TECHNICAL REPORT

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Recommendations for Prevention and Control of Influenza in Children, 2021–2022

COMMITTEE ON INFECTIOUS DISEASES

Technical Report Update—Data Updates

The FDA approved an expansion in age indication from 2 years and older to 6 months and older for Flucelvax Quadrivalent (the cell culture-based inactivated influenza vaccine) on October 14, 2021. Data in this Technical Report have been updated to reflect this change. New or updated data are indicated in bold typeface.

abstract

This technical report accompanies the recommendations of the American Academy of Pediatrics for the routine use of the influenza vaccine and antiviral medications in the prevention and treatment of influenza in children during the 2021–2022 season. Influenza vaccination is an important intervention to protect vulnerable populations and reduce the burden of respiratory illnesses during circulation of severe acute respiratory syndrome coronavirus 2, which is expected to continue during this influenza season. In this technical report, we summarize recent influenza seasons, morbidity and mortality in children, vaccine effectiveness, vaccination coverage, and detailed guidance on storage, administration, and implementation. We also provide background on inactivated and live attenuated influenza vaccine recommendations, vaccination during pregnancy and breastfeeding, diagnostic testing, and antiviral medications for treatment and chemoprophylaxis.

INTRODUCTION

This technical report accompanies the recommendations of the American Academy of Pediatrics (AAP) for the routine use of influenza vaccine and antiviral medications in the prevention and treatment of influenza in children during the 2021–2022 season.[1]

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SUMMARY OF RECENT INFLUENZA SEASONS IN THE UNITED STATES

2017–2018, 2018–2019, and 2019–2020 Influenza Seasons

The 2017–2018 influenza season was the first season classified as a high-severity season for all age groups, with high levels of outpatient clinic and emergency department visits for influenzalike illness, high rates of influenza-related hospitalization, and high mortality.[2–4] Influenza A (H3N2) predominated early, followed by a second wave of influenza B/Yamagata from March 2018 onward. Although hospitalization rates for children did not exceed those reported during the 2009 pandemic, they did surpass rates reported in previous high-severity A(H3N2)-predominant seasons. Excluding the 2009 pandemic, the 188 pediatric deaths reported during the 2017–2018 season (approximately half of which occurred in otherwise healthy children) were the highest reported since influenza-associated pediatric mortality became a nationally notifiable condition in 2004.[2–4] Among pediatric deaths of children 6 months and older who were eligible for vaccination and for whom vaccination status was known, approximately 80% had not received the influenza vaccine during the 2017–2018 season.[2] Influenza vaccine effectiveness (VE) for the 2017–2018 season in children is shown in Table 1.[3]

The 2018–2019 influenza season was the longest-lasting season reported in the United States in the past decade, with elevated levels of influenzalike illness activity for a total duration of 21 consecutive weeks (compared with an average duration of 16 weeks).[5] Variations in circulating strains affected vaccine efficacy. Influenza A(H1N1)pdm09 viruses predominated from October to mid-February, and influenza A(H3N2) viruses were identified more frequently from February to May. Influenza B (B/Victoria lineage predominant) represented approximately 5% of circulating strains. Most characterized influenza A(H3N2) viruses were antigenically distinct from the A(H3N2) component of the 2018–2019 vaccine. The vaccine's A(H3N2) virus belonged to subclade 3C.2a1. Cocirculation of multiple genetically diverse subclades of A(H3N2) was documented. Circulating viruses identified belonged to subclade 3C.2a1 or clade 3C.3a, with 3C.3a viruses accounting for >70% of the A(H3N2) viruses in the United States. This likely contributed to an overall lower VE against influenza A(H3N2) this season, despite achieving the highest vaccination coverage reported in the last decade in children (62.6% overall) (Table 1, Fig 1).[5,6]

The 2018–2019 season was of moderate severity, with similar hospitalization rates in children as during the 2017–2018 season (71 per 100 000 among children 0–4 years old and 20.4 per 100 000 among children 5–17 years old), which were higher than those observed in previous seasons from

TABLE 1 Adjusted VE in Children in the United States, by Season, as Reported by the CDC, US Influenza VE Network

Influenza Type and Age Group	2017–2018 H3N2 and B/Yamagata, VE% (95% CI)	2018–2019 H1N1 and H3N2, VE% (95% CI)	2019–2020 B/Victoria and H1N1, VE% (95% CI)
Influenza A and B			
Overall all ages	38 (31 to 43)	29 (21 to 35)	39 (32 to 44)
6 mo to 8 y	68 (55 to 77)	48 (37 to 58)	34 (19 to 46)
9–17 y	32 (16 to 44)	7 (–20 to 28)	40 (22 to 53)
Influenza A(H1N1)pdm09			
Overall all ages	62 (50 to 71)	44 (37 to 51)	30 (21 to 39)
6 mo to 8 y	87 (71 to 95)	59 (47 to 69)	23 (–3 to 42)
9–17 y	70 (46 to 67)	24 (–18 to 51)	29 (–7 to 52)
Influenza A(H3N2)			
Overall all ages	22 (12 to 31)	9 (–4 to 20)	NA
6 mo to 8 y	54 (33 to 69)	24 (1 to 42)	NA
9–17 y	18 (–6 to 36)	3 (–30 to 28)	NA
Influenza B/Victoria			
Overall all ages	76 (45 to 89)	Not reported	45 (37 to 52)
6 mo to 8 y	Not reported	Not reported	39 (20 to 54)
9–17 y	Note reported	Not reported	43 (23 to 58)
Influenza B/Yamagata			
Overall all ages	48 (39 to 55)	Not reported	NA
6 mo to 8 y	77 (49 to 90)	Not reported	NA
9–17 y	28 (1 to 48)	Not reported	NA

VE is estimated as 100% × (1 – odds ratio [ratio of the odds of being vaccinated among outpatients with influenza-positive test results on the CDC's real-time reverse transcriptase–polymerase chain reaction to the odds of being vaccinated among outpatients with influenza-negative test results]); odds ratios were estimated by using logistic regression. Adjusted for study site, age group, sex, race and/or ethnicity, self-rated general health, number of days from illness onset to enrollment, and month of illness using logistic regression. NA, not applicable.

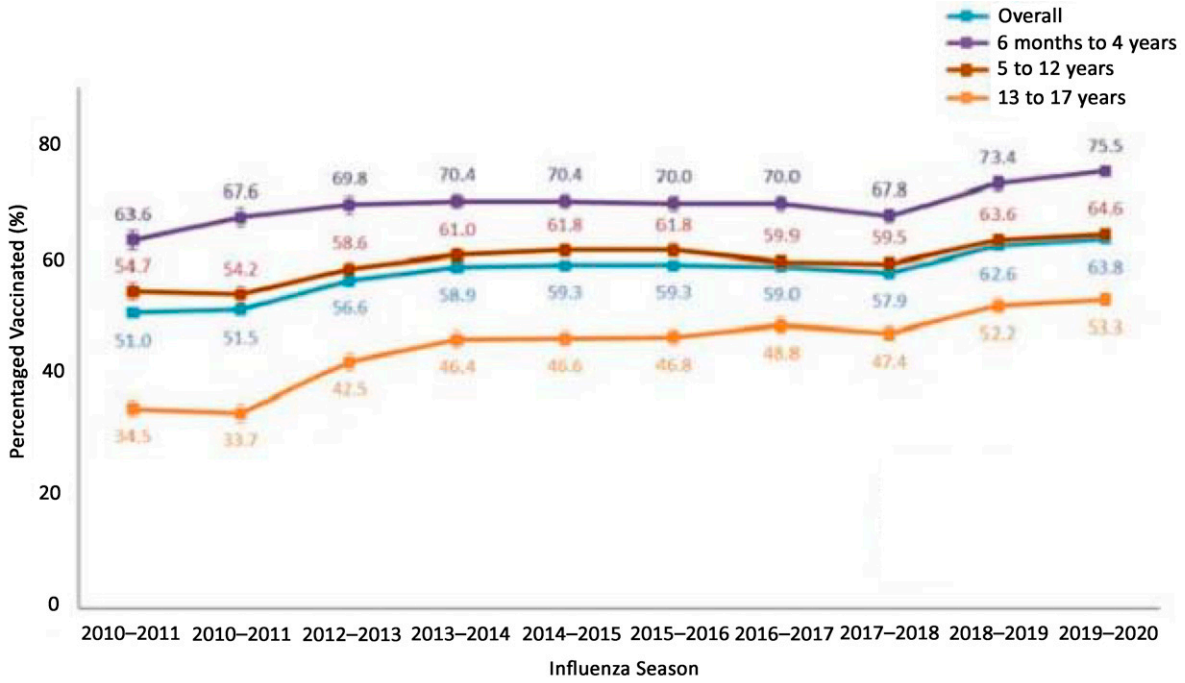

FIGURE 1 Influenza vaccination coverage in children 6 months to 17 years of age in the United States, 2010–2020. Error bars represent 95% CIs around the estimates. Adapted from Centers for Disease Control and Prevention. Flu vaccination coverage, United States, 2019–20 influenza season. Available at: https://www.cdc.gov/flu/fluvaxview/coverage-1920estimates.htm#ref10. Accessed July 12, 2021; and National Immunization Survey-Flu (NIS-Flu) (https://www.cdc.gov/vaccines/imzmanagers/nis/about.html).

