 season was 57% (95%CI 43, 68) for children aged 6 months through 8 years and 36% (95%CI 15, 52) for children aged 9 through 19 years (145). For the 2017-18 season, estimated effectiveness was 68% (95%CI 55, 77) for children aged 6 months through 4 years and 32% (95%CI 16, 44) for children aged 5 through 17 years (146).

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 (147, 148). 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). A 2017 systematic review concluded that receipt of influenza vaccine was associated with a small decrease in the occurrence of at least one episode of acute otitis media over a minimum of six months following vaccination; however, this decrease was not statistically significant (RR=0.84; 95%CI 0.69, 1.02) This result was pooled from 4 studies which included different vaccines (two of IIV3, one of IIV3 administered with measles/mumps/rubella vaccine, and one of LAIV3) (149). 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 (150). 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 (37, 39). 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 (151).

In analyses of data from the U.S. Flu VE Network, (within which the majority of vaccine used in recent seasons has been IIV3 or IIV4), estimated effectiveness against MAARI due to all viral types and subtypes for adults aged 18 through 49 years was 19% (95%CI 0, 34) during the 2016-17 season (145) and 33% (95%CI 21, 44) during the 2017-18 season (146). For those aged 50 through 64 years, estimated effectiveness during the 2016-17 season was 40% (95%CI 24, 53) (145). During the 2017-18 season VE was 30% (95%CI 13, 44) for this age group (146).

### *Older Adults*

Older adults have long been recognized as a high-risk group for severe influenza illness, and have been recommended to receive annual influenza vaccination since the 1960s (75). Historically, most effectiveness data in this population pertain to standard-dose IIVs, which contain 15 µg of HA of each vaccine virus per dose. Discussion of the more recently licensed high-dose IIV3 (HDIIV3), adjuvanted IIV3 (aIIV3), and quadrivalent recombinant influenza vaccine (RIV4) in this age group is presented below.

Studies suggest that antibody responses to influenza vaccination are decreased in older adults. 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 (152). 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 (8), 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 vaccine virus was well-matched to the circulating virus, but higher titers were required with poor match (153). Limited or no increase in antibody response is reported among elderly adults when a second dose is administered during the same season (154-156).

Because older adults have been recommended to receive routine annual influenza vaccine for many decades (75), there are relatively few randomized, placebo-controlled trials which estimate VE against LCI outcomes in this population. One randomized controlled trial conducted among community-dwelling (not institutionalized) 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 (157). 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 HAI 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 (117).

Other evidence of effectiveness of influenza vaccines among older adults is derived from observational studies and from analyses of health care system data. A 2018 Cochrane review of influenza vaccine effectiveness studies among older adults concluded that older adults who are vaccinated may have a lower risk of influenza (RR=0.42, 95%CI 0.27, 0.66), with the evidence quality characterized as “low certainty” because of the paucity of randomized clinical trials (158). A 2014 review of data from 35 test-negative design case-control studies involving community-dwelling elderly 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), and 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) (159).

Influenza vaccine effectiveness against medically-attended influenza illness among adults aged ≥65 years is also assessed annually by the U.S. Flu VE Network. In recent seasons, IIV3 and IIV4 have been

the predominant type used with this network. For the 2016-17 and 2017-18 seasons, estimated effectiveness of influenza vaccines was not statistically significant for this age group (145, 146).

Influenza vaccination might reduce risk for influenza-related hospitalizations among older adults with and without other high-risk conditions (160-164). A test-negative case-control analysis from a multinational European network noted moderate vaccine effectiveness against hospitalization among persons aged ≥65 years during the 2015-16 season. Estimated vaccine effectiveness was 42% (95%CI 22, 57) for influenza A(H1N1)pdm09 and 52% (95%CI 24, 70) for influenza B. Vaccine effectiveness estimates were similar for both virus types among persons with diabetes, cancer, lung, and heart disease, except in the instance of influenza B among persons with heart disease, for which vaccine effectiveness was not statistically significant (165). A systematic review and meta-analysis of test-negative case-control studies of vaccine effectiveness for influenza-associated hospitalizations among older adults reported pooled VE of 48% (95%CI 37, 59) for influenza A(H1N1)pdm09 viruses, 37% (95%CI 24, 50) for influenza A(H3N2) viruses, and 38% (95%CI 23, 53) for influenza B viruses. Vaccine effectiveness for H3N2 viruses varied substantially depending upon match of circulating viruses with vaccine viruses: 43% (95%CI 33, 53) when vaccine viruses were antigenically similar, vs. 14% (95%CI -3, 30) when they were not (166).

Some studies of severe influenza illness among older adults have used less specific, non-LCI outcomes such as all-cause mortality of hospitalizations associated with influenza-related diagnostic codes. Such methods have been challenged because results might not be adjusted adequately to control for frailty bias or for the possibility that healthier persons might be more likely to be vaccinated than less healthy persons (106, 107, 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 ~10% or less (168-170). In a test-negative case-control study of community-dwelling adults aged ≥65 years, effectiveness of 2010–11 seasonal influenza vaccine against hospitalization for LCI was 42% (95%CI 29, 53). By type and subtype, estimated effectiveness was 40% (95%CI 26, 52) for influenza A(H3N2) and 90% (95%CI 51, 98) for influenza A(H1N1); no significant reduction 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 and ≥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). 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 (177, 178).

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 (179-181). Protection of infants though 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, 5) in preventing LCI in their breastfed infants during the first 6 months of life (182). A randomized placebo-controlled trial of IIV3 among HIV-infected and uninfected women in South Africa reported efficacy against RT-PCR–confirmed influenza of 50.4% (95%CI 14.5, 71.2) among the HIV-uninfected mothers and 48.8% (95%CI 11.6, 70.4) among their infants (183). In a study conducted in Mali in which pregnant women were randomized to receive either IIV3 or quadrivalent meningococcal vaccine (as a non-influenza control vaccine) during the third trimester and infants were followed to detect LCI through 6 months of age, vaccine efficacy against LCI among the infants was 67.9% (95%CI 35.1, 85.3) through 4 months and 57.3% (95%CI 30.6, 74.4) through 5 months; by six months of follow up efficacy was 33.1% (95%CI 3.7, 53.9) (184). A randomized placebo-controlled trial of year-round influenza vaccination in Nepal (where influenza circulates year-round, rather than seasonally), vaccine efficacy against LCI among infants 0--6 months of age was 30% (95%CI 5, 48) for the full study period. Vaccines with two different HA compositions were used during this period; vaccine efficacy for the vaccine used during the first period was 16% (95%CI -19, 41), while that for the latter was 60% (95%CI 26, 88) (185).

Among observational studies, in a matched case-control study of infants admitted to a large urban hospital in the United States during 2000–2009, maternal vaccination was associated with significantly lower likelihood of hospitalization for LCI among infants aged <6 months (91.5%; 95%CI 61.7, 98.1) (186). A prospective cohort study among Native Americans reported that infants aged <6 months of vaccinated mothers had a 41% lower risk of LCI (RR=0.59; 95%CI 0.37, 0.93) and a 39% lower risk of ILI-associated hospitalization (RR=0.61; 95%CI 0.45, 0.84) (187). 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 unvaccinated mothers (aOR=0.55; 95%CI = 0.32, 0.95) (188). In a case control study covering the 2010-

11 and 2011-12 influenza seasons, vaccination of pregnant women reduced their risk of LCI by approximately half (189). In a multiseason (2010-2016), multinational test-negative case-control study which included 19,450 pregnant women, IIV was protective against hospitalizations associated with LCI (VE 40%, 95%CI 12, 59) (190).

### *Persons with Chronic Medical Conditions*

Data evaluating clinical efficacy and effectiveness of vaccination among populations with specific chronic medical conditions are variable, with more data being available for some conditions than others. As is the case with influenza vaccine effectiveness in general, effectiveness estimates vary with the seasons and outcomes studied, as well as the health condition(s) of the recipients. These factors make it difficult to draw generalizable conclusions regarding effectiveness of influenza vaccines for individuals with some health conditions.

A recent TND case-control study covering four seasons (2012-13 through 2015-16) reported a moderate protective effect of vaccination against LCI (VE 41%; 95%CI 35, 47) among persons with at least one recognized high-risk medical condition. This estimate was somewhat lower than that obtained for those without such conditions (VE=48%; 95%CI 43; 52; p=0.02 for comparison). Among children, VE was estimated to be 51% (95%CI 39, 61) for those with a high-risk condition and 52% (95%CI 44; 58) for those without such conditions; these estimates did not differ significantly (p=0.31). For adults aged ≥18 years, VE was 38% (95%CI 30–45%) among those with high-risk conditions and 44% (95%CI 38, 50%) for those without (p=0.21) (191).

#### Pulmonary Conditions

Much of the literature concerning influenza vaccine effectiveness among children with pulmonary conditions focuses on asthma. In a nonrandomized controlled trial during the 1992–93 season involving 137 children with moderate to severe asthma, VE against laboratory-confirmed influenza A(H3N2) infection was 54% (p<0.01) among children aged 2 through 6 years and 78% (p<0.01) among children aged ≥7 through 14 years; VE against laboratory-confirmed influenza B infection was 60% (p<0.01) among children aged ≥7 through 14 years, but was 22% and nonsignificant (p>0.05) for the younger age group (192). Among adults with asthma in a four-season TND case-control study, vaccine effectiveness against LCI was estimated to be 27% (95%CI 10, 41), lower than that for adults without high risk conditions (VE=44%; 95%CI 38, 50; p=0.02) (191).

Studies of the association between vaccination and prevention of asthma exacerbations have provided variable results. A retrospective uncontrolled cohort study based on medical and vaccination records during three seasons (1993–94 through 1995–96) among asthmatic children aged 1 through 6 years showed an association between receipt of IIV3 and reduced rates of exacerbations in two of the three seasons (193). In a study of 80 asthmatic children aged 3–18 years, vaccination was associated with a

lower risk of oral steroid use (OR=0.29; 95%CI 0.10, 0.84) (194). A 2012-13 season study of 93 children with mild persistent asthma between the ages of 1 and 14 years, found that vaccinated children had significantly fewer ARI episodes (2.2 vs 6.9, p<0.001) and asthma exacerbations (1.6 vs. 6.2, p<0.001), as well as less use of bronchodilators (1.6 vs 6.2, p>0.001) and systemic steroids (0.1 vs 1.1, p<0.001) (195). In the year following vaccination, these children also had fewer hospitalizations (0.2 vs 1.3, p<0.001) and shorter length of stay (5.3 vs 7.2, p<0.034) (195). Other studies have noted no benefit of influenza vaccination against asthma exacerbation among children (196, 197). Several studies (198-200) indicate that vaccination does not appear to increase risk of asthma exacerbations.

Asthma exacerbations are commonly treated with systemic steroid medications, which may potentially interfere with immune responses. 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 (201).

A multi-center prospective cohort study of patients with COPD over the 2011-15 influenza seasons enrolling 4,198 patients estimated an overall adjusted VE against influenza-related hospitalizations to be 37.5% (95%CI 27, 46) (202). Estimates over the first 3 years of the study ranged between 43%-49%, though protection was significantly lower in the final year due to vaccine and circulating strain mismatch (aVE=6%; 95%CI -24, 28). Some observational studies reported an association between influenza vaccination and lower all-cause mortality among persons with COPD (203, 204)

**Cardiovascular Conditions**

Limited influenza vaccine effectiveness data are available for children with cardiovascular conditions. In an analysis of data for individuals with high-risk conditions from a test-negative case-control study conducted over four seasons, only 8% of children aged <18 years presented with heart disease; an adjusted effectiveness estimate was not calculated due to the limited sample size (191). Among adults with cardiovascular conditions, the same observational study reported an estimated vaccine effectiveness of 47% (95%CI 35, 58).