2013–2014 to 2016–2017.[5] Among 1132 children hospitalized with influenza and for whom data were available, 55% had at least 1 underlying medical condition; the most commonly reported underlying conditions were asthma or reactive airway disease (26%), neurologic disorders (15.6%), and obesity (11.6%).[7] A total of 144 influenza-associated pediatric deaths were reported.

The 2019–2020 influenza season was unusual and complicated by the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in early 2020. Influenza activity began early in October 2019, continuing through mid-March 2020, with an abrupt decline after the implementation of social distancing measures for mitigation of the SARS-CoV-2 pandemic. Although influenza B/Victoria viruses predominated early in the season, influenza A(H1N1)pdm09 viruses were the most predominant circulating strain. Influenza A(H3N2) and the B/Yamagata lineage represented approximately 4.1% and 0.8% of circulating strains, respectively. A majority of characterized influenza A(H1N1)pdm09 (82.5%) and influenza B/Victoria (59.7%) viruses were antigenically similar to the viruses included in the 2019–2020 influenza vaccine. Less than half (46.5%) of influenza A(H3N2) viruses were antigenically similar to the A(H3N2) component of the 2019–2020 vaccine. During this season, the predominant A(H3N2) circulating clade was 3C.2a, subclade 3C.2a1, with cocirculation of a small proportion of 3C.3a, in contrast to the 2018–2019 season, when 3C.3a strains predominated. Estimates of the effectiveness of the 2019–2020 seasonal influenza vaccines against medically attended influenza illness from the US Flu VE Network are shown in Table 1.[8] Susceptibility to available antiviral agents remained greater than 99% for all circulating strains, but 0.5% of A(H1N1)pdm09 isolates tested by the Centers for Disease Control and Prevention (CDC) exhibited substantially reduced inhibition to oseltamivir and peramivir. Reduced susceptibility to baloxavir has not been reported in the United States to date.[9]

The 2019–2020 season was of moderate severity, although 3 peaks of influenzalike illness activity and the highest hospitalization rates in children, 68.2 per 100 000 population overall, were reported this season. The first peak of activity occurred in early January, likely associated with influenza B circulation; the second peak occurred in February, when influenza A(H1N1)pdm09 became predominant; and the third peak in March was associated with cocirculation of influenza and SARS-

CoV-2. The CDC now has a separate surveillance report for novel coronavirus disease 2019 (COVID-19)–like illness.[10] The cumulative influenza hospitalization rates per 100 000 population were 92.3 among children 0 to 4 years old and 23.5 among children 5 to 17 years old. Hospitalization rates in children 0 to 4 years old were higher than those seen for this age group during the 2009 influenza pandemic, higher than the rate in adults 50 to 64 years old this season (89.4 per 100 000), and the highest on record for this age group. Among children hospitalized with influenza and for whom data were available, 48.6% had no recorded underlying condition and 42.9% had at least 1 underlying medical condition; the most commonly reported underlying conditions were asthma or reactive airway disease (22.1%), neurologic disorders (17.5%), and obesity (12%).

There were 199 laboratory-confirmed influenza-associated pediatric deaths. Most (62.2%) of those children died after being admitted to the hospital. The median age of the pediatric deaths was 6.1 years (range, 2 months to 17 years). Seventy-seven of the pediatric deaths were associated with influenza A viruses, and 122 were associated with influenza B viruses. Among the 183 children with a known medical history, 42.6% of deaths occurred in children who had at least 1 underlying medical condition recognized by the Advisory Committee on Immunization Practices (ACIP) to increase the risk of influenza-attributable disease severity. Therefore, most (57.4%) had no known underlying medical conditions. The majority of the deaths occurred in children 2 to 12 years of age: 6.0% were younger than 6 months, 17.1% were 6 to 23 months of age, 20.6% were 2 to 4 years of age, 36.2% were 5 to 11 years of age, and 20.1% were 12 to 17 years of age. Among 72 children who died and were tested, 50% had a bacterial coinfection. Among 141 children who were 6 months or older at the time of illness onset, and therefore would have been eligible for influenza vaccination and for whom vaccination status was known, most (74%) were unvaccinated. Only 37 (26%) had received at least 1 dose of the influenza vaccine (30 had complete vaccination, and 7 had received 1 of 2 ACIP-recommended doses).

2020–2021 Influenza Season

The 2020–2021 influenza season was substantially and unusually mild, likely because of the circulation of SARS-CoV-2 and the implementation of pandemic mitigation measures. The circulation of influenza viruses was low, without a typical seasonal peak. From September 2020 to May 22, 2021, $<0.2\%$ of specimens tested were positive for influenza. Among public laboratory isolates, both influenza A (61.4%) and B (38.9%) viruses had been isolated. Among influenza A strains, 52.2% were influenza A(H3N2), 45% were A(H1N1)pdm09, and 2.5% were H3N2v. Furthermore, 1 human infection with a novel influenza A(H1N2) virus variant (A(H1N2)v) was reported in a child who recovered from the illness. This is the first influenza A(H1N2)v virus identified in the United States. Among influenza B strains, both Victoria (60%) and Yamagata (40%) lineages were reported. VE data could not be obtained because of low virus circulation. However, the A(H1N1)pdm09, A(H3N2), and B/Victoria strains that were genetically characterized were similar to the strains included in the vaccine. No antiviral resistance was observed among tested isolates.

The hospitalization rate during the 2020–2021 influenza season (0.8 per 100 000) is the lowest reported since routine data collection began in 2005 by the CDC. As a reference, the end-of-season hospitalization rate was only one-tenth of the previous lowest-severity season in 2011–2012. As such, age-specific hospitalization rates and rates by patient characteristics, including underlying medical conditions, are not available. The overall pneumonia, influenza, and/or COVID-19 mortality observed this season was attributable primarily to COVID-19 and not influenza. No influenza-associated pediatric deaths were identified from this past season. One influenza-associated pediatric death that occurred in January 2020 was reported during the 2020–2021 season.

INFLUENZA MORBIDITY AND MORTALITY IN CHILDREN

Influenza viruses are a common cause of acute lower respiratory tract infection (ALRTI) in children. Pediatric hospitalizations and deaths caused by influenza can be substantial. A recent study estimated that globally, influenza virus accounts for 7% of all ALRTIs, 5% of ALRTI hospitalizations, and 4% of ALRTI deaths in children younger than 5 years.[11] In the United States, the rates of influenza-associated hospitalization for children younger than 5 years consistently exceed the rates for children 5 to 17 years of age, and during the 2019–2020 season, they exceeded the hospitalization rates of adults 50 to 64 years of age.[7] Children 5 to 17 years of age also experienced higher than usual hospitalization rates during the 2019–2020 season. The impact of the anticipated SARS-CoV-2 cocirculation with influenza in the 2021–2022 season is unknown at this time. It is, therefore, particularly important that children

TABLE 2

People at High Risk of Influenza Complications
Children <5 y, and especially those <2 y,[a] regardless of the presence of underlying medical conditions
Adults ≥50 y, and especially those ≥65 y
Children and adults with chronic pulmonary disease (including asthma and cystic fibrosis); hemodynamically significant cardiovascular disease (except hypertension alone); or renal, hepatic, hematologic (including sickle cell disease and other hemoglobinopathies), or metabolic disorders (including diabetes mellitus)
Children and adults with immunosuppression attributable to any cause, including that caused by medications or by HIV infection
Children and adults with neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle, such as cerebral palsy, epilepsy, stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
Children and adults with conditions that compromise respiratory function or handling of secretions (including tracheostomy and mechanical ventilation)[124]
Women who are pregnant or post partum during the influenza season
Children and adolescents <19 y who are receiving long-term aspirin therapy or salicylate-containing medications (including those with Kawasaki disease and rheumatologic conditions) because of increased risk of Reye syndrome
American Indian/Alaska Native people[b]
Children and adults with obesity (ie, BMI ≥40 for adults and based on age for children)
Residents of chronic care facilities and nursing homes

Adapted from Grohskopf LA, Alyanak E, Ferdinands JM, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2021–22 influenza season. *MMWR Recomm Rep.* 2021;70(5):1–28

[a] The CDC recommendations state that although all children younger than 5 y old are considered at higher risk for complications from influenza, the highest risk is for those younger than 2 y old, with the highest hospitalization and death rates among infants younger than 6 mo old.

[b] American Indian/Alaska Native (AI/AN) children have higher rate of influenza complications.[125–128] Most at-risk AI/AN children will also qualify in other high-risk categories to receive appropriate antiviral treatment. In the setting of a shortage, AI/AN children should be prioritized to receive influenza vaccine or antiviral medications according to local public health guidelines.

are protected against influenza through timely vaccination in the 2021–2022 influenza season.

HIGH-RISK GROUPS IN PEDIATRICS

Children and adolescents with certain underlying medical conditions have a high risk of complications from influenza (Table 2). In addition, influenza vaccination is particularly important in African American and Hispanic/Latinx populations who have been identified as having higher rates of hospitalization from influenza and being more vulnerable to COVID-19.[12] Although universal influenza vaccination is recommended for everyone starting at 6 months of age, emphasis should be placed on ensuring that people in high-risk groups and their household contacts and caregivers receive the annual influenza vaccine.

EFFECTIVENESS OF INFLUENZA VACCINATION ON HOSPITALIZATION AND MORTALITY

Several studies demonstrated that influenza vaccination effectively decreased hospitalization in children in places where universal pediatric immunization was implemented. In a study conducted by the US New Vaccine Surveillance Network in 2015–2016, among 1653 children enrolled from 7 pediatric hospitals, the adjusted VE in children with complete influenza immunization against any influenza-associated hospitalization was 56% (95% confidence interval [CI], 34% to 71%), 68% (95% CI, 36% to 84%) against A(H1N1)pdm09, and 44% (95% CI, −1% to 69%) against B viruses.[13] A study in children 6 months to 8 years of age conducted in Israel over 3 influenza seasons from 2015 to 2017 demonstrated that over all seasons, fully vaccinated children had a VE against hospitalization of 53.9% (95% CI, 38.6% to 68.3%), whereas partial vaccination was not effective (25.6%; 95% CI, −3% to 47%).[14] In this study, a VE against hospitalization as high as 60% to 80% was observed when circulating and vaccine influenza A and B strains matched. After establishing free vaccination for preschool-aged children and children at risk because of comorbid medical conditions in Australia in 2018, VE of the influenza vaccine in preventing influenza hospitalization was estimated to be 78.8% (95% CI, 66.9% to 86.4%).[15] In the United Kingdom, during the 2018–2019 season, the overall adjusted VE against influenza-confirmed hospitalization was reported to be 53% (95% CI, 33.3% to 66.8%), with protection varying by strain. Protection was 63.5% (95% CI, 34.4% to 79.7%) against influenza A(H1N1)pdm09, but there was no protection against influenza A(H3N2).[16] Finally, in a systematic review and meta-analysis of 28 studies, Kalligeros et al[17] concluded that the influenza vaccine offered significant protection against any type of influenza-related hospitalization in children 6 months to 17 years of age, with a VE of 57.5% (95% CI, 54.8% to 65.5%). Strain-specific VE was higher for influenza A(H1N1)pdm09 (75.1%; 95% CI, 54.8% to 93.3%) and influenza B (50.9%; 95% CI, 41.7% to 59.9%), compared with influenza A(H3N2) (40.8%; 95% CI, 25.6% to 55.9%). As expected, children who were fully vaccinated were better

protected (VE 61.8%; 95% CI, 54.4% to 69.1%) compared with those who were partially vaccinated (VE 33.91%; 95% CI, 21.1% to 46.7%). Notably, VE was higher in children younger than 5 years (61.7%; 95% CI, 49.3% to 74.1%) than in children 6 to 17 years of age (54.4%; 95% CI, 35.1% to 73.6%). In the United States, the CDC estimated that during the 2018–2019 season, influenza vaccination prevented 20% of projected hospitalizations associated with infection with the A(H1N1)pdm09 virus among children 5 to 17 years of age and 43% among children 6 months to 4 years of age.[18]

Historically, up to 80% of influenza-associated pediatric deaths have occurred in unvaccinated children 6 months and older. Influenza vaccination is associated with reduced risk of laboratory-confirmed influenza-related pediatric death.[19] In one case-cohort analysis comparing vaccination uptake in laboratory-confirmed influenza-associated pediatric deaths to estimated vaccination coverage among pediatric cohorts in the United States from 2010 to 2014, Flannery et al[19] found that only 26% of children had received the vaccine before illness onset, compared to an average vaccination coverage of 48%. Overall VE against influenza-associated death in children was 65% (95% CI, 54% to 74%). More than half of children in this study who died of influenza had ≥1 underlying medical condition associated with increased risk of severe influenza-related complications; only 1 in 3 of these at-risk children had been vaccinated; yet VE against death in children with underlying conditions was 51% (95% CI, 31% to 67%). Similarly, influenza vaccination reduces by three-quarters the risk of severe life-threatening laboratory-confirmed influenza in children requiring admission to the ICU.[20] The influenza virus type might also affect the severity of disease. In a study of hospitalizations for influenza A versus B, the odds of mortality were significantly greater with influenza B than with influenza A and were not entirely explained by underlying health conditions.[21]

SEASONAL INFLUENZA VACCINES

The seasonal influenza vaccines licensed for children and adults for the 2021–2022 season are shown in Table 3. More than one product may be appropriate for a given patient, and vaccination should not be delayed to obtain a specific product.

All 2021–2022 seasonal influenza vaccines will be quadrivalent and contain the same influenza strains as recommended by the World Health Organization (WHO) and the US Food and Drug Administration's (FDA's) Vaccines and Related Biological Products Advisory Committee for the Northern Hemisphere.[22] Both influenza A(H1N1) and A(H3N2) components are different in this season's vaccine. The B components are unchanged. The influenza A strains may be different for egg-based versus cell- or recombinant-based vaccines on the basis of their optimal characteristics for each platform, but all are matched to the strains expected to circulate in the 2021–2022 season.

1. Quadrivalent vaccines contain the following:
   a. influenza A(H1N1) component:
      i. egg-based vaccines: A/Victoria/2570/2019 (H1N1) pdm09-like virus (new this season); and
      ii. cell- or recombinant-based vaccines: A/Wisconsin/588/2019 (H1N1) pdm09-like virus (new this season);
   b. influenza A(H3N2) component:
      i. egg-based vaccines: A/Cambodia/e0826360/2020 (H3N2)-like virus (new this season); and
      ii. cell- or recombinant-based vaccines: A/Cambodia/e0826360/2020 (H3N2)-like virus (new this season);
   c. B/Victoria component:
      i. all vaccines: B/Washington/02/2019-like virus (B/Victoria/2/87 lineage) (unchanged); and
   d. B/Yamagata component:
      i. all vaccines: B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage) (unchanged).
2. Trivalent vaccines do not include the B/Yamagata component (not available in United States).

Inactivated Influenza Vaccine

For the 2021–2022 season, all licensed inactivated influenza vaccines (IIVs) for children and adults in the United States are quadrivalent vaccines, with specific age indications for available formulations (Table 3). Among vaccines available for children, 4 are egg based (seed strains grown in eggs) and 1 is cell culture based (seed strains grown in Madin-Darby canine kidney cells). All inactivated egg-based vaccines (Afluria Quadrivalent, Fluarix Quadrivalent, Flulaval Quadrivalent, and Fluzone Quadrivalent) are licensed for children 6 months and older and are available in single-dose, thimerosal-free, prefilled syringes. The only pediatric cell culture–based vaccine (Flucelvax Quadrivalent) is now licensed for children **6 months** and older.[23] The extension of the age indication down from 4 years to 2 years of age in March 2021 was based on data from a randomized double-blind clinical efficacy study conducted among children 2 to 18 years of age over 3 seasons (2017 in the Southern Hemisphere and

TABLE 3 Recommended Seasonal Influenza Vaccines for Different Age Groups: United States, 2021–2022 Influenza Season