Some evidence suggests that acute respiratory infections might trigger atherosclerosis-related acute vascular events (205). Several studies have suggested protective efficacy of influenza vaccination against vascular events. In one randomized study, participants with known coronary artery disease who received IIV3 had 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 outcome including cardiovascular death, nonfatal MI, 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) (206, 207). A randomized placebo-controlled trial found a reduced risk of a composite cardiac ischemic event endpoint (including cardiovascular death, myocardial infarction, coronary revascularization or hospitalization for myocardial ischemia) one year after vaccination compared with

placebo (HR=0.54; 95%CI 0.29, 0.99) (208); there was no reduction in risk for cardiovascular death alone or for a second composite endpoint which did not include hospitalization for myocardial ischemia. A third randomized study found association between vaccination and reduced risk of a composite endpoint including death, hospitalization for acute coronary syndrome, hospitalization for heart failure, and hospitalization for stroke at 12 months postrandomization (aHR=0.67; 95%CI 0.51, 0.86), but not cardiovascular death (0.62; 95%CI 0.34, 1.12) (209). In a systematic review and meta-analysis including the studies described above, vaccination was effective at reducing or preventing major cardiovascular events (pooled effectiveness=44%; 95%CI 25, 58), cardiovascular deaths (pooled effectiveness=60%; 95%CI 29, 78); and hospitalization (pooled effectiveness=51%, 95%CI 16—72) in vaccinated participants at one-year follow up (210).

A retrospective study covering 13 influenza seasons found that among elderly adults, vaccination was associated with lower risk of hospitalization associated with diagnostic codes for MI (aOR=0.80; 95%CI 0.76, 0.84), and ischemic stroke (aOR=0.80; 95%CI 0.77, 0.82) (211). However, these data contrast with a more recent case series analysis which revealed an association between influenza and MI, and found that vaccination did not attenuate this increased risk (45).

Use of statin medications (a class of drugs commonly prescribed to persons with vascular disease) have been evaluated for potential associations with diminished response to influenza vaccine. 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 (GMTs) following vaccination among persons receiving chronic statin therapy (by 38%; 95%CI 27, 50 for A(H1N1), by 67%; 95%CI 54, 80 for A(H3N2), and by 38%; 95%CI 28, 49 for B). The effect was more pronounced among those receiving synthetic statin drugs (fluvastatin, atorvastatin, and rosuvastatin) relative to those receiving fermentation-derived statins (pravastatin, simvastatin, and lovastatin) (212). A retrospective cohort study covering nine influenza seasons found reduced effectiveness of influenza vaccine against MAARI among statin users (213); 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, 59 for statin nonusers vs. -21%; 95%CI -84, 20 for statin users); statin use was not associated with lower vaccine effectiveness against H1N1pdm09 or B viruses (214). In a large observational TND case-control study retrospectively including 11,692 participants aged ≥ 45 years who were enrolled over 6 influenza seasons (2011-2 through 2016-17), overall vaccine effectiveness was 38% (95%CI 32, 44) (215), and was not meaningfully changed after adjustment for statin use. Upon stratification, VE was estimated to be 36% (95%CI 22, 47) among statin users compared to 29% (95%CI 32, 45) among non-users. Statin use alone was not significantly associated with decreased VE in analyses by viral type/subtype, and type of statin (synthetic or non-synthetic) did not have a significant effect on VE.

**Neurologic and Neuromuscular Disorders**

Among adults with neurologic disorders, a TND case-control study over four seasons reported effectiveness against LCI of 49% (95%CI 22, 66), which was similar to those without any high-risk conditions (44%; 95%CI 38, 50, p=0.30) (191). No vaccine effectiveness estimate was reported for children, as there were few children with neurologic disorders in this sample.

**Renal Disorders**

In a small study of pediatric patients with renal disease, seroconversion and seroprotection rates and changes in GMTs after vaccination were similar among those with chronic renal insufficiency, those on hemodialysis, and healthy controls (216). Among adults, studies have shown adequate immune responses among persons with chronic renal insufficiency on dialysis (217, 218). In a four-season test-negative case-control study, estimated influenza vaccine effectiveness was 32% (95%CI -6, 57) among adults with renal diseases; though not statistically significant, this estimate did not differ significantly compared to healthy patients without any high-risk conditions (p=0.39) (191). A systematic review and meta-analysis which reviewed 5 observational studies of patients with end-stage renal disease receiving dialysis reported adjusted effectiveness against all-cause mortality of 32% (95%CI 24, 39), against cardiac death of 16% (95%CI 2, 29), and against hospitalization due to influenza and pneumonia (VE=14%, 95%CI 7, 20) (219); evidence was judged to be of very low quality for all outcomes.

**Hepatic Disorders**

Most available data concerning influenza vaccination of persons with hepatic conditions come from adult populations. In a small prospective study among patients who either had cirrhosis or who were inactive carriers of hepatitis B, there were no significant differences in seroprotective response rates between these persons and healthy controls (220). Similar results were observed in studies evaluating the immunogenicity of IIV3 among persons with cirrhosis, hepatitis B and hepatitis C (221, 222). In a prospective study of 311 persons with cirrhosis, IIV3 reduced the rate of ILI (14% vs. 23%; p= 0.064) and of culture-positive influenza (2.3% vs. 8.8%; p= 0.009) in the vaccinated group when compared to healthy controls (223). Vaccination was also associated with reduced risk of hepatic decompensation (p=0.018). A retrospective study of persons with chronic hepatitis B infection found lower rates of hospitalization among vaccinated individuals (16.29 vs. 24.02 per 1,000 person-years) (224). Among adults enrolled within a prospective TND study over the 2012-13 through 2015-16 influenza seasons, VE in outpatients with liver diseases was 61% (95%CI 31, 78) (191).

**Metabolic Disorders and Diabetes**

Studies of adults with diabetes have reported an association between vaccination and reduced risk of hospitalizations for acute respiratory illness, MI, congestive heart failure, stroke, or death (220, 225, 226). However, studies using LCI outcomes are limited. A prospective TND study has reported significant influenza vaccine effectiveness against any LCI among outpatient adults with diabetes (aVE=46%, 95%CI 30, 58) (191).

**Obesity**

A prospective study 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 (227). A study comparing 1-month and 12-month post-vaccination immune response showed that obese persons mounted a vigorous initial antibody response to IIV3 (228); however, higher BMI was associated with a decline in influenza antibody titers after 12 months post-vaccination. A second study of older adults reported immunogenicity of IIV3 was similar in obese and normal-weight older adults, with a slight increase in seroconversion for the influenza A(H3N2) virus among those who were obese, but not for the other vaccine components (229). In a non-randomized prospective study of a school-based vaccination program in the 2010-11 season, VE against PCR-confirmed influenza was 72.7% (95%CI 25.7, 90.0%) in obese children and 63.5% (95%CI 34.6, 79.6%) in non-obese children, though the difference was not statistically significant (230).

**Autoimmune and Inflammatory Disorders**

Literature evaluating the efficacy and effectiveness of the influenza vaccine among children with inflammatory diseases is limited. Among analyses from studies of children with conditions such as rheumatic arthritis and inflammatory bowel disease, some suggest immune response to vaccine comparable to healthy controls while others suggest a diminished response, particularly among those on immunomodulatory therapy (231-235). Some have noted less responsiveness to influenza B as compared with influenza A vaccine components.

Among adults with Crohn's disease or ulcerative colitis, a prospective randomized comparison study found no significant difference in immune response to IIV4 between healthy controls and patients with inflammatory bowel disease, though immune response did vary based on drug therapy (patients were receiving immunomodulatory monotherapy, anti-tumor necrosis factor-α [anti-TNF-α] single-agent therapy, or some combination of the two at the time of vaccination) (236). Immune response in the setting of rheumatoid arthritis may be diminished but is generally satisfactory (237-240), even when immunomodulatory agents are used, though decreases in antibody levels have been reported with increasing time post-vaccination (238). One such study found timing of vaccination in relation to timing of immunotherapy, such as infliximab (anti-TNF-α), had no effect on seroprotection (241). Another study, a prospective multicenter randomized clinical trial among adults with rheumatoid

arthritis, found that more patients who took a 2-week pause/discontinuation from methotrexate therapy seroconverted to all four strains of the 2016-17 IIV4 than those who continued with routine therapy (75.5% vs 54.5%, p<0.001) (242).

**Persons with Malignancies**

Predictors of successful seroconversion in children with cancer noted in some studies have included higher white cell count, lymphocyte count, IgG levels, increasing age, phase of therapy, and completion of therapy (243-249). Immunogenicity was evaluated in a two season prospective cohort study of 259 children and young adults on chemotherapy (250). Of the 157 pre- and post-vaccination serologic samples, 62% seroresponded to at least one influenza A subtype post-vaccination. There was no statistically significant difference in the proportion of seroresponders compared to non-seroresponders with RT-PCR confirmed influenza or ILI (11% vs. 19%, respectively). However, the study was not powered to detect a difference in this outcome. Additional analysis of predictors failed to show any significant relationship between cancer type and seroresponse (stratified as acute lymphoblastic leukemia vs solid/brain tumors) or vaccination during chemotherapy treatment and seroresponse.

In a retrospective review of 498 patient-seasons occurring between the 2010-2011 and 2012-2013 influenza seasons, there was no significant difference in the overall rates of influenza between children with acute leukemia who had been appropriately vaccinated and those who had not in any individual season (251). There was also no significant difference in the rate of ILI between vaccinated and unvaccinated patients overall or in any individual season, suggesting IIV3 did not protect children with acute leukemia against LCI or ILI. In a prospective study of 100 children and adolescents aged 6 months through 18 years who were within 4 weeks of receiving or completing immunosuppressive therapy for cancer, the infection occurred among 2% among the vaccinated cases (n=2/100), compared to 6.8% among the unvaccinated community controls (n=11/161); adjusted for age group and tumor type, VE against LCI was 72% (95%CI −26, 94)(243).

A case-control study of adults with malignant lymphoma found that 10% of the 29 subjects in the group with lymphoma were able to mount a 4-fold increase in titer to one of the influenza A vaccine antigens, compared to 45% of the control group (n=29). Among the those with lymphoma, none responded to both A and B antigens, whereas 24% (n=7) age-matched controls had a 4-fold titer to both A and B antigens contained in the vaccine (252). In a systematic review of 16 studies measuring the serological response and clinical outcomes of patients with solid cancer or hematologic malignancies after influenza vaccination, decreased rates of seroconversion were reported among those receiving chemotherapy compared to those not receiving chemotherapy, though protective HAI antibody titers were still achieved among those receiving chemotherapy (253).

One study compared adjuvanted IIV3 with unadjuvanted IIV3 among 67 allogeneic hematopoetic stem cell transplant recipients, and found seroconversion rates were not significantly higher with the

adjuvanted vaccine (254). In a randomized double-blind study comping immunogenicity and safety of HD-IIV3 and SD-IIV3 among allogenic hematopoetic stem cell transplant recipients, post-vaccination GMTs were higher in the high-dose group for influenza A(H1N1) and influenza A(H3N2) (p=0.45 and p=0.004, respectively) (255). Also, HD IIV3 had a significantly higher percentage of individuals with titers ≥40 against the A/H3N2 vaccine component. Both the HD and adjuvanted vaccines are currently only licensed for use in persons ≥65 years of age within the US.