Vaccine	Trade Name (Manufacturer)	Age Group	Presentation and Hemagglutinin Antigen Content (IIVs and RIV4) or Virus Count (LAIV4) per Dose for Each Antigen	Thimerosal Mercury Content, µg Hg/0.5-mL Dose	CPT Code
Quadrivalent standard dose: egg-based vaccines					
IIV4	Afluria Quadrivalent (Seqirus)	6–35 mo	0.25-mL prefilled syringe (7.5 µg/0.25 mL)	0	90685
	—	≥36 mo	0.5-mL prefilled syringe (15 µg/0.5 mL)	0	90686
	—	≥6 mo	5.0-mL multidose vial[a] (15 µg/0.5 mL)	24.5	90687
IIV4	Fluarix Quadrivalent (GlaxoSmithKline)	≥6 mo	0.5-mL prefilled syringe (15 µg/0.5 mL)	0	90686
IIV4	FluLaval Quadrivalent (GlaxoSmithKline)	≥6 mo	0.5-mL prefilled syringe (15 µg/0.5 mL)	0	90686
IIV4	Fluzone Quadrivalent (Sanofi Pasteur)	≥6 mo	0.5-mL prefilled syringe (15 µg/0.5 mL) (0.25 mL no longer available)	0	90686
	—	≥6 mo	0.5-mL single-dose vial (15 µg/0.5 mL)	0	90686
	—	≥6 mo	5.0-mL multidose vial[a] (15 µg/0.5 mL)	25	90687
Quadrivalent standard dose: cell culture–based vaccines					
ccIIV4	Flucelvax Quadrivalent (Seqirus)	≥**6 mo**	0.5-mL prefilled syringe (15 µg/0.5 mL)	0	90674
	—	≥**6 mo**	5.0 mL multidose vial[a] (15 µg/0.5 mL)	25	90756
Quadrivalent standard dose: egg-based with adjuvant vaccines					
aIIV4 MF-59 adjuvanted	Fluad Quadrivalent (Seqirus)	≥65 y	0.5-mL prefilled syringe (15 µg/0.5 mL)	0	90653
Quadrivalent high dose: egg-based vaccine					
IIV4	Fluzone High-Dose Quadrivalent (Sanofi Pasteur)	≥65 y	0.7-mL prefilled syringe (60 µg/0.7 mL)	0	90662
Recombinant vaccine					
RIV4	Flublok Quadrivalent (Sanofi Pasteur)	≥18 y	0.5-mL prefilled syringe (45 µg/0.5 mL)	0	90682
Live attenuated vaccine					
LAIV4	FluMist Quadrivalent (AstraZeneca)	2–49 y	0.2-mL prefilled intranasal sprayer (virus dose: 10 6.5–7.5 FFU/0.2 mL)	0	90672

Adapted from Grohskopf LA, Alyanak E, Ferdinands JM, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2021–22 influenza season. *MMWR Recomm Rep*. 2021;70(5):1–28. The implementation guidance on supply, pricing, payment, CPT coding, and liability issues can be found at www.aapredbook.org/implementation. aIIV4, quadrivalent adjuvanted inactivated influenza vaccine; ccIIV4, quadrivalent cell culture–based inactivated influenza vaccine; CPT, *Current Procedural Terminology*; FFU, fluorescent focus unit; —, not applicable.

[a] For vaccines that include a multidose vial presentation, a maximum of 10 doses can be drawn from a multidose vial.

2017–2018 and 2018–2019 in the Northern Hemisphere), in which Flucelvax Quadrivalent demonstrated efficacy against laboratory-confirmed influenza illness of 54.6% (95% CI, 45.7% to 62.1%), compared with a control vaccine (meningococcal serogroup ACWY conjugate vaccine).[24] **Subsequently, the FDA approved an expansion in age indication from 2 years and older to 6 months and older for Flucelvax Quadrivalent on October 14, 2021 (https://www.fda.gov/media/153137/download).**

A quadrivalent recombinant baculovirus-expressed hemagglutinin influenza vaccine (quadrivalent recombinant influenza vaccine [RIV4]) (Flublok Quadrivalent) is licensed only for people 18 years and older. A high-dose quadrivalent inactivated influenza vaccine (IIV4) (Fluzone High-Dose Quadrivalent) containing 4 times the amount of antigen for each virus strain compared with the standard-dose vaccines is licensed only for people 65 years and older. The quadrivalent MF-59 adjuvanted inactivated vaccine (Fluad Quadrivalent) was licensed for people 65 years and older in February 2020.[23] Adjuvants may be included in a vaccine to elicit a more robust immune response, which could lead to a reduction in the number of doses required for children. In one pediatric study, the relative vaccine efficacy of an MF-59 adjuvanted influenza vaccine was significantly greater than that of a nonadjuvanted vaccine in the 6- to 23-month age group.[25] Adjuvanted seasonal influenza vaccines are not licensed for children in the United States.

Children 36 months (3 years) and older can receive any age-appropriate licensed IIV, administered at a 0.5-mL dose containing 15 μg of hemagglutinin (HA) from each strain. Children 6 to 35 months of age may receive any age-appropriate licensed IIV without preference for one product over another. Several vaccines have been licensed for children 6 to 35 months of age since 2017 (Table 3). All are quadrivalent, but the dose volume, and therefore the antigen content, may vary among different IIV products. In addition to a 0.25-mL (7.5 μg of HA per vaccine virus) Fluzone Quadrivalent vaccine, a 0.5-mL formulation of Fluzone Quadrivalent containing 15 μg of HA per vaccine virus per dose was licensed in January 2019 after these 2 formulations were shown to have comparable safety and immunogenicity in a single randomized multicenter study.[26–28] Only the 0.5-mL Fluzone prefilled syringe will be available this season. In addition, 2 other vaccines, Fluarix Quadrivalent[29] and FluLaval Quadrivalent,[30] are licensed at a 0.5-mL dose in children 6 to 35 months of age. These 2 vaccines do not have a 0.25-mL dose formulation. Afluria Quadrivalent is the only pediatric vaccine that has a 0.25-mL presentation for children 6 to 35 months of age. Afluria 0.5 mL is licensed for children 3 years and older only.[31]

Given that different formulations of IIV for children 6 to 35 months of age are available, care should be taken to administer the appropriate volume and dose for each product. In each instance, the recommended volume may be administered from an appropriate prefilled syringe, a single-dose vial, or a multidose vial, as supplied by the manufacturer. For vaccines that include a multidose vial presentation, a maximum of 10 doses can be drawn from a multidose vial. Importantly, dose volume is different from the number of doses needed to complete vaccination. Children 6 months to 8 years of age who require 2 doses of the vaccine for the 2021–2022 season should receive 2 separate doses at the recommended dose volume specified for each product.

IIVs are well tolerated in children and can be used in healthy children as well as those with underlying chronic medical conditions. CDC best practice guidelines should be followed for administration (https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/). The most common injection site adverse reactions after administration of IIV in children are injection site pain, redness, and swelling. The most common systemic adverse events are drowsiness, irritability, loss of appetite, fatigue, muscle aches, headache, arthralgia, and gastrointestinal tract symptoms.

IIVs can be administered concomitantly with other inactivated or live vaccines.[32–36] The influenza vaccine may be administered simultaneously or at any time before or after administration of the currently available COVID-19 vaccines.[37] In general, although data are not available for concomitant administration of COVID-19 with other vaccines in children, extensive experience with non-COVID-19 vaccines has demonstrated that immunogenicity and adverse event profiles are generally similar when vaccines are administered simultaneously as when they are administered alone. Furthermore, concomitant administration with the influenza vaccine is being evaluated in adults (unpublished observations presented at ACIP Influenza Workgroup meeting, February 2, 2021), and data in children are anticipated to inform recommendations. Given that it is unknown whether reactogenicity of COVID-19 vaccines will be increased with coadministration of the

influenza vaccine, the reactogenicity profile of the vaccines should be considered, and providers should consult the most current ACIP and AAP guidance regarding coadministration of COVID-19 vaccines with influenza vaccines.[38] Overall, the benefits of timely vaccination with same-day administration of IIV and other recommended vaccines outweigh the risk of potential reactogenicity in children.

Thimerosal-containing vaccines are not associated with an increased risk of autism spectrum disorder in children. Thimerosal from vaccines has not been linked to any neurologic condition. The AAP supports the current WHO recommendations for use of thimerosal as a preservative in multiuse vials in the global vaccine supply.[39] Despite the lack of evidence of harm, some states have legislation restricting the use of vaccines that contain even trace amounts of thimerosal. The benefits of protecting children against the known risks of influenza are clear. Therefore, to the extent permitted by state law, children should receive any available formulation of IIVs rather than delaying vaccination while waiting for reduced thimerosal-content or thimerosal-free vaccines. IIV formulations that are free of even trace amounts of thimerosal are widely available (Table 3).

Live Attenuated (Intranasal) Influenza Vaccine

The intranasal live attenuated influenza vaccine (LAIV) was initially licensed in the United States in 2003 for people 5 to 49 years of age as a trivalent formulation (trivalent live attenuated influenza vaccine [LAIV3]), and the approved age group was extended to 2 years of age in 2007. The quadrivalent formulation (quadrivalent live attenuated influenza vaccine [LAIV4]), licensed in 2012, was first available during the 2013–2014 influenza season, replacing the LAIV3.

The CDC conducted a systematic review of published studies evaluating the effectiveness of the LAIV3 and LAIV4 in children from the 2010–2011 to the 2016–2017 influenza seasons, including data from US and European studies.[40] The data suggested that the effectiveness of the LAIV3 or LAIV4 for the influenza A(H1N1)pdm09 strain was lower than that of the IIV in children 2 to 17 years of age. The LAIV was similarly effective against influenza B and A/H3N2 strains in some age groups compared with the IIV. The LAIV was not recommended by the CDC or AAP for use in children during the 2016–2017 and 2017–2018 seasons, given concerns about its effectiveness against A(H1N1)pdm09. For the 2017–2018 season, a new A(H1N1)pdm09-like virus strain (A/Slovenia/2903/2015) was included in the LAIV4, replacing the previous A/Bolivia/559/2013 strain. A study conducted by the LAIV4 manufacturer evaluated viral shedding and immunogenicity associated with the LAIV4 formulation containing the new A(H1N1) pdm09-like virus among US children 24 to 48 months of age.[41] Shedding and immunogenicity data suggested that the new influenza A(H1N1)pdm09-like virus included in its latest formulation had improved replicative fitness over previous LAIV4 influenza A(H1N1)pdm09-like virus strains, resulting in an improved immune response comparable to that of the LAIV3 available before the 2009 pandemic. Shedding and replicative fitness are not known to correlate with efficacy, and no published effectiveness estimates for this revised formulation of the vaccine against influenza A(H1N1)pdm09 viruses were available before the start of the 2018–2019 influenza season because influenza A(H3N2) and influenza B viruses predominated during the 2017–2018 Northern Hemisphere season. Therefore, for the 2018–2019 influenza season, the AAP recommended the IIV4 or trivalent inactivated influenza vaccine as the primary choice for influenza vaccination in children, with LAIV4 use reserved for children who would not otherwise receive an influenza vaccine and for whom LAIV use was appropriate for age (2 years and older) and health status (ie, healthy, without any underlying chronic medical condition).

In February 2019, the AAP Committee on Infectious Diseases reviewed available data on influenza epidemiology and VE for the 2018–2019 season and agreed that harmonizing recommendations between the AAP and CDC for the use of LAIVs in the 2019–2020 season was appropriate. After the February 2020 ACIP meeting, the AAP Committee on Infectious Diseases reviewed available epidemiological and effectiveness data for the previous and current seasons to inform recommendations for the 2020–2021 season. Despite the early circulation of A(H1N1)pdm09 during the 2018–2019 season and its predominance during the 2019–2020 season, low use of the LAIV4 in the US population has limited the evaluation of product-specific VE, and no additional US data on VE for the LAIV4 are available. Although the proportion of the LAIV used for vaccination is unknown, interim overall VE (not specific to a type of vaccine) for the 2019–2020 influenza season showed reassuring protection in children against circulating influenza A and B strains (Table 1).[42] Furthermore, influenza vaccine coverage rates in

children were stable until the COVID-19 pandemic.[6] In European surveillance networks where uninterrupted use of the LAIV has continued from the 2016–2017 to the 2019–2020 seasons, the United Kingdom was the only country to report final VE against medically attended influenza for the 2018–2019 season. In children 2 to 17 years of age, the reported VE was 49.9% (95% CI, −14.3% to 78.0%) for A(H1N1)pdm09 and 27.1% (95% CI, −130.5% to 77%) for A(H3N2).[43] The final adjusted VE in the United States (where mostly the IIV was used) for 2018–2019 against A(H1N1)pdm09 was 59% (95% CI, 47% to 69%) for children 6 months to 8 years of age but only 24% (95% CI, −18% to 51%) for children 9 to 17 years of age. The reported US VE was 24% (95% CI, 1% to 42%) in children 6 months to 8 years of age and 3% (95% CI, −30% to 28%) in children 9 to 17 years of age for A(H3N2).[44] Direct comparisons cannot be made given differences in reporting of VE for various age groups. Other countries that use the LAIV (Canada, Finland) have not reported LAIV4-specific VE in the past several seasons. Small case numbers and low LAIV use may also limit accurate VE calculations in these countries. In general, as long as use of the LAIV is low relative to the IIV, it will be difficult to estimate LAIV VE accurately. Furthermore, important variability in VE against all strains is reported for both the IIV and LAIV.

Influenza VE varies from season to season and is affected by many factors, including age and health status of the recipient, influenza type and subtype, existing immunity from previous infection or vaccination, and degree of antigenic match between vaccine and circulating virus strains. It is possible that VE also differs among individual vaccine products; however, product-specific comparative effectiveness data are lacking for most vaccines. Additional experience over multiple influenza seasons will help to determine optimal use of the available vaccine formulations in children. The AAP will continue to monitor annual influenza surveillance and VE reports to update influenza vaccine recommendations if necessary.

The most commonly reported reactions of the LAIV4 in children are runny nose or nasal congestion, headache, decreased activity or lethargy, and sore throat. The LAIV4 may be administered simultaneously with other inactivated or live vaccines, but if not given simultaneously, it is recommended that administration of other live vaccines is separated by a 4-week interval from LAIV4 vaccination.

LAIV and Immunocompromised Hosts

The IIV is the vaccine of choice for anyone in close contact with a subset of severely immunocompromised people (ie, those requiring a protected environment). The IIV is preferred over the LAIV for contacts of severely immunocompromised people because of a theoretical risk of infection attributable to LAIV strains in an immunocompromised contact of an LAIV-immunized person. Available data indicate a low risk of transmission of the virus from both children and adults vaccinated with the LAIV. Health care personnel (HCP) immunized with the LAIV may continue to work in most units of a hospital, including the NICU and general oncology ward, using standard infection-control techniques. As a precautionary measure, people recently vaccinated with the LAIV should restrict contact with severely immunocompromised patients for 7 days after immunization, although there have been no reports of LAIV transmission from a vaccinated person to an immunocompromised person. In the theoretical scenario in which symptomatic LAIV infection develops in an immunocompromised host, LAIV strains are susceptible to antiviral medications.

INFLUENZA VACCINE CONTRAINDICATIONS AND PRECAUTIONS

Anaphylactic and severe allergic reactions to any influenza vaccine are contraindications to vaccination. The AAP recommends that children who have had an allergic reaction after a previous dose of any influenza vaccine should be evaluated by an allergist to determine if future receipt of the vaccine is appropriate.

Minor illnesses, with or without fever, are not contraindications to the use of influenza vaccines, including among children with mild upper respiratory infection symptoms or allergic rhinitis. In children with a moderate to severe febrile illness (eg, high fever, active infection, requiring hospitalization), on the basis of the judgment of the clinician, vaccination should be deferred until resolution of the illness. Children with confirmed COVID-19 can receive the influenza vaccine when the acute illness has resolved and/or illness is mild. Children with an amount of nasal congestion that would notably impede vaccine delivery into the nasopharyngeal mucosa should have the LAIV deferred until resolution or may receive the IIV.

A precaution for vaccination is a condition in a recipient that might increase the risk or seriousness of a possible vaccine-related adverse reaction. A precaution also may exist for conditions that might

compromise the ability of the host to develop immunity after vaccination. Vaccination may be recommended in the presence of a precaution if the benefit of protection from the vaccine outweighs the potential risks.

A history of Guillain-Barré syndrome (GBS) after influenza vaccination is considered a precaution for the administration of influenza vaccines. GBS is rare, especially in children, and there is a lack of evidence on risk of GBS after influenza vaccination in children. Nonetheless, regardless of age, a history of GBS <6 weeks after a previous dose of the influenza vaccine is a precaution for administration of the influenza vaccine. GBS may occur after influenza infection. The benefits of influenza vaccination might outweigh the risks for certain people who have a history of GBS (particularly if not associated with previous influenza vaccination) and who also are at high risk for severe complications from influenza.

Specific precautions for the LAIV include a diagnosis of asthma in children 5 years and older and the presence of certain chronic underlying medical conditions, including metabolic disease, diabetes mellitus, other chronic disorders of the pulmonary or cardiovascular systems, renal dysfunction, or hemoglobinopathies. Because the safety of the LAIV has not been definitively established in these situations, the IIV should be considered, and vaccination should not be delayed in these high-risk groups. People who should not receive the LAIV are listed below.

People in whom the LAIV is contraindicated include the following:

- children younger than 2 years;
- children 2 to 4 years of age with a diagnosis of asthma or a history of recurrent wheezing or a medically attended wheezing episode in the previous 12 months because of the potential for increased wheezing after immunization; in this age range, many children have a history of wheezing with respiratory tract illnesses and are eventually diagnosed with asthma;
- children with cochlear implants or active cerebrospinal fluid leaks;
- children who have a known or suspected primary or acquired immunodeficiency or who are receiving immunosuppressive or immunomodulatory therapies;
- children with anatomic or functional asplenia, including from sickle cell disease;
- close contacts and caregivers of those who are severely immunocompromised and require a protected environment;
- children and adolescents receiving aspirin or salicylate-containing medications;
- children who have received other live-virus vaccines within the previous 4 weeks (except for the rotavirus vaccine); however, the LAIV can be administered on the same day with other live-virus vaccines if necessary;
- children taking an influenza antiviral medication until 48 hours (oseltamivir, zanamivir), 5 days (peramivir), or 2 weeks (baloxavir) after stopping the influenza antiviral therapy; if a child recently received the LAIV but has an influenza illness for which antiviral agents are appropriate, the antiviral agents should be given; if antiviral agents are necessary for treatment within 2 weeks of LAIV immunization, reimmunization or administration of IIV is indicated because of the potential effects of antiviral medications on LAIV replication and immunogenicity; and
- pregnant women.