### *Immunocompromised Persons*

Persons with compromised immunity due to congenital immunodeficiencies, HIV infection, or medications are potentially at an increased risk of influenza-associated complications. However, the conditions that result in immune compromise are heterogeneous, and susceptibility to influenza and its complications and responsiveness to vaccination may vary with the specific disease state and its severity in a given individual. Among enrollees within a test-negative case-control study over the 2012-16 influenza seasons, adjusted vaccine effectiveness against LCI among adults ≥ 18 years with immunosuppressive conditions as a group (defined by the presence of medical encounters with ICD-10 diagnostic codes) was estimated to be 46% (95%CI 26, 60) (191). By virus type, vaccine effectiveness was significant against influenza A(H3N2) (47%; 95%CI 24, 68) and influenza B (49%; 95%CI 9, 71), but not against influenza A(H1N1) (34%; 95%CI -14, 61) (191).

HIV-infected persons with minimal AIDS-related symptoms and normal or near-normal CD4+ T lymphocyte cell counts who receive IIV have been shown to develop adequate antibody responses (256, 257). Among persons who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, IIV might not induce protective antibody titers (256, 258); a second dose of vaccine might not improve immune response (258, 259). In a randomized study comparing the immunogenicity of high-dose versus standard-dose IIV3 among HIV-infected adults (10% of whom had CD4 counts under 200 cells/µL), seroprotection rates were higher in the high-dose group for all three viruses (260). However, in a comparative study of 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 (261).

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 (262). In a randomized study conducted among 506 HIV-infected adults, (349 on antiretroviral treatment and 157 treatment-naïve) efficacy of IIV3 against LCI was 75% (95%CI 9, 96) (263). In a randomized study of a two-dose regimen of IIV3 versus placebo conducted among 410 children aged 6-59 months (92% receiving ART), and estimated vaccine efficacy was 18% (95%CI 0, 62). The authors suggested that poor immunogenicity and drift of the circulating A(H3N2) viruses might have contributed to the poor vaccine efficacy observed in this study (264).

## *Transplant Recipients*

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 (265). In a study of pediatric liver transplant patients, one month after vaccination, the majority of patients had seroprotective levels of antibody against all strains of vaccine antigens (67%, 56% and 56% against A/H3N2, A/H1N1 and B respectively) (266). Predictors of seroprotection included age and time since transplantation.

Among persons who have undergone kidney transplantation, seroresponse rates have been observed that were similar or slightly reduced compared with healthy persons (267-271). Antibody response among persons who were 6 months post kidney transplant were lower than observed for healthy controls in one prospective study (269). In another, among persons 3–10 years post- kidney transplant, the postvaccination seroprotection rate was 93% to A(H1N1) (270). 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 (aHR=0.82; 95%CI 0.76, 0.89; p<0.001) in one study (272).

A study which compared antibody response to IIV3 among liver transplant recipients (on average, 3 years post-transplant), persons with cirrhosis, and cirrhosis, and healthy controls, noted significantly lower post-vaccination titers among the transplant recipients compared with controls (273). However, titers ≥1:40 were noted in 68% of transplant recipients after 1 dose of IIV3. Another study noted seroprotection rates were lower if vaccination occurred within the four months after the transplant procedure (274).

In a prospective observational study which compared immune response to IIV3 and 23-valent pneumococcal vaccine among and of 16 persons who were one year post-heart transplant vs. healthy controls, response to IIV3 was significantly reduced in transplant recipients though approximately 50% of patients had seroprotection against two of the three vaccine antigens. Immune response among transplant recipients to each vaccine strain was significantly lower compared to controls; furthermore, following additional booster vaccination 4 weeks after the initial dose, antiviral titers in transplant patients remained nearly identical 4 weeks after initial vaccination, and 8 weeks after booster injection (275). This finding contrasts with that from an additional randomized controlled trial comparing multiple doses of IIV3 among persons who had received various solid organ transplants (kidney, liver, heart, and lung), which found seroprotection rates were higher at 10 weeks post-vaccination among those who received two doses, but did not have a significantly lasting effect one year post-vaccination (276).

High-dose IIV3 was more immunogenic than standard-dose IIV3 in a randomized trial in 161 adult solid organ transplant recipients (277). In a comparison of the immunogenicity of adjuvanted IIV3 with unadjuvanted IIV3 among 67 allogeneic hematopoietic stem cell transplant recipients, seroconversion rates were not significantly higher with the adjuvanted vaccine (254). Both of these vaccines are currently only licensed for use in persons ≥65 years of age.

***Update September 2024:*** For additional information concerning solid organ transplant recipients, visit the June 2024 evidence review of HD-IIV, aIIV, and RIV compared with standard-dose unadjuvanted IIVs for this population:

- https://www.cdc.gov/acip/grade/influenza-solid-organ-transplant.html#:~:text=The%20number%20of%20solid%20organ%20transplants%20(SOTs)%20performed%20each%20year
- https://www.cdc.gov/acip/evidence-to-recommendations/influenza-solid-organ-transplant-etr.html#:~:text=ACIP%20Recommendation.%20ACIP%20recommends%20high-dose%20inactivated%20(HD-IIV3)%20and.

## 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, was licensed in 2016 (RIV4; now produced by Sanofi Pasteur, Swiftwater, Pennsylvania). For the 2018-19 season, only RIV4 will be available in the U.S. RIV4 contains 45 µg of HA protein per vaccine virus component (180 µg total). 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 (124).

As a relatively new type of influenza vaccine, fewer post-marketing effectiveness data are available for RIVs than IIVs. Initial licensure of RIV3 was for persons aged 18 through 49 years. In pre-licensure studies comparing RIV3 versus placebo among persons aged 18 through 49 years, serum antibody responses were induced to all three vaccine components (278). In a randomized placebo-controlled study conducted among healthy persons aged 18 through 49 years during the 2007–08 influenza season (124, 279), 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 (124). Estimated vaccine effectiveness without regard to match was 44.6% (95%CI 18.8, 62.6) (279).

In October 2014, the approved age indication for RIV3 was expanded to ≥18 years on the basis of data from randomized trials demonstrating adequate immunogenicity among persons aged ≥50 years (280, 281). More recently, a pre-licensure randomized controlled trial of RIV4 vs. a licensed comparator IIV4 was performed among persons aged ≥50 years during the 2014-15 season (282, 283). This study is discussed in a later section (see *HD-IIV3, aIIV3, and RIV4 for Older Adults)*. The immunogenicity of RIV4 was comparable with that of a licensed comparator IIV4 among 18 through 49-year-olds in a randomized trial (284). When evaluated in children 6 through 59 months of age, RIV3 was found be

safe but less immunogenic than comparable volumes of IIV3, particularly among children <36 months of age (285). RIV4 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 and lesser benefit of vaccination among older adults, 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; Fluzone High-Dose) and adjuvanted IIV3 (aIIV3; Fluad). In recent years, studies have been conducted comparing the benefits for older adults of these vaccines, as well as for quadrivalent recombinant influenza vaccine (RIV4; Flublok Quadrivalent), with those conferred by standard-dose, unadjuvanted IIVs (SD-IIVs). Some have been studies of LCI-related outcomes. For each of these vaccines, there is at least some evidence of benefit as compared with SD-IIVs.

***Update September 2024:*** For additional information concerning this topic, see the June 2022 evidence review of HD-IIV, aIIV, and RIV compared with standard-dose unadjuvanted IIVs for older adults:

- https://www.cdc.gov/acip/grade/influenza-older-adults.html
- https://www.cdc.gov/acip/evidence-to-recommendations/influenza-older-adults-etr.html).

### *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), four times the amount of HA in standard-dose IIVs (286). Licensure was based on superior immunogenicity compared with standard-dose IIV3 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 (287-289). In pre-licensure studies, pre-specified criteria for superiority (defined by a lower bound of the 95%CI for the ratio of geometric mean HAI 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%) were met for influenza A(H1N1) and influenza A(H3N2) virus antigens, but not for the influenza B virus antigen (for which criteria for non-inferiority were met) (288, 290).

Superior efficacy of Fluzone High-Dose compared to Fluzone SD-IIV3 was demonstrated in a large randomized comparative efficacy trial conducted among nearly 32,000 persons aged ≥65 years over the 2011–12 and 2012–13 influenza seasons (291). 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, 36.5) greater relative efficacy of the HD-IIV3 compared to SD-IIV3 for protection against LCI caused by any viral type or subtype. 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 (286). 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, 72.0) (291). While this study did not initially examine health care utilization, pneumonia, and deaths confirmed to be due to influenza; a subsequent analysis of these data examined all-cause hospitalizations, deaths, and pneumonia cases judged to be related to influenza. In this analysis, in which serious adverse events (SAEs) from the study were evaluated for possible relatedness to influenza illness by blinded physician reviewers, HD-IIV3 was associated with a relative vaccine efficacy of 39.8% (95%CI 19.3, 55.1) for serious pneumonia and 17.7% (95%CI 6.6, 27.4) for serious cardiopulmonary events possibly related to influenza; relative efficacy against all-cause hospitalizations was lower (6.9%, 95%CI 0.5, 12.8) (292).

In addition to the analyses of clinical outcomes described above, healthcare consumption data derived from this trial were used to perform a cost-effectiveness analysis (293). 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, 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, 33.30). A probabilistic sensitivity analysis indicated that the HD-IIV3 is 93% likely to be cost saving relative to SD-IIV3.

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 the risk of hospital admissions related to pulmonary or influenza-like illnesses (294). The nursing home 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, 0.982). Also significantly lower were rates for pneumonia admissions (aRR=0.791; 95%CI 0.267, 0.953), and all-cause hospital admissions (aRR=0.915; 95%CI 0.863, 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, 0.9) (295). In a retrospective cohort study of Veterans Health Administration patients during the 2015-16 season, HD-IIV3 was associated with a relative effectiveness of 25% (95%CI 2, 43%) for pneumonia/influenza hospitalizations compared to SD-IIV3. Relative effectiveness against laboratory-confirmed influenza was 38% (95%CI -5, 65%) (296).

HD-IIV3 has also been evaluated among persons aged ≥65 years through analysis of Medicare data. Among 929,730 HD-IIV3 recipients and 1,615,545 SD-IIV3 recipients 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, 29) and hospital admissions with a billing code for influenza (relative VE=22%; 95%CI 16, 27) (297). 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%, 56%), when A(H3N2) viruses predominated; but not during the 2013-14 season (2.5%; 95%CI –47%, 35%], in which A(H1N1) viruses predominated (298).

### *aIIV3 (Fluad)*

The only adjuvanted influenza vaccine in the U.S., Fluad (aIIV3; Seqirus, Holly Springs, North Carolina), was initially licensed in the U.S. in November 2015. It contains the oil-in-water adjuvant, MF59 (299). Like 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 aIIV3 and unadjuvanted IIV3, aIIV3 met criteria for non-inferiority for all three vaccine viruses based on predefined thresholds for seroconversion rate differences and GMT ratios; criteria for superiority were not met (299, 300). A Canadian observational study of 282 persons aged ≥65 years (165 receiving aIIV3, 62 receiving SD-IIV3, and 55 unvaccinated) conducted during the 2011–12 season that compared Fluad with unadjuvanted IIV3 reported an estimated relative effectiveness of Fluad against LCI among the 227 vaccinated participants of 63% (95%CI 4, 86) (301). 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, 0.98) (302). 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, 68 for aIIV3 vs. adjusted VE=46%; 95%CI 24, 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, 78 for IIV3 vs. adjusted VE=34%; 95%CI 24, 65) (303). That the two vaccines were not compared during the same season is a limitation of this study.

### *RIV4 (Flublok Quadrivalent)*

Flublok Quadrivalent (RIV4; Sanofi Pasteur, Swiftwater, Pennsylvania) is licensed for persons aged ≥18 years. 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 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 (281). 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, 47). This season was characterized by a predominance of drifted A(H3N2) viruses, and consequent poor match between vaccine and circulating viruses (283, 304). 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, 53) and for influenza B was 4% (95%CI -72, 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, 43), but was more effective than IIV4 against culture-confirmed protocol-defined ILI (relative efficacy=42%; 95%CI 9, 65).

## Immunogenicity, Efficacy, and Effectiveness of Live Attenuated Influenza Vaccine (LAIV)

LAIV contains live influenza viruses which replicate in the nasopharynx following intranasal administration. Each season, the vaccine viruses are produced via genetic reassortment from a master strain that includes genes conferring three phenotypic characteristics: attenuation (to restrict reactogenicity and pathogenicity), temperature sensitivity (to restrict replication in the lower respiratory tract), and cold adaptation (to permit replication in the nasopharynx) (305). Intranasal administration of LAIV appears to induce both serum and nasal secretory antibodies, as well as cell-mediated immune responses, but antibody response is not a reliable correlate of protection (306).

LAIV3 (FluMist; AstraZeneca/MedImmune, Gaithersburg, Maryland) was licensed in the United States in 2003. The humoral immunogenicity of LAIV was demonstrated in a number of studies (307-309). Subsequently, LAIV4 (FluMist Quadrivalent) was licensed in 2012, and replaced LAIV3 beginning with the 2013–14 season. Pre-licensure studies comparing HAI antibody responses following LAIV4 to LAIV3 demonstrated noninferiority of LAIV4 among healthy children and adults ≤49 years (310, 311).

### *LAIV3 in Children*

In a large randomized, double-blind, placebo-controlled trial among 1,602 healthy children aged 15–71 months conducted during 1996-97 and 1997-98, LAIV3 demonstrated efficacy against culture-confirmed influenza (312, 313). During the first season, when vaccine and circulating virus strains were well matched, efficacy was 94% (95%CI 88, 97) for participants who received 2 doses separated by >6 weeks, and 89% (95%CI 65, 96) for those who received 1 dose (312). During the second season, when the A(H3N2) component in the vaccine was not well matched with circulating viruses, 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) (313). 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 and 73.5% (95%CI 63.6, 81) after 2 doses during the first year of the study (314). In the second year, VE estimates following a single dose were 73.6% (33.3, 91.2) and 65.2% (31.2,88.8) among those who had received 2 doses, or 1 dose, respectively, during the first year. Other two-season, randomized, placebo-controlled trials have demonstrated similar efficacy rates of LAIV3 among young children (315, 316).

Other studies have noted protection from outcomes other than LCI with LAIV3 use. In a 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 (317). Receipt of LAIV3 resulted in 21% fewer febrile illnesses (95%CI 11, 30) and 30% fewer febrile otitis media diagnoses (95%CI 18, 45) in a randomized controlled trial (312). 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) (318).

### *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 conducted during the 1997–98 influenza season (when the vaccine and circulating A(H3N2) viruses were not well matched) noted no significant decrease in the frequency of febrile illnesses among LAIV3 recipients compared with placebo. However, vaccine recipients had an 18.8% reduction in severe febrile illnesses (95%CI 7.4, 28.8), and a 23.6% reduction in

febrile upper respiratory tract illnesses (95%CI 12.7, 33.2); as well as 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 (319). Estimated efficacy of LAIV3 against influenza confirmed by culture or RT-PCR in a randomized, placebo-controlled study among 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 (320-322).

### *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 (320-325). 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 (326).

Several studies, comparing LAIV3 with IIV3 prior to the 2009 pandemic demonstrated superior efficacy of LAIV3 against LCI among young children (323, 327-330). A randomized controlled trial conducted among 7,852 children aged 6–59 months during the 2004–05 influenza season demonstrated a 54.9% reduction (95%CI 45.4, 62.9) in cases of culture-confirmed influenza among children who received LAIV3 compared with those who received IIV3. In this study, LAIV3 efficacy was higher compared with IIV3 against antigenically drifted viruses and well-matched viruses (328). LAIV3 provided 31.9% relative efficacy (95%CI 1.1, 53.5) in preventing culture-confirmed influenza compared with IIV3 in one study conducted among children aged ≥6 years and adolescents with asthma (329) and 52.4% relative efficacy (95%CI 24.6, 70.5) compared with IIV3 among children aged 6–71 months with recurrent respiratory tract infections (327).

In June 2014, on the basis of the data from two randomized comparative trials of LAIV3 vs. IIV3 among healthy children, the ACIP made a preferential recommendation for LAIV3 for healthy children aged 2 through 8 years who have no contraindications or precautions (331). 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 (332-334). 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) (335). During the 2014-15 season, when antigenically drifted A(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 (336-338), in contrast to earlier studies in which LAIV3 provided better protection than LAIV against drifted H3N2 viruses (328). 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, the ACIP concluded that a preference of LAIV4 over IIV was no longer warranted (339).

The diminished effectiveness of LAIV4 against A(H1N1)pdm09 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 (340). Exposure during U.S. distribution of some LAIV lots to temperatures above those recommended for storage was also considered a potential contributing factor (341). This led to development and inclusion of a different influenza A(H1N1)pdm09 virus, A/Bolivia/559/2013(H1N1), in LAIV4 for 2015-16 (342). A(H1N1)pdm09 viruses were again predominant during this season. However, data from the U.S. Flu VE Network, U.S. Department of Defense, and MedImmune demonstrated no statistically significant effectiveness of LAIV4 among children aged 2 through 17 years against A(H1N1)pdm09 (343). 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, the ACIP made the interim recommendation that LAIV4 should not be used for the 2016–17 influenza season (344). This recommendation was extended into the 2017-18 season (345).

Estimates of the effectiveness of LAIV against A(H1N1)pdm09 during the 2013-14 and 2015-16 seasons were not consistent among all studies and all countries. While most estimates were statistically insignificant, point estimates varied. In the United Kingdom, estimated effectiveness of LAIV4 among 2 through 17 year olds during the 2015-16 season was 57.6% (95%CI 25.1, 76.0) for all influenza, 41.5% (95%CI -8.5, 68.5) for A(H1N1)pdm09, and 81.4% (95%CI 39.6, 94.3) against influenza B (346). In Finland during the 2015-16 season, effectiveness of LAIV4 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 (347). 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 influenza A 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 A(H1N1)pdm09 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) (348). Two other

Canadian studies, a cluster-randomized comparative trial of LAIV3 and IIV3 conducted among Hutterite populations in Alberta and Saskatchewan during the 2012-13 through 2013-14 seasons (349) and a test-negative case-control study comparing LAIV and IIV conducted in Alberta during the 2012-13 through 2015-16 seasons (350), showed no overall difference in effectiveness between the two vaccine types. 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 (351).

The mechanism for the decreased effectiveness of LAIV4 against A(H1N1)pdm09 that was observed during 2013-14 and 2015-16 has been the subject of considerable investigation. Vaccine virus interference associated with the introduction of the fourth virus in LAIV has been cited as a potential contributing factor. However, reduced effectiveness against influenza A(H1N1)pdm09 was also noted with LAIV3 in the U.S. during 2010-11 (335). 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 (335). Investigations by the manufacturer, presented to the ACIP in February (352) and October 2017 (353), revealed reduced replicative fitness of both the A/California/7/2009 and A/Bolivia/559/2013 (H1N1) LAIV viruses, which is currently accepted as the primary root cause of poor effectiveness against circulating H1N1pdm09 influenza viruses (354).

In February 2018, the manufacturer presented data to ACIP from a US pediatric shedding and immunogenicity study of a new LAIV4 A(H1N1)pdm09-like virus, A/Slovenia/2903/2015. This study was conducted among 200 children aged 2 through <4 years, assigned 1:1:1 to receive LAIV3 containing A/Bolivia/559/2013, LAIV4 containing A/Bolivia/559/2013, or LAIV4 containing A/Slovenia/2903/2015. A/Slovenia/2903/2015 was shed by a higher proportion of children during days 4 through 7 following the first dose of vaccine than the comparator A(H1N1)pdm09-like viruses. A/Slovenia/2903/2015 also induced significantly higher antibody responses than A/Bolivia/559/2013. Seroconversion rates to A/Slovenia/2903/2015 were comparable to seroconversion rates obtained in response to pre-pandemic A(H1N1) LAIV strains used during seasons in which the vaccine was observed to be effective against A(H1N1) viruses (355). Additional data discussed at ACIP included a combined individual patient-level data analysis of the effectiveness of LAIV4 and IIV during the 2013-14 through 2015-16 seasons, using data pooled from 5 US observational studies, and a systematic review and meta-analysis of LAIV effectiveness for the 2010-11 through 2016-17 seasons, which included data from within and outside the US (355). These analyses of previous seasons' data revealed that while LAIV4 was poorly effective or ineffective against influenza A(H1N1)pdm09 viruses in most studies, it generally was effective against influenza B viruses, and generally no less effective than IIV against influenza A(H3N2) viruses.

For the 2018-19 and 2019-20 U.S. influenza seasons, ACIP has again recommended that LAIV4 was an acceptable option for vaccination of persons for whom it is appropriate. No U.S. effectiveness

estimates are available for the 2018-19 season, during which the vaccine contained A/Slovenia/2903/2015 as the influenza A(H1N1)pdm09 component.

## Duration of Immunity

The composition of influenza vaccines changes in most seasons, with one or more vaccine viruses 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 post-vaccination (356-358). Observed rates and degrees of decline have varied. One study of HA and NA antibody levels following vaccination of adults noted a slow decline, with an estimated time to 2-fold decline of >600 days (359). A review of studies reporting post-vaccination seroprotection rates among adults aged ≥60 years noted that seroprotection levels meeting the Canadian 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 (360).

Nonetheless, concerns have arisen regarding waning of protection within the course of a single influenza season, particularly among adults. Recent observational studies have evaluated changes in influenza vaccine effectiveness over the course of a single influenza season. Some have noted decline in vaccine effectiveness over the course of a season (361-370). In some studies this effect has been more pronounced for influenza A(H3N2) than influenza A(H1N1) and influenza B viruses, and among older adults. 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. Being vaccinated >120 days before diagnosis was associated with increased risk for influenza, compared with vaccinated <100 days prior (OR=3.45; 95%CI 1.10, 10.85; p = 0.034). This effect was most pronounced among 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 (362). 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 (364). 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). This pattern was not observed among older children and younger adults (361).