INFLUENZA VACCINES AND EGG ALLERGY

There is strong evidence that individuals with egg allergies can safely receive the influenza vaccine without any additional precautions beyond those recommended for any vaccine.[45,46] The presence of an egg allergy in an individual is not a contraindication to receive the IIV or LAIV. Vaccine recipients with egg allergies are at no greater risk for a systemic allergic reaction than those without egg allergies. Therefore, precautions, such as choice of a particular vaccine, special observation periods, or restriction of administration to particular medical settings, are not warranted and constitute an unnecessary barrier to immunization. It is not necessary to inquire about an egg allergy before the administration of any influenza vaccine, including on screening forms. Routine prevaccination questions regarding anaphylaxis after receipt of any vaccine are appropriate. Standard vaccination practice for all vaccines in children should include the ability to respond to rare acute hypersensitivity reactions. Children who have had a previous allergic reaction to the influenza vaccine should be evaluated by an allergist to determine if future receipt of the vaccine is appropriate.

INFLUENZA VACCINES DURING PREGNANCY AND BREASTFEEDING

The influenza vaccine is recommended by the ACIP, the American College of Obstetrics and Gynecology, and the American Academy of Family Physicians for all women during any trimester of gestation for the protection of mothers against influenza and its complications.[23,47] Substantial evidence has accumulated regarding the efficacy of maternal influenza immunization in preventing

laboratory-confirmed influenza disease and its complications in both mothers and their infants in the first 2 to 6 months of life.[47–52] Pregnant women who are immunized against influenza at any time during their pregnancy provide protection to their infants during their first 6 months of life, when they are too young to receive the influenza vaccine themselves, through transplacental passage of antibodies.[49–57] Infants born to women who receive influenza vaccination during pregnancy have been shown to have a risk reduction of up to 72% (95% CI, 39% to 87%) for laboratory-confirmed influenza hospitalization in the first few months of life.[55]

It is safe to administer the IIV to pregnant women during any trimester of gestation and post partum. Any licensed, recommended, and age-appropriate influenza vaccine may be used, although experience with the use of the RIV4 in pregnant women is limited. The LAIV is contraindicated during pregnancy. Data on the safety of influenza vaccination at any time during pregnancy continues to support the safety of influenza immunization during pregnancy.[47,49–54,58] In a 5-year retrospective cohort study from 2003 to 2008 with more than 10 000 women, influenza vaccination in the first trimester was not associated with an increase in the rates of major congenital malformations.[59] Similarly, a systematic review and meta-analysis of studies of congenital anomalies after vaccination during pregnancy, including data from 15 studies (14 cohort studies and 1 case-control study), did not show any association between congenital defects and influenza vaccination in any trimester, including the first trimester of gestation.[60] Assessments of any association with influenza vaccination and preterm birth and infants small for gestational age have yielded inconsistent results, with most studies reporting a protective effect or no association against these outcomes.[61,62] The authors of a cohort study from the Vaccines and Medications in Pregnancy Surveillance System of vaccine exposure during the 2010–2011 to 2013–2014 influenza seasons found no significant association of spontaneous abortion with influenza vaccine exposure in the first trimester or within the first 20 weeks' gestation.[63] One observational Vaccine Safety Datalink study conducted during the 2010–2011 and 2011–2012 influenza seasons indicated an association between receipt of the IIV containing H1N1pdm09 and risk of spontaneous abortion when an H1N1pdm09-containing vaccine had also been received the previous season.[64] A follow-up study conducted by the same investigators with a larger population and stricter outcome measures did not show this association and further supported the safety of the influenza vaccine during pregnancy.[65]

Women in the postpartum period who did not receive influenza vaccination during pregnancy should be encouraged to discuss receiving the influenza vaccine before discharge from the hospital with their obstetrician, family physician, nurse midwife, or other trusted provider. Women who traditionally experience barriers to preventive care (eg, women who do not qualify for Medicaid) should be offered vaccination before hospital discharge or offered information in their preferred language about free vaccine clinics. Vaccination during breastfeeding is safe for mothers and their infants.

Breastfeeding is strongly recommended to protect infants against influenza viruses by activating innate antiviral mechanisms, specifically type 1 interferons. Human milk from mothers vaccinated during the third trimester also contains higher levels of influenza-specific immunoglobulin A.[66] Greater exclusivity of breastfeeding in the first 6 months of life decreases the episodes of respiratory illness with fever in infants of vaccinated mothers. For infants born to mothers with confirmed influenza illness at delivery, breastfeeding is encouraged, and guidance on breastfeeding practices can be found at https://www.cdc.gov/breastfeeding/breastfeeding-special-circumstances/maternal-or-infant-illnesses/influenza.html and at https://www.cdc.gov/flu/professionals/infectioncontrol/peri-post-settings.htm. Breastfeeding should be encouraged even if the mother or infant has influenza illness. The mother should pump and feed expressed milk if she or her infant is too sick to breastfeed. If the breastfeeding mother requires antiviral agents, treatment with oral oseltamivir is preferred. The CDC does not recommend use of baloxavir for treatment of pregnant women or breastfeeding mothers. There are no available efficacy or safety data in pregnant women, and there are no available data on the presence of baloxavir in human milk, the effects on the breastfed infant, or the effects on milk production.

VACCINE STORAGE AND ADMINISTRATION

The AAP storage and handling tip sheet provides resources for practices to develop comprehensive vaccine management protocols to keep the temperature for vaccine storage constant during a power failure or other disaster.[67] The AAP

recommends the development of a written disaster plan for all practice settings. During the COVID-19 pandemic, the AAP recommends that influenza vaccine administration follow CDC guidance for administration of immunizations (https://www.cdc.gov/vaccines/pandemic-guidance/index.html). Vaccination in the medical home is ideal to ensure that pediatric patients receive other vaccinations and routine care in a timely manner and receive catch-up immunizations if delays have occurred because of the pandemic. In general, infection-prevention measures should be in place for all patient encounters, including screening for symptoms, physical distancing, respiratory and hand hygiene, and surface decontamination. In addition to standard precautions and hand hygiene, during the COVID-19 pandemic, it is recommended that vaccine administrators wear a surgical face mask (not N95 or respirator) at all times and eye protection if the level of community spread is moderate or elevated.[68] Administration of the LAIV intranasally is not an aerosol-generating procedure; however, vaccine administrators are advised to wear gloves when administering the LAIV given the potential for contact with respiratory secretions. Gloves used for intranasal or intramuscular vaccine administration should be changed with every patient. Gowns are not required.

IIVs

IIVs for intramuscular injection are shipped and stored at 2°C to 8°C (36°F–46°F); vaccines that are inadvertently frozen should not be used. These vaccines are administered intramuscularly into the anterolateral thigh of infants and young children and into the deltoid muscle of older children and adults. Given that various IIVs are available, careful attention should be paid to ensure that each product is used according to its approved age indication, dosing, and volume of administration (Table 3). A 0.5-mL unit dose of any IIV should not be split into 2 separate 0.25-mL doses. If a lower dose than recommended is inadvertently administered to a child 36 months or older (eg, 0.25 mL), an additional 0.25-mL dose should be administered to provide a full dose of 0.5 mL as soon as possible. The total number of full doses appropriate for age should be administered. If a child is inadvertently vaccinated with a formulation only approved for adults, the dose should be counted as valid.

LAIV

The cold-adapted, temperature-sensitive LAIV4 formulation is shipped and stored at 2°C to 8°C (35°F–46°F) and administered intranasally in a prefilled single-use sprayer containing 0.2 mL of the vaccine. A removable dose-divider clip is attached to the sprayer to facilitate administration of 0.1 mL separately into each nostril. If the child sneezes immediately after administration, the dose should not be repeated.

TIMING OF VACCINATION AND DURATION OF PROTECTION

Although peak influenza activity in the United States tends to occur from January to March, influenza can circulate from early fall (October) to late spring (May), with one or more disease peaks. This pattern of circulation was substantially altered during the COVID-19 pandemic. Predicting the onset and duration or the severity of the influenza season with accuracy is impossible. It is also challenging to balance public health strategies needed to achieve high vaccination coverage with achieving optimal individual immunity for protection against influenza at the peak of seasonal activity, knowing that the duration of immunity after vaccination can wane over time. Initiation of influenza vaccination before influenza is circulating in the community and continuing to vaccinate throughout the influenza season are important components of an effective influenza vaccination strategy.