In addition to the single-season studies above, several multi-season studies have noted intra-season waning of influenza vaccine effectiveness (366-368, 371, 372). A multi-season (2011-12 through 2014-

15) analysis from Spain noted that persons aged ≥65 years who were vaccinated later in the season had a lower risk of hospital admission for influenza than those who were vaccinated earlier in the season (366). An analysis of the 2011-12 through 2014-15 seasons from the U.S. Flu VE Network found that vaccine effectiveness declined by about 7% per month for H3N2 and influenza B, and 6—11% per month for H1N1pdm09. Vaccine effectiveness remained greater than zero for at least five to six months after vaccination (371). In an analysis of data from a European multicenter study covering the 2010-11 through 2014-15 seasons, vaccine effectiveness against influenza A(H3N2) viruses declined from 50.6% (95%CI 30.0, 61.1) 38 days after vaccination to 0% (95%CI -18.1, 15.2) 111 days after vaccination. For influenza B viruses, vaccine effectiveness declined from 70.7% (95%CI 51.3, 82.5) 44 days post-vaccination to 24.1% (95%CI -57.4, 60.8) by the end of the season. Vaccine effectiveness for influenza A(H1N1) viruses remained relatively stable, from 55.3% (95%CI 37.9, 67.9) at day 54 to 50.3 (95%CI 34.8, 62.1%) at the end of the season (368). In a multi-season (2010-11 through 2013-14) study of US Department of Defense non-active duty beneficiaries, vaccine effectiveness against all influenza and against influenza A(H3N2) viruses was statistically significant and comparable at 15-90 days and 91-180 days after vaccination, though was insignificant from 181 days onwards. Vaccine effectiveness against influenza B viruses was no longer significant by 91 days post-vaccination (367).

Overall, 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. Nonetheless, these findings raise considerations for timing of vaccination. Delaying timing of vaccination may be beneficial in some seasons, but this is dependent upon the presence and rate of decline in immunity (373). This issue is complicated by the variability of the timing of onset of influenza activity each season, which precludes prediction of the optimal time to vaccinate this season. The potential negative effects of deferring vaccination until later in the season, such as missed opportunities to vaccinate, programmatic issues associated with vaccinating a defined population in a more constrained time period, and vaccinating after the start of influenza circulation, are also important considerations (374).

## Repeated Vaccination

Observations of a potential negative effect of repeat vaccination on vaccine effectiveness were initially made during the 1970s (375-378). 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 IIV3s were used (with the exception of addition of a monovalent split-virus A(H1N1) to supplement the trivalent vaccine in 1986), moderate reductions in serum antibody response during the last seasons of the study were associated with

increased number of annual exposures to vaccine over the previous seasons. However, no decrease in protection against infection was noted (379).

In more recent studies, decreased vaccine effectiveness associated with vaccination in the previous season has not been noted consistently (380-382). In a community-based study in Michigan conducted in 2010-11 (during which influenza A[H3N2] viruses predominated), overall vaccine effectiveness was low and not significant (31%; 95%CI -7, 55%). When stratified by whether vaccine had been received the previous season, vaccine effectiveness was lower in 2010-11 among those who had been vaccinated during both 2010-11 and 2009-10 (-45%; 95%CI -226, 35), as compared with those who received vaccine during only the latter season (62%; 95%CI 17, 82%) (382). 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 (380). A study in Australia conducted over the 2010 through 2015 seasons noted no significant difference in effectiveness of hospitalization for influenza illness between those vaccinated in the current season only (35%; 95%CI 21, 46) vs the prior season only (33%; 95%CI 17, 47). Vaccine effectiveness was highest among those who had received vaccine during both seasons (51%; 95%CI 45, 57) (381).

Other studies have evaluated vaccination history over more than one prior season. A case-control study conducted in a healthcare system in Wisconsin, examined VE against influenza A(H3N2) and influenza B viruses over eight seasons between 2004-05 and 2012-13. 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 (383). In a Spanish study which evaluated the effectiveness of vaccination against H1N1pdm09 from the 2010-11 through 2015-16 seasons, the highest effectiveness was seen among those who had received the current season vaccine and also had received 1-2 doses in earlier seasons. Effectiveness was lower among those vaccinated in the current season after >2 prior doses (384). Other multi-season studies, including a four-season (2011-12 through 2014-15) study in Canada (385) and a six-season (2011-12 through 2016-17) study in Sweden (386), did not find a negative impact of repeated vaccination on influenza vaccine effectiveness.

Systematic reviews of studies of repeated vaccination have reported somewhat varied findings. A review of four randomized controlled trials of LAIV3 vs. placebo administered to a total of 6,090 children over 2 consecutive seasons found that VE against antigenically matched strains was highest for those who received LAIV3 for both seasons (VE=86.7%; 95%CI 76.8, 92.4). In contrast, VE was lower for receipt of LAIV3 in season 2 only (VE=56.4%; 95%CI 37.0, 69.8) (387). A review of 20 observational studies of all vaccine types found a negative effect of vaccination in two consecutive seasons as

compared with vaccination in the current season only for influenza A(H3N2) and influenza B viruses, but not for influenza A(H1N1)pdm09 viruses (388). A review of studies conducted during the 2010-11 through 2014-15 seasons noted considerable heterogeneity in estimates of the effect of prior year vaccination. Negative effects were most pronounced for influenza A(H3N2) viruses during the 2014-15 season (378). A larger review of studies conducted between the 1983-84 and 2016-17 seasons included 5 randomized controlled trials and 28 observational studies concluded that the reviewed evidence did not support a negative effect of revaccination over consecutive seasons, but also noted heterogeneity and imprecision in effect estimates (389). Such variation might perhaps be expected given the variability of circulating viruses VE in different seasons, the large variety of different influenza vaccines available in different seasons and different geographic areas, and the different populations under study. The authors note that the overall quality of the studies reviewed was very low, and that the possibility of reduced effectiveness could not be ruled out.

Negative effects of prior vaccination on VE have not been observed consistently across all studies and seasons, and may differ by influenza virus type or subtype. Better understanding of these effects is needed in order to guide recommendations. Importantly, in 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 post-licensure 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; About the Vaccine Safety Datalink (VSD) | Vaccine Safety Systems | CDC) during 1993–1999 (390). This study noted 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. In a retrospective cohort study of 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 (391). 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. 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 (392). Upon medical record review, none of the events were determined to be serious, and none was associated with complications.

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) (393). These reactions are generally self-limited and subside after 1–2 days. Studies suggest the frequency of fever after IIV in children may vary in different influenza seasons and settings. In a study of 791 healthy children aged 1 through 15 years, post-vaccination 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 (112). 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 (394). A clinical trial assessed fever in 142 children aged 6-47 months randomized to receive acetaminophen, oral placebo, or ibuprofen immediately following IIV and for 24 hours after vaccination. In this study, post-vaccination fever was observed in only two children (one in the acetaminophen group and one in the ibuprofen group) (395).

Since the 2013–14 season, several IIV4 formulations have been licensed. Over the subsequent seasons, fewer IIV3s have been marketed, while available IIV4s have increased. For the 2019-20 season, it is anticipated that all IIVs licensed for children will be IIV4s. IIV4s include products licensed for children as young as age 6 months. In pre-licensure studies of IIV4s, overall frequencies of most solicited adverse events (AEs) were similar to the corresponding comparator IIV3s. Most injection site and systemic AEs are temporary and mild to moderate in severity. Among children, the most common safety complaint was a modest increase in injection site pain (127, 128, 130, 396). The first post-licensure review of VAERS reports covering the 2013–14 and 2014–15 seasons noted that the most common AEs 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 (397).

**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 (398). 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 in Australia between March 2012 and October 2013, influenza was isolated from 19 (13%) (399). 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 (391, 400). During the 2010–11 influenza season, CDC and FDA conducted enhanced monitoring for febrile seizures (primarily among children under 5 years of age) and febrile reactions following receipt of influenza vaccines. This heightened surveillance followed reports of an increased risk for fever and febrile seizures (up to 9 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) (401).

Following these events in Australia, from July 2010 through the 2016-17 season, the ACIP did not recommend use of the U.S.-licensed CSL IIV3, Afluria, for children aged <9 years (344, 402). 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 (403). At the time, lower concentrations of the detergent splitting agent taurodeoxycholate (TDOC) were used for the influenza A(H1N1) and influenza B viruses (0.9% and 0.5%, respectively) than for the influenza A(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 (404, 405). 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 versus 9.2% for the comparator IIV4) (406). 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% versus 3.6% for 5- through 8-year-olds and 2.1% versus 0.8% for 9- through 17-year-olds); these differences were not statistically significant (407). In a more recent clinical trial comparing Afluria IIV4 with a licensed comparator IIV4 among children aged 6 through 59 months, no febrile seizures occurred in either group within 7 days post vaccination; two occurred in the Afluria IIV4 arm, but were late after vaccination (at 43 and 104 days following vaccination) and were judged to be unrelated to receipt of vaccine. The proportion of children who experienced fever was similar between the two groups (408, 409).

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 (410, 411). 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 (411), 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 (401). 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 (412, 413).

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 (2006-07 through 2010-11) (414). 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 U.S. study performed in follow-up the 2010–11 season findings analyzed data from the separate FDA-sponsored PRISM (Post-licensure Rapid Immunization Safety Monitoring) system population. This analysis found no association between receipt of IIV3 (adjusted for concomitant 13-valent pneumococcal conjugate vaccine [PCV13] or diphtheria, tetanus, and acellular pertussis vaccine [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) (415). 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 some 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 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 (416). 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 (417). 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 (418). 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. Inactivated influenza vaccines and other childhood vaccines (including PCV13) may be given concomitantly.

**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 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 (419-423). Whole-virus IIVs are no longer available in the United States, having been replaced with split-virus and subunit IIVs.

As a group, the currently available IIVs are generally less reactogenic than the previous whole-virus products (424). Evaluations of several currently available IIVs have been conducted and have reported favorable safety profiles when administered at a 0.5mL dose for children in this age group (144, 425-427). Recent comparative studies of 0.5mL doses of IIV4s among children aged 6 through 35 months have included FluLaval Quadrivalent (426), and Fluzone Quadrivalent (427), each compared with 0.25mL Fluzone Quadrivalent. In each instance, safety and reactogenicity were comparable between the two groups. In a randomized trial of Fluarix Quadrivalent vs. non-influenza control vaccines that was conducted among 11,795 children aged 6 through 35 months, frequencies of injection site and systemic reactions were similar between Fluarix Quadrivalent and the control vaccines (144).

### *Adults*

In placebo-controlled studies of IIV3 among older adults, the most frequent adverse reaction of vaccination was soreness at the vaccination site (affecting 10%–64% of recipients) that lasted <2 days (428, 429). These injection site reactions typically were mild and not commonly associated with interference with recipients' ability to conduct usual daily activities. Placebo-controlled trials demonstrate that among older persons and healthy younger 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 (428-430). In a VAERS analysis of 18,245 reports from 1990 through 2005, in the most common AEs among adults aged ≥18 years included injection site reactions, pain, fever, myalgia, and headache (431). This VAERS review identified no new safety concerns. Fourteen percent of the IIV3 VAERS reports in adults were classified as SAEs; (defined as those involving death, life-threatening illness, hospitalization or prolongation of hospitalization, or permanent disability (432)), similar to proportions seen in VAERS for other adult vaccines. The most common SAE 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. During the 2013-14 and 2014-2015 influenza seasons, VSD found no increased risk after IIVs for 6 outcomes in populations that included adults (acute disseminated encephalomyelitis [ADEM], anaphylaxis, Bell's palsy, GBS, encephalitis, and transverse myelitis) (417). Another VSD study found that overall there was no increased risk for venous thromboembolism (VTE) after IIV in adults in adults aged ≥50 years (433).