Complete influenza vaccination by the end of October is recommended by the CDC and AAP. Children who need 2 doses of the vaccine should receive their first dose as soon as possible when the vaccine becomes available, to allow sufficient time for receipt of the second dose ≥4 weeks after the first, before the onset of the influenza season. Children who require only 1 dose of the influenza vaccine should also ideally be vaccinated by the end of October. Recent data in adults suggest that early vaccination (July or August) might be associated with suboptimal immunity before the end of the influenza season, and the CDC now discourages vaccination in the summer months, particularly among older adults.[37]

Although the evidence is limited in children, recent reports raise the possibility that early vaccination might contribute to reduced protection later in the influenza season.[69–80] In these studies, VE decreased within a single influenza season, and this decrease was correlated with increasing time after vaccination. However, this decay in VE was not consistent across different age groups and varied by season and virus subtypes. In some studies, waning VE was more evident among older adults and younger children[72,74] and with influenza A(H3N2) viruses more than influenza A(H1N1) or B viruses.[73,76,78] A multiseason analysis from the US Flu VE Network found that VE declined by approximately 7% per month for

influenza A (H3N2) and influenza B and by 6% to 11% per month for influenza A (H1N1)pdm09 in individuals 9 years and older.[71] VE remained greater than 0 for at least 5 to 6 months after vaccination. A more recent study of children older than 2 years also found evidence of declining VE, with an odds ratio increasing approximately 16% with each additional 28 days from vaccine administration.[77] Another study evaluating VE from the 2011–2012 to the 2013–2014 influenza seasons demonstrated 54% to 67% protection from 0 to 180 days after vaccination.[75] Finally, a multiseason study in Europe from 2011–2012 to 2014–2015 showed a steady decline in VE down to 0% protection by 111 days after vaccination.[76]

Further evaluation is needed before any policy change in timing of influenza administration in children is made. An early onset of the influenza season is a concern when considering delaying vaccination. Until there are definitive data demonstrating waning immunity influences VE in children, administration of the influenza vaccine should not be delayed to a later date because this increases the likelihood of missing influenza vaccination altogether.[81] Providers may continue to offer vaccination as long as influenza is circulating and until June 30 of each year, when the seasonal influenza vaccine expires, because the duration of influenza circulation is unpredictable. Furthermore, a person may experience more than 1 influenza infection during a given season because of the various cocirculating strains. Although influenza activity in the United States is typically low during the summer, influenza cases and outbreaks can occur, particularly among international travelers, who may be exposed to influenza year-round, depending on the destination.

VACCINE IMPLEMENTATION

The AAP Partnership for Policy Implementation has developed a series of definitions using accepted health information technology standards to assist in the implementation of vaccine recommendations in computer systems and quality measurement efforts. This document is available at https://www.aap.org/enus/professional-resources/quality-improvement/Pages/Partnership-for-Policy-Implementation.aspx. In addition, the AAP has developed implementation guidance on supply, payment, coding, and liability issues; these documents can be found at https://www.aap.org/en/patient-care-pages-in-progress/influenza/managing-influenzavaccination-in-your-practice/. The committee supports adequate payment from public and private payers for the vaccine product and administration in the pediatric population. Information on preparing your practice to administerinfluenza vaccines during the COVID-19 pandemic can be found at https://services.aap.org/en/pages/2019-novel-coronaviruscovid-19-infections/help-for-pediatricians/preparing-for-flu-season/. HCP, influenza campaign organizers, and public health agencies are encouraged to collaborate to develop improved strategies for planning, distribution, communication, and administration of vaccines. For example, pediatricians can play a key role in educating and assisting early childhood education centers and schools in educating parents on the importance of influenza immunization. Resources for effective communication and messaging strategies, including promoting vaccinations and providing resources for pediatricians to communicate with patients, families, and the communities they serve, are available on the AAP Web site (https://services.aap.org/en/news-room/campaigns-and-toolkits/immunizations and https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/immunizations/Influenza-Implementation-Guidance/Pages/Patient-Family-and-Community.aspx).

Pediatricians and other pediatric health care providers should plan to make the influenza vaccine easily accessible for all children. Examples include sending alerts to families that vaccine is available (eg, e-mails, texts, letters, patient portals, practice-specific Web sites, or social media platforms); creating walk-in influenza vaccination clinics; extending hours beyond routine times during peak vaccination periods; administering the influenza vaccine during both well-child examinations and sick visits as well as in hospitalized patients, especially those at high risk of influenza complications, before hospital discharge (unless medically contraindicated); implementing standing orders for influenza vaccination; considering how to immunize parents, adult caregivers, and siblings (see risk management guidance associated with adult immunizations in ref 85) at the same time as children; and working with other institutions (eg, schools, child care programs, local public health departments, and religious organizations) or alternative care sites, such as pharmacies and hospital emergency departments, to expand venues for administering the vaccine. If a child receives the influenza vaccine outside his or her medical home, such as at a pharmacy, retail-based clinic, or another practice setting, appropriate documentation of vaccination should be provided to the patient to be

shared with his or her medical home and entered into the state or regional immunization information system (ie, registry).

Concerted efforts among the aforementioned groups, plus vaccine manufacturers, distributors, and payers, are necessary to prioritize distribution appropriately to the primary care office setting and patient-centered medical home before other venues, especially when vaccine supplies are delayed or limited. Payers should eliminate remaining patient responsibility cost barriers to the influenza vaccine where they still exist. Similar efforts should be made to eliminate the vaccine supply discrepancy between privately insured patients and those eligible for vaccination through the Vaccines for Children program. American Indian and Alaskan native children, who are eligible for vaccines through the Vaccines for Children program, are at higher risk for influenza complications and should be prioritized in a vaccine shortage (Table 2).

Population health can benefit from pediatricians' discussions about vaccine safety and effectiveness. Pediatricians and their office staff can influence vaccine acceptance by explaining the importance of annual influenza vaccination for children and emphasizing when a second dose of the vaccine is indicated. The AAP and CDC have created communication resources to convey these important messages and to help the public understand influenza recommendations. Resources will be available on *Red Book Online* (https://redbook.solutions.aap.org/selfserve/ssPage.aspx?SelfServeContentId=influenza-resources).

The AAP supports mandatory influenza vaccination programs for all HCP in all settings, including outpatient settings. Optimal prevention of influenza in the health care setting depends on the vaccination of at least 90% of HCP. Vaccine coverage among HCP was 81.1% during the 2018–2019 season, up from 78.4% the previous year.[86] Influenza vaccination programs for HCP benefit the health of employees, their patients, and members of the community, especially because HCP frequently come into contact with patients at high risk of influenza illness in their clinical settings. Mandatory influenza immunization for all HCP is considered to be ethical, just, and necessary to improve patient safety. For the prevention and control of influenza, HCP must prioritize the health and safety of their patients, honor the requirement of causing no harm, and act as role models for both their patients and colleagues by receiving influenza vaccination annually.

INFLUENZA VACCINE COVERAGE

Although national influenza vaccination coverage among children had remained stable and even increased in the past several seasons before the COVID-19 pandemic, overall vaccination coverage remains suboptimal (Fig 1). The Healthy People 2020 national target of 70% of children and adults vaccinated against influenza was not achieved, with coverage lagging by 6 percentage points for children and almost 20 percentage points for adults. The newly launched Healthy People 2030 has, therefore, set a target for influenza vaccination of people $\geq$6 months of age at 70%.[87] Additional options for vaccination of children may provide a means to improve coverage, particularly in pharmacies and child care and school-based settings. Achieving high coverage rates of the influenza vaccine in infants and children is a priority to protect them against influenza disease and its complications.

The AAP and CDC recommend vaccine administration at any visit to the medical home during influenza season when it is not contraindicated, at specially arranged vaccine-only sessions, and through cooperation with public health departments, community sites, schools, and Head Start and child care facilities to provide the influenza vaccine. It is important that annual delivery of the influenza vaccine to primary care medical homes be timely to avoid missed opportunities. If alternate venues, including pharmacies and other retail-based clinics, are used for vaccination, a system of patient record transfer is crucial to maintain the accuracy of immunization records. Immunization information systems should be used whenever available and prioritized to document influenza vaccination. Two-dimensional barcodes have been used to facilitate more efficient and accurate documentation of vaccine administration, with limited experience to date. Additional information concerning current vaccines shipped with two-dimensional barcodes can be found at www.cdc.gov/vaccines/programs/iis/2d-vaccine-barcodes/.

Children's likelihood of being immunized according to recommendations appears to be associated with the immunization practices of their parents. The authors of one study found that children were 2.77 times (95% CI, 2.74 to 2.79) more likely to be immunized against seasonal influenza if their parents were immunized.[48] When parents who were previously not immunized had received immunization for seasonal influenza, their children were 5.44 times (95% CI, 5.35 to 5.53) more likely to receive the influenza vaccine.

Pediatric offices may choose to serve as a venue for providing influenza vaccination for parents and other care providers of children,

if the practice is acceptable to both pediatricians and the adults who are to be vaccinated, particularly when it can help reduce inequities in vaccination access. Medical liability and payment issues, along with medical record documentation requirements, need to be considered before a pediatrician begins immunizing adults (see risk management guidance associated with adult immunizations in ref 85). Pediatric practices should be aware of payment implications, including nonpayment or having the parent inappropriately attributed by a payer as a patient of the pediatrician's office. The AAP supports efforts to overcome these payment barriers with insurance payers to maximize influenza immunization rates. To avoid errors in claims processing and payment and in the exchange of immunization data, pediatricians are reminded that parents should have their own basic medical record, in which their influenza vaccination should be documented. Adults should be encouraged to have a medical home and communicate their vaccination status to their primary care provider. Offering adult vaccinations in the pediatric practice setting should not undermine the adult medical home model. Vaccination of close contacts of children at high risk of influenza-related complications (Table 2) is intended to reduce children's risk of exposure to influenza (ie, "cocooning"). The practice of cocooning also may help protect infants younger than 6 months, who are too young to be immunized with the influenza vaccine.

SURVEILLANCE

Information about influenza surveillance is available through the CDC Voice Information System (influenza update at 1-800-232-4636) or at www.cdc.gov/flu/index.htm. Although yearly influenza data on circulating strains do not necessarily predict which and in what proportion strains will circulate in the subsequent season, it is instructive to be aware of the previous season's influenza surveillance data to use as a guide to empirical therapy until current seasonal data are available from the CDC. Information is posted weekly on the CDC Web site (www.cdc.gov/flu/weekly/fluactivitysurv.htm).

INFLUENZA ANTIVIRALS

Antiviral agents available for both influenza treatment and chemoprophylaxis in children of all ages can be found in Table 4 (including doses for preterm infants that have not been evaluated by the FDA) and on the CDC Web site (www.cdc.gov/flu/professionals/antivirals/index.htm). These include the neuraminidase inhibitors (NAIs) (oseltamivir, zanamivir, peramivir) and a selective inhibitor of influenza cap-dependent endonuclease (baloxavir), all of which have activity against influenza A and B viruses.[88]

Oral oseltamivir (Tamiflu) remains the antiviral drug of choice for the management of illness caused by influenza virus infections. Although more difficult to administer, inhaled zanamivir (Relenza) is an equally acceptable alternative for patients who do not have chronic respiratory disease. Options are limited for children who cannot absorb orally or enterally administered oseltamivir or tolerate inhaled zanamivir. Intravenous (IV) peramivir (Rapivab), a third NAI, was approved in September 2017 as a treatment of acute uncomplicated influenza in nonhospitalized children 2 years and older who have been symptomatic for no more than 2 days. The efficacy of peramivir in patients with serious influenza requiring hospitalization has not been established.[88] IV zanamivir is not approved in the United States and has not been available for compassionate use since the 2017–2018 season.[69,70] Baloxavir marboxil (Xofluza) was approved in 2018 for the early treatment of uncomplicated influenza in outpatients 12 years and older who have been ill for no more than 2 days.[89] This antiviral agent for influenza has a different mechanism of action (cap-endonuclease inhibitor) than NAIs and requires only a single oral dose for treatment of uncomplicated influenza. A recently completed phase 3 randomized, double-blind, active controlled study in children 1 to 12 years of age demonstrated that baloxavir treatment was well tolerated and resulted in a similar median time to alleviation of signs and symptoms of influenza as oseltamivir in ambulatory children with acute influenza.[90] Another study suggests that baloxavir is also effective in reducing viral titers and achieving comparable time to alleviation of symptoms as NAIs in high-risk patients ≥12 years of age with uncomplicated influenza.[91] A clinical trial of baloxavir treatment of influenza in hospitalized patients 12 years and older is ongoing (https://clinicaltrials.gov/ct2/show/NCT03684044?cond=baloxavir&rank=6). In November 2020, baloxavir was approved by the FDA for single-dose postexposure prophylaxis in people 12 years of age an older after exposure to someone with influenza.[92,93]

INFLUENZA TREATMENT

Randomized controlled trials (RCTs) conducted to date to evaluate the efficacy of influenza antiviral medications among outpatients with uncomplicated influenza have found that timely treatment can reduce the duration of influenza symptoms and fever in pediatric populations.[94–98] Observational studies in pediatric and adult populations suggest that antiviral agents are safe and could

TABLE 4 Recommended Dosage and Schedule of Influenza Antiviral Medications for Treatment and Chemoprophylaxis in Children for the 2021–2022 Influenza Season: United States

Medication	Treatment	Chemoprophylaxis[a]
Oseltamivir[b]		
Adults	75 mg, twice daily for 5 d	75 mg, once daily for 5 d
Children ≥12 mo (based on body wt)	Duration in all groups is 5 d	Duration in all groups is 10 d
≤15 kg (≤33 lb)	30 mg, twice daily	30 mg, once daily
>15–23 kg (>33–51 lb)	45 mg, twice daily	45 mg, once daily
>23–40 kg (>51–88 lb)	60 mg, twice daily	60 mg, once daily
>40 kg (>88 lb)	75 mg, twice daily	75 mg, once daily
Infants 9–11 mo[c]	3.5 mg/kg per dose, twice daily	3.5 mg/kg per dose, once daily
Term infants 0–8 mo[c]	3 mg/kg per dose, twice daily	3 mg/kg per dose, once daily for infants 3–8 mo; not recommended for infants <3 mo old because of limited safety and efficacy data in this age group
Preterm infants[d]		
<38 wk postmenstrual age	1.0 mg/kg per dose, twice daily	—
38–40 wk postmenstrual age	1.5 mg/kg per dose, twice daily	—
>40 wk postmenstrual age	3.0 mg/kg per dose, twice daily	—
Zanamivir[e]		
Adults	10 mg (two 5-mg inhalations), twice daily for 5 d	10 mg (two 5-mg inhalations), once daily for 10 d
Children (≥7 y for treatment, ≥5 y for chemoprophylaxis)	10 mg (two 5-mg inhalations), twice daily for 5 d	10 mg (two 5-mg inhalations), once daily for 10 d
Peramivir		
Adults	One 600-mg IV infusion, given over 15–30 min	Not recommended
Children (2–12 y)	One 12 mg/kg dose, up to 600 mg maximum, via IV infusion for 15–30 min	Not recommended
Children (13–17 y)	One 600 mg dose, via IV infusion for 15–30 min	Not recommended
Baloxavir		
People ≥12 y who weigh >40 kg	40–80 kg: one 40-mg dose, orally ≥80 kg: one 80-mg dose, orally	40–80 kg: one 40-mg dose, orally ≥80 kg: one 80-mg dose, orally

Adapted from Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza [published correction appears in *Clin Infect Dis*. 2019;68(10):1790]. *Clin Infect Dis*. 2019;68(6):e1–e47; and https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. —, not applicable.

[a] The CDC recommends routine chemoprophylaxis with oseltamivir or zanamivir for 7 d and for 10 d only if part of an institutional outbreak (https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm).

[b] The duration of treatment with oseltamivir is 5 d. Oseltamivir is administered orally regardless of meals, although administration with meals may improve gastrointestinal tolerability. Oseltamivir is available as Tamiflu in 30-, 45-, and 75-mg capsules and as a powder for oral suspension that is reconstituted to provide a final concentration of 6 mg/mL. For the 6-mg/mL suspension, a 30-mg dose is given with 5 mL of oral suspension, a 45-mg dose is given with 7.5 mL oral suspension, a 60-mg dose is given with 10 mL oral suspension, and a 75-mg dose is given with 12.5 mL oral suspension. If the commercially manufactured oral suspension is not available, a suspension can be compounded by retail pharmacies (final concentration also 6 mg/mL) on the basis of instructions contained in the package label. In patients with renal insufficiency, the dose should be adjusted on the basis of creatinine clearance. For treatment of patients with creatinine clearance 10–30 mL/min: 75 mg once daily for 5 d. For chemoprophylaxis of patients with creatinine clearance 10–30 mL/min: 30 mg once daily for 10 d after exposure or 75 mg, once every other day, for 10 d after exposure (5 doses). See https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm and Infectious Diseases Society of America guidelines.[88]

[c] Approved by the FDA for children as young as 2 wk of age. Given