Injection site and systemic AEs were more frequent after vaccination with high-dose IIV3 (HD-IIV3; Fluzone High-Dose; Sanofi Pasteur, Swiftwater, Pennsylvania), which contains 180 µg of HA antigen (60 per vaccine virus) than following 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 HD-IIV3 reported injection site pain, compared with 306 (24%) of 1,262 who received SD-IIV3 (288). Among Fluzone High-Dose recipients, 1.1% reported moderate to severe fever; this was significantly higher than the 0.3% of Fluzone recipients who reported this systemic AE (RR=3.6; 95%CI 1.3, 10.1). A randomized study of HD-IIV3 versus SD-IIV3 including 9,172 participants found no difference in occurrence of SAEs or several specific AEs of interest (including GBS, Bell's Palsy, encephalitis/myelitis, optic neuritis, Stevens-Johnson syndrome, and toxic epidermal necrolysis) (434). Safety monitoring of HD-IIV3 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 (435). A survey of adults aged ≥65 years in the Minneapolis Veterans Affairs Health Care System who received influenza vaccines (547 high-dose and 541 standard dose) during October 2015 found that injection site and systemic adverse reactions were more common after HD-IIV3 than after SD-IIV3 during the week after vaccination (with 37% of HD-IIV3 recipients and 22% of SD-IIV3 recipients

reporting at least one such symptom). There was no significant difference in prevalence of severe adverse reactions or healthcare visits between groups (436).

A trivalent MF59-adjuvanted IIV3 (aIIV3), Fluad (Seqirus, Summit, New Jersey) 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 AEs were observed to occur more frequently following aIIV3 compared with unadjuvanted SD-IIV3; most were mild in severity. Proportions of persons experiencing SAEs was similar between the two groups (299, 300). In addition, rates of immune-mediated diseases after aIIV3 and SD-IIV3 were similar. In a post-marketing review of 630 VAERS reports of adverse events among aIIV3 recipients submitted between July 2016 and June 2018, no new patterns of events were noted, though a relatively high proportion of reports involved administration of the vaccine to persons under 65 years of age (a population for which the vaccine is not currently licensed). Proportions of the most commonly reported adverse events, injection site pain and erythema, was similar to that observed with HD-IIV3 and SD-IIVs (437).

Fewer post-marketing safety data have thus far accumulated for IIV4s, 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 (126, 129, 131, 132, 438). The first post-licensure 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 AE reported following receipt of IIV4 among adults aged 18 through 64 years was injection-site pain. No specific safety concerns were identified (397).

Cell culture-based IIV3 (ccIIV3), was licensed by FDA in 2013; a quadrivalent formulation was licensed in 2016. ccIIV3 appeared 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 AEs; no concerning pattern of AEs was identified (439). In pre-licensure studies, the safety profile of ccIIV4 was similar to that of ccIIV3 (440).

### *Persons at Higher Risk of Influenza-Related Complications*

Overall, fewer safety data pertaining to persons with specific underlying medical conditions are available relative to data from healthy populations. Most studies in these populations are small, limiting the extent to which uncommon or rare AEs may be captured. Few studies directly compare outcomes among persons with high risk conditions with those observed in healthier populations.

A study of 52 children aged 6 months through 4 years with chronic lung disease or congenital heart disease reported fever among 27% and irritability and insomnia among 25% (441). Another of 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 (424). No placebo comparison group was used in these studies. One prospective cohort study found that the rate of AEs

was similar among hospitalized persons who were either ≥65 years or 18–64 years of age and who had one or more chronic medical conditions compared with outpatients; injection site soreness was the most common complaint (442).

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) (443). The most common injection site reactions among vaccinated patients were swelling, itching and pain when touched. However, these symptoms were generally rated as mild and lasted <48 hours. 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 1 and 4 weeks.

Evidence indicates that IIVs are well tolerated in children (444) and adults (200) with asthma. A multicenter, randomized, double-blind, placebo-controlled crossover trial involving 2,032 asthmatic subjects aged 3–64 years found a similar 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) (199). A randomized study of IIV3 versus placebo among 262 adults with asthma 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 colds (445). A randomized crossover design study of IIV3 versus saline placebo showed no significant difference in the occurrence of asthma exacerbations during the 14 days post-vaccination (446).

A non-randomized study compared AEs following receipt of IIV among 105 adults with type 2 diabetes with those occurring among 108 in nondiabetics. Local reactions such as tenderness, pain, redness, and swelling occurred less frequently in the diabetic group. Differences in systemic reactions such as myalgia, tiredness, headache, malaise, chills, and arthralgia were not statistically significant (447).

### *Immunocompromised Persons and Transplant Recipients*

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 (448-453). 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 (452). Limited information is available about the effect of antiretroviral therapy on increases in HIV RNA levels after either influenza virus infection or influenza vaccination (454, 455).

IIV generally has been shown to be well-tolerated in both adult and pediatric solid organ transplant recipients (265). In small studies, IIV vaccination did not affect allograft function or cause acute rejection episodes in recipients of kidney (267, 270, 456, 457), heart (458), lung (456) or liver transplants (274, 459, 460). A literature review concluded that there is no convincing epidemiologic link between vaccination and allograft dysfunction (265). Guillain-Barré syndrome in a liver transplant recipient (461) and rhabdomyolysis leading to acute renal allograft dysfunction (462) after IIV vaccination have been reported. Several case reports of corneal graft rejection have been reported following receipt of IIV (463-466). However, no studies specifically designed to evaluate whether IIV is associated with increased risk for corneal graft rejection have been conducted.

Some studies have evaluated safety of high-dose or adjuvanted IIVs in immunocompromised populations. A randomized trial compared HD-IIV3 and SD-IIV3 in 190 persons with HIV infection; injection site pain was reported more frequently among the high-dose recipients, but overall the authors reported that no significant differences were observed in injection site or systemic reactions between the two groups (260). In a randomized trial of HD- versus SD-IIV3 among 161 adult solid organ transplant recipients, frequencies of injection site reactions and fever were similar between the two groups. Participants who received HD-IIV3 had a higher frequency of systemic symptoms, particularly gastrointestinal symptoms and arthralgia, but this difference was not statistically significant (277). In a randomized trial of adjuvanted versus unadjuvanted IIV3 which enrolled 73 adult allogeneic hematopoietic stem cell transplant recipients (≥12 weeks post-transplant), no significant differences were reported in the prevalence of injection site or systemic reactions between the two groups. Fever occurred more frequently among those who received the adjuvanted vaccine (254).

### *IIVs and Checkpoint Inhibitors*

Immune checkpoint inhibitors (including drugs such as nivolumab, pembrolizumab, ipilimumab, and atezolizumab) are medications used to treat cancer which block pathways that inhibit activity of T-cells, enhancing anti-tumor activity of these cells (467). Because they inhibit processes which down-regulate immune response, there is concern for immune-related adverse events. In a 2018 report which described 23 lung cancer patients receiving checkpoint inhibitors who received IIV3, 52% experienced an adverse event which was considered immune-related. Six of these events were considered severe or life threatening (including 2 cases of colitis, 2 of encephalitis, and one each of pneumonitis and neuropathy) (468). Subsequent reports have noted fewer safety concerns for influenza vaccination of persons receiving these agents (469-471). In a cohort study of 127 persons with lung cancer receiving nivolumab, 42 of whom received IIV3 and 85 of whom were unvaccinated, risk of immune-related adverse events did not differ significantly between the two groups (rate ratio=1.20; 95%CI 0.51, 2.65 for all events; rate ratio=2.07; 95%CI 0.28, 15.43 for serious events) (469). In a case-control study comparing 101 persons receiving checkpoint inhibitors who had been diagnosed with myocarditis with 201 patients also receiving these agents who had not been diagnosed with myocarditis, receipt of influenza vaccine was more common among those persons who had not been diagnosed with

myocarditis (40%) than those who had received this diagnosis (25%) (470). In a retrospective review including 370 persons who received IIV within 65 days of checkpoint inhibitor therapy, overall 75 (20%) experienced an immune-related adverse event; the majority of these were judged mild to moderate in severity (471).

### *Guillain-Barré Syndrome and IIVs*

Guillain-Barré Syndrome (GBS) is an autoimmune demyelinating disease of the peripheral nervous system which most commonly presents with rapid-onset muscle weakness (472). The annual incidence of GBS is 10–20 cases per 1 million adults (472). Multiple bacterial and viral infectious illnesses, most notably *Campylobacter jejuni* gastrointestinal infections and upper respiratory tract infections, have been implicated as triggers of the autoimmune processes associated with GBS (473-476). Influenza infection has also been associated with the onset of GBS. 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 (477).

An association between GBS and receipt of IIVs has been noted during some influenza seasons. In particular, 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 (478). Since that time, evidence for an association between IIVs and GBS has been variable and inconsistent across influenza seasons, but in general an association of similar magnitude to that noted during the 1976-77 season has not been demonstrated (479, 480). During three of four influenza seasons studied during 1977–1991, the overall relative risk estimates for GBS after influenza vaccination were not statistically significant (481-483). 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. Cases occurred most frequently in the second week after vaccination (480). Similarly, 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 (484-490). An analysis of chart-confirmed GBS cases from the Medicare population during the 2009-10 season estimated that vaccination was associated with an attributable risk of 2.84 per 1 million doses (491). A subsequent four-season study in this population (2010-11 through 2013-14) obtained a similar estimate of excess risk for the 2010-11 season, but not for the three subsequent seasons (during which time the vaccine continued to contain an H1N1pdm09-like virus) (492). Of note, some studies have observed a higher risk for GBS following influenza infection than that following influenza vaccination (477, 493).

Because GBS is more likely to occur in persons who have experienced it previously, (472), the likelihood of coincidentally experiencing GBS after influenza vaccination is expected to be greater among persons who have had a prior episode than those who have not. Whether influenza vaccination specifically

might increase the risk for recurrence of GBS is unknown. 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 previously developed GBS within 6 weeks of influenza vaccination (494).

### *Thimerosal*

Thimerosal is an ethyl mercury-containing antimicrobial compound. It is primarily used in multi-dose vial preparations of IIVs as a preservative to inhibit microbial growth. For these preparations, the mercury content from thimerosal (as reported in package inserts) is ≤25 µg of mercury per 0.5 mL dose.

Although the evidence is reassuring regarding health risks associated with exposure to vaccines containing thimerosal (495-507), 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 (495, 499). Single-dose vial and syringe preparations of IIVs, as well as LAIV4 and RIV4, which are expected to be available during the 2019-20 season do not contain thimerosal.

### *Adjuvants*

Adjuvants are compounds added to vaccines to improve immune response. Only one adjuvanted influenza vaccine, Fluad (adjuvanted inactivated influenza vaccine, trivalent [aIIV3], Seqirus) is currently licensed in the United States (299). Fluad contains the squalene-based oil-in-water adjuvant, MF59. Currently, it is indicated for persons aged 65 years and older. In a randomized controlled study comparing aIIV3 with IIV3 among 7,000 persons aged ≥65 years, prevalence of some injection site and systemic reactions within the first 7 days after vaccination were higher in the aIIV3 group (300). Those who received aIIV3 were more likely to experience pain or tenderness, or myalgia; however, most of these reactions were mild in severity. Prevalence of SAEs was similar between the two groups. Though not licensed for children in the U.S., aIIV3 has been used in the pediatric population in Europe and Canada. In studies conducted among children, MF59-adjuvanted vaccines were associated with greater likelihood of injection site redness and pain, fever, irritability, and loss of appetite than non-adjuvated control vaccines (508).

During the 2009 pandemic, three monovalent H1N1pdm09 vaccines containing squalene-based oil in water adjuvants were used globally (in addition to unadjuvanted inactivated and live attenuated H1N1pdm09 vaccines). The AS03-adjuvanted vaccine, Pandemrix (GSK), was used widely in some European nations, particularly in Scandinavian countries; the AS03-adjuvanted vaccine, Arepanrix (GSK), was used in Canada; and the MF59-adjuvanted vaccine, Focetria (Novartis), was widely used globally. Epidemiological studies conducted in European countries after the pandemic have

consistently found an increased risk of narcolepsy associated with Pandemrix, especially in children (509); although like all retrospective observational studies, they are subject to limitations, including possible awareness and detection bias (510-513). No similar risk has been detected with Arepanrix or Focetria (514, 515). The reasons for the Pandemrix finding, as well as the lack of association with Arepanrix and Focetria, are still the subject of scientific investigation. Adjuvanted monovalent H1N1pdm09 were not licensed or used in the United States during the 2009 pandemic and no AS03-adjuvanted seasonal influenza vaccines are currently licensed in the United States. An MF59-adjuvanted trivalent seasonal influenza vaccine is approved for individuals aged 65 years and older.

### *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 (516, 517). 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 (517). After changes in the manufacturing process of the vaccine preparation associated with ORS during the 2000–01 season, the incidence of ORS in Canada diminished greatly (518). The cause of ORS has not been established; however, studies suggest that the reaction is not IgE-mediated (519). 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.

## Safety of Recombinant Influenza Vaccines (RIVs)

RIV was initially available in the U.S. during the 2013-14 season as RIV3 (Flublok, Protein Sciences, Meriden, Connecticut). RIV4 (Flublok Quadrivalent, Protein Sciences, Meriden Connecticut; now manufactured by Sanofi Pasteur, Swiftwater, Pennsylvania) was licensed in late 2016 and was first available for the 2017-18 season. Since the 2018-19 season, all RIV in the U.S. is quadrivalent (RIV4). RIV4 contains HA which is produced via introduction of the HA genetic sequence into an insect cell line, and contains some residual insect proteins (124).

In pre-licensure studies of RIV4, the most frequently reported injection site reaction (reported in ≥10% of recipients) were tenderness (48% among those aged 18 through 49 years; 34% among those aged ≥50 years) and pain (37% and 19%, respectively). The most common solicited systemic reactions were headache (20% and 13%, respectively), fatigue (17%, and 12%, respectively), myalgia (13% among those aged 18 through 49 years) and arthralgia (10% among those aged 18 through 49 years) (124). 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 AEs was generally similar between the two groups (282).

As a relatively new category of vaccine, fewer post-marketing safety data have accumulated for RIVs. Although RIVs do not contain egg protein, anaphylactic and other, less severe reactions have been reported to VAERS (520), illustrating that allergic reactions to influenza vaccines can occur in the absence of egg proteins. In a randomized study conducted among adults 50 years of age and older in which incidence of rash, urticaria, swelling, or other potential hypersensitivity reactions were actively solicited for 30 days following vaccination, 2.4% of RIV3 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 RIV3 and IIV3 recipients, respectively, reported these events within 7 days following vaccination. Of these solicited events, rash was most frequently reported (RIV3 1.3%; IIV3 0.8%) over the 30 day follow-up period (521).

## Safety of Live Attenuated Influenza Vaccine (LAIV)

### *Shedding, Transmission, and Phenotypic Stability of LAIV Viruses*

Shedding of the live attenuated vaccine virus is common after receipt of LAIV. In general, shedding is more common among younger recipients, among whom it may also be of longer duration. Among 345 LAIV3 recipients aged 5–49 years for whom shedding was assessed by viral culture of nasal swabs, 29% had detectable virus in nasal secretions. Prevalence of shedding was inversely related to age, and maximal shedding occurred within 2 days of vaccination. The symptoms most frequently reported after vaccination (runny nose, headache, and sore throat) did not correlate with the presence of shedding (522). In a study of 200 children aged 6 through 59 months, shedding of at least one vaccine virus was detected in 79% of children overall, and was more common among younger children (89% of 6- through 23-month-olds as compared with 69% of 24- through 59-month-olds) (523). Shedding had stopped in most cases by 11 days post vaccination. 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 (524), and in three (13%) of 24 HIV-infected children compared with seven (28%) of 25 children who were not HIV-infected (525).

Transmission of shed LAIV vaccine viruses from vaccine recipients to unvaccinated persons has been documented, but has not been reported to be associated with serious illness. One study of 197 children aged 9–36 months (98 of whom received LAIV3 and 99 of whom received placebo) in a child care center assessed the potential for transmission of LAIV3 vaccine viruses. Among vaccine recipients, 80% shed one or more vaccine virus (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. This transmitted virus isolate retained the cold-adapted, temperature-sensitive, attenuated characteristics. 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) (526).

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 cold-adapted and temperature-sensitive phenotypes (527). In a separate experimental 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 (528).

### *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% vs. 44%), headache (18% vs. 12%), vomiting (5% vs. 3%), and myalgia (6% vs. 4%, respectively). However, these differences were not statistically significant (529). 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%) (308, 309, 315, 530-534). In general, 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 pre-specified 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 SAEs was 0.2% in LAIV3 and placebo recipients; none of the SAEs was judged to be related to the vaccine by the study investigators (530).

LAIV3 has been associated with wheezing among younger children in some studies. In a comparison of LAIV3 and IIV3 children in aged 6– 59 months which excluded children with recent medically diagnosed or treated wheezing or a history of severe asthma (328), the proportion of children who experienced medically significant wheezing following vaccination did not differ between the two vaccines among children 24 through 59 months of age. Wheezing was observed more frequently following the first dose among previously unvaccinated younger LAIV3 recipients, primarily those aged <12 months (an age group for which LAIV is not licensed). In a 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 (530). A 14-year follow-up study conducted among children who had enrolled in this

trial at <3 years of age reported no findings indicating that the children who received LAIV had an increased risk of subsequent asthma diagnosis (535).

In an open-label trial conducted between 1990 and 2002, 18,780 doses of LAIV3 were administered to 11,096 children aged 18 months through 18 years. Among those aged 18 months through 4 years, no increase was reported in asthma visits 0–14 days after vaccination compared with the pre-vaccination period. A significant increase in asthma events was noted 15–42 days after vaccination, but only in the first year of the study (536). Among the 2,196 children in this study who had a history of intermittent wheezing but were otherwise healthy, no increased risk was observed for MAARI, including acute asthma exacerbation either 0–14 or 0–42 days after receipt of LAIV3 compared with the pre- and post-vaccination reference periods (537).

A review of 460 VAERS reports (including persons aged 2 through 70 years) 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 (538) (note, however, that LAIV4 is licensed for persons aged 2 through 49 years). Respiratory events (such as influenza-like illness, rhinitis, pharyngitis, sinusitis, and asthma) were the most common conditions reported. Few (9%) of the reports described events considered serious. During 2005–2012, VAERS received 2,619 reports in children aged 2 through 18 years after receipt of LAIV3 (539). Consistent with the earlier VAERS study, few (7.5%) of these reports were serious and no new AE patterns were identified. A VSD self-controlled case series analysis of 396,173 children who received LAIV3 from September 2003 through March 2013 revealed a significant association of anaphylaxis and syncope with receipt of LAIV (540). Among the 5 syncope cases, 4 had also received injectable vaccines concurrently. Both of these AEs were rare, with an estimated rate of 1.7 events per 1 million doses for anaphylaxis and 8.5 events per 1 million doses for syncope.

LAIV4 has been available in the U.S. since the 2013-14 season, and was not recommended for use in the U.S. during the 2016-17 and 2017-18 seasons. Fewer post-marketing surveillance data specific to this formulation have accumulated than are available for LAIV3. For the 2013–2014 influenza season, in which approximately 12.7 million doses of LAIV4 were distributed, VAERS received 779 reports of events occurring following LAIV4 (599 of which occurred in children aged 2 through 17 years). The safety profile of LAIV4 was consistent with pre-licensure clinical trials and data from post-licensure assessment of LAIV3 (541). In an analysis of health maintenance organization data for the 2013-14 season including persons aged 2 through 49 years, risk of wheezing after LAIV4 was not higher than after IIV or unvaccinated children when the analysis was conducted in the total population. There was 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, 4 were assessed in an emergency department, but not hospitalized (542). An open label safety study of LAIV4 among 100 children aged 2 through 6 years conducted in Japan during the 2014-15 season reported a safety profile consistent with that of previous studies. The most frequently reported solicited symptoms were runny/stuffy nose (51%), cough (34%), fever (10%), and sore throat (7%). The only AE that occurred among greater than 5% of children was nasopharyngitis, in

13% (543). All AEs were characterized as mild in severity. In a randomized placebo-controlled trial of LAIV conducted among 1,301 children aged 7 through 18 years in Japan, the prevalence of AEs was similar among the LAIV4 and placebo groups (24.3% and 25.9%, respectively). Only 2.9% of these events were characterized as moderate in severity; none were rated as severe. The most commonly reported AE was nasopharyngitis, occurring in 8.1% of LAIV4 recipients and 8.3% of placebo recipients. SAEs were uncommon, occurring in 0.3% of LAIV4 recipients and 0.7% of placebo recipients; those in the LAIV4 recipients occurred > 100 days post-vaccination and were judged unrelated to receipt of study vaccine (543).

Published data on the use of LAIV for children with diagnosed asthma and other medical conditions conferring higher risk for severe influenza illness are relatively limited compared with available data for children without such conditions. A prospective nonrandomized population-based study conducted in the United Kingdom which compared rates of hospitalization and selected adverse events through 6 days and 42 days post-vaccination among 11,463 children and adolescents during the 2013-14 and 2014-15 seasons found no difference in risk of all-cause hospitalization or hospitalizations for lower respiratory events between LAIV recipients and unvaccinated children at either time interval. Risk of hospitalization for any cause and for lower respiratory conditions were significantly lower among LAIV recipients compared to IIV recipients, at both 6 days and 42 days. While vaccine recipients and unvaccinated controls had been matched on various factors in order to control for severity of underlying illness, the investigators noted that the different vaccine groups could have differed in inherent risk for hospitalization, and that residual confounding could have contributed to the differences observed between the two vaccine groups (544).

### *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 (8% versus 6%), and tiredness/weakness (25% versus 21%) (529). A review of 460 reports (involving persons aged 2 through 70 years) to VAERS after administration of approximately 2.5 million doses of LAIV3 during the 2003–04 and 2004–05 influenza seasons did not indicate any new safety concerns. Respiratory symptoms were the most common types of events reported. Serious adverse events were uncommon (538).

### *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. In a study of 57 HIV-infected persons aged 18–58 years with CD4+ counts >200 cells/µL who received LAIV3, no SAEs judged to be related to vaccine were reported during a 1-

month follow-up period (524). No significant difference was noted in the frequency of AEs 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 (525). In a study comparing immunogenicity and shedding of LAIV4 among 46 HIV-infected (CD4+ counts >200 cells/µL) and 56 uninfected persons aged 2 through 25 years, prevalence of most AEs 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 post-vaccination, compared with 50% of uninfected participants (p = 0.14) (545).

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. Among 1,940 children aged 2 through 5 years with asthma or prior wheezing enrolled in multinational randomized trials of LAIV3 and IIV3, risk of 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 (546). A study of LAIV and IIV3 among children aged 6 through 17 years with asthma noted no significant difference in wheezing events after receipt of LAIV3 (329). In a study conducted between 2007 and 2014 among children aged ≥2 years with a history of asthma who received either LAIV or IIV, LAIV was associated with a lower likelihood of asthma exacerbation than IIV (547). A VSD study of the safety of LAIV in persons with asthma conducted during 3 influenza seasons (2008-2009 through 2010-2011) found no association between receipt of LAIV and increased risk of medically attended respiratory AEs (548). Available data are insufficient to determine the level of severity of asthma for which administration of LAIV would be inadvisable.

A two-season Canadian retrospective cohort study was conducted among 198 persons aged 2 through 19 years with cystic fibrosis who received LAIV3 compared rates of hospitalization, antibiotic prescriptions and diary-recorded symptoms during days 0 through 6 post-vaccination (defined as the at-risk period) with those occurring during days 7 through 55 (the control period). Hospitalization and antibiotic prescription events were not greater during the at-risk period. Self-reported symptoms occurred more commonly during the at-risk period; the pulmonary symptoms with the greatest magnitude of risk were chest congestion/increased sputum, and wheezing (549).

## Influenza Vaccine Safety in Pregnant Women and Neonates

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 these 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, most influenza vaccines are now labeled using the new format.

In general, there are no pre-licensure studies of influenza vaccines among pregnant women. The majority of available data come from post-licensure studies. However, influenza vaccines have been administered to pregnant women for more than five decades, and overall have a reassuring safety profile. The vast majority of published data and clinical experience involve use of IIVs, which have been available for the longest period of time, and which have been recommended for use for some populations of pregnant women since the early 1960s. Data are more limited for RIV (which has only been available since 2013), and for LAIV (which has not been recommended for use during pregnancy because it is a live vaccine).

In a retrospective cohort analysis of healthcare organization data covering nine influenza years (2008-2016) and including 247,036 pregnant women, 53% were vaccinated. The vast majority of women received IIV; only 156 received LAIV (550). Vaccination was distributed relatively evenly by trimester (32% during the first, 31% during the second, and 30% during the third). Vaccination was significantly associated with lower risk of several outcomes, including maternal influenza illness (OR=0.49; 95%CI 0.39, 0.62), maternal fever (OR=0.40; 95%CI 0.35, 0.45), preeclampsia (OR=0.93; 95%CI 0.90, 0.96), placental abruption (OR=0.89; 95%CI 0.82, 0.96), stillbirth (OR=0.88; 95%CI 0.78, 0.99), and infant admission to a neonatal intensive care unit (OR=0.89; 95%CI 0.87, 0.92).

### *IIVs*

Overall experience with the use of IIVs during pregnancy has been reassuring. Substantial data have accumulated which do not indicate fetal harm associated with IIVs administered during pregnancy. However, data specifically concerning administration of these vaccines during the first trimester are limited (551). A 2015 review of studies of maternal influenza vaccination and pregnancy outcomes noted that women vaccinated in the first trimester were underrepresented in these studies, contributing to imprecision in estimates for risk of outcomes such as fetal death, spontaneous abortion and congenital malformations (552). Most available data are from observational studies rather than controlled trials. Differences in methodology (for example, clinical definitions for outcomes of interest) complicates pooling of data and comparisons among estimates.

Background rates of spontaneous abortion (miscarriage) vary from 10.4% in women aged <25 years to 22.4% in women aged >34 years (553). Considering the number of pregnant women vaccinated, spontaneous abortion following (but not attributable to) influenza vaccination would be expected to occur due to chance. Most studies (554-562) and systematic reviews (552, 563, 564) that have evaluated risk of spontaneous abortion following receipt of IIVs have not found an association. However, data on the use of influenza vaccines are more limited during the early first trimester, when spontaneous abortions are more likely to occur. As discussed above, small sample sizes limit ability to obtain a precise estimate of risk. 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 no significant difference in risk for spontaneous abortion between vaccinated and unvaccinated women (RR=0.91; 95%CI 0.68, 1.22) (563). Some reviews of studies involving seasonal and 2009(H1N1) monovalent IIV in pregnancy have concluded that no evidence exists to suggest harm to the fetus from maternal vaccination (565, 566). 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 (554).

Several case-control studies evaluating receipt of IIVs and subsequent spontaneous abortion have been conducted within the VSD. The first of these, conducted during the 2005–06 and 2006–07 seasons, found no significant increase in the risk for pregnancy loss in the 4 weeks following seasonal influenza vaccination (557). A subsequent study using similar methods reported an increased risk for spontaneous abortion during days 1 to 28 days after receiving IIV3 during either the 2010–11 or the 2011– 12 seasons; the increased risk was seen among women who had also received a H1N1pdm09-containing vaccine in the previous season (567). A larger follow-up study conducted over three seasons (2012-13 through 2014-15) found no association between IIV receipt and spontaneous abortion in any of the studied seasons, regardless of vaccination status in the previous season (568).

Multiple studies have found no increased risk for stillbirth among women who received IIV during pregnancy (185, 552, 555, 563, 569-574). 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 (63). 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) reported decreased risk for stillbirth among women who were vaccinated (RR=0.73; 95%CI 0.55, 0.96 for all studies; RR=0.69; 95%CI 0.52, 0.90 for studies of influenza A(H1N1)pdm09 vaccines) (563).

A matched case-control study of 225 pregnant women who received IIV3 within the 6 months before delivery determined that no SAEs 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 (575). Reviews of VAERS reports during 1990–2009 (576) and 2010–2016 (577), concerning pregnant women after receipt of IIV3 did not find any new or unexpected pattern of adverse pregnancy events or fetal outcomes.

Data are reassuring with regard to the risk of congenital malformations following maternal influenza vaccination, with a large number of studies noting no association (552, 554, 573, 578-582). 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, found 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, 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) (581). A case-control analysis from VAMPSS of data from the 2011-12 through 2013-14 seasons noted an elevated OR for omphalocele (OR=5.19; 95%CI 1.44, 18.7) during the 2011-12 season, no other significant associations were found (579). A study examining safety of exposure to pandemic H1N1pdm09-containing vaccine during the 2009-2010 and 2010-11 seasons noted an increased risk for anophthalmia/microphthalmia (OR=8.67; 95%CI 1.10, 68.5); the authors noted the possibility that this association could be due to chance, in the context of multiple comparisons (582). A VSD analysis comparing occurrence of selected major birth defects among women with and without first trimester IIV exposure found no increased risk of the selected defects (578). A retrospective cohort study including 15,510 infants born to active duty military mothers who received IIVs while pregnant during 2008-09 (seasonal vaccine) and 2009-2010 (pandemic vaccine) found no increased risk of birth defects (as reported in medical records through the first year after birth) following receipt of pandemic vaccines as compared with seasonal vaccines (583).

Assessments of association between 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 (574, 584-590). Some authors have noted that protective effects observed in some studies may be attributable to biases (589). A VSD study of 46,549 pregnancies during the 2009-2010 season found a strong protective effect against preterm birth of monovalent H1N1pdm09 vaccination which was no longer present with adjustment for potential biases such as differences in vaccine availability, timing of vaccination, and likelihood of vaccination associated with baseline characteristics of the study populations (591).

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 HR=1.20; 95%CI 1.04, 1.39) (592). This association was no longer statistically significant after adjusting for multiple comparisons. A VSD matched case-control study of 413,034 infants born between January 2004 through June 2014 found no association between maternal receipt of influenza vaccine and infant hospitalization during the first 6 months of life (aOR=1.00; 95%CI 0.96, 1.04) or death (aOR=0.96; 95%CI 0.54, 1.69) (593).

### *RIVs*

Experience with the use of RIVs in pregnancy is limited compared to that with IIVs, as these vaccines have been available only since the 2013-14 influenza season. In two pre-licensure studies, 23 pregnancies occurred among participants who received RIV3. Complete follow-up was available for 18, for which outcomes included 11 uneventful, normal, term births; 2 in which the recipients experienced pregnancy-related AEs but delivered healthy infants; 4 elective terminations; and one spontaneous abortion (594). VAERS has received 3 RIV3 reports and 7 RIV4 reports involving pregnant women (CDC, unpublished data). A pregnancy registry has been established for RIVs (124).

### *LAIVs*

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 noted (576). Of 127 reports of administration of LAIV3/4 to pregnant women submitted to VAERS from July 2010 through May 2016, no AE 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 (577). Among 138 instances of administration of LAIV3 to pregnant women noted in a health insurance claims database, reported outcomes occurred at similar rates to those reported in literature among unvaccinated women (595).

## 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 (596). 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 (596, 597).

Vaccines contain multiple components that may potentially cause allergic reactions. These include 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 should be consulted for additional information. The ACIP has recommended that all vaccine providers be familiar with their office emergency plan and be certified in cardiopulmonary resuscitation (598). The Clinical Immunization Safety Assessment (CISA) Project (About the Clinical Immunization Safety Assessment (CISA) Project | Vaccine Safety Systems | CDC), 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 (596).

Anaphylaxis after receipt of influenza vaccines is rare. In a review of VAERS reports from 2010 through 2016, an estimated median annual rate of 0.2 per million administered doses was calculated (599). 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 doses administered in all ages (600). Anaphylaxis occurring after receipt of influenza vaccines is occasionally reported to VAERS (431, 538, 601, 602). A VSD study of children aged <18 years in four health maintenance organizations during 1991–1997 estimated the overall risk for post-vaccination anaphylaxis after any type of childhood vaccine to be approximately 1.5 cases per million doses administered. In this study, no cases were identified among IIV3 recipients (603).

## Influenza Vaccination and Egg Allergy

Most currently available influenza vaccines (with the exceptions of RIV4 and ccIIV4) are prepared by propagation of influenza viruses in embryonated eggs. These vaccines therefore may contain residual egg proteins, such as ovalbumin. Among influenza vaccines for which ovalbumin content was disclosed during the 2018–19 season, reported maximum amounts were ≤1 µg/0.5 mL dose for IIVs and <0.024 µg/0.2 mL dose for LAIV4.

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 (of whom 513 reported a history of severe allergic reaction) there were no noted occurrences of anaphylaxis following administration of IIV3, though some milder reactions did occur (604). 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 post-vaccination observation. Moreover, none reported adverse reactions that were suggestive of allergic reaction or that required medical attention after 24 hours (605). 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 (606). 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 (607). 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). In a study that compared adverse reactions in eight egg-allergic and five non-egg-allergic children given increasing doses of egg protein (608), the egg allergic children showed only mild symptoms of rhinitis after exposure to 10–100 µg. This is substantially more than the concentration of ovalbumin reported in the LAIV package insert (<0.024 µg per 0.2 mL dose). All eight egg-allergic children tolerated LAIV doses without any allergic symptoms. These data indicate that LAIV4 may be administered safely to persons with a history of egg allergy.

Occasional cases of anaphylaxis in egg-allergic persons have been reported to VAERS after administration of influenza vaccines (601, 602). The ACIP will continue to review available data regarding anaphylaxis cases following influenza vaccines.

***Update September 2024:*** For additional information concerning this topic, see the June 2023 evidence review of safety of egg-based influenza vaccines among egg-allergic persons:

- https://www.cdc.gov/acip/grade/influenza-egg-allergy.html#:~:text=A%20systematic%20literature%20review%20using%20the%20Grading%20of%20Recommendations,%20Assessment
- https://www.cdc.gov/acip/evidence-to-recommendations/influenza-egg-allergy-etr.html#:~:text=ACIP%20recommends%20that%20all%20persons%20ages%20%E2%89%A56%20months%20with%20egg

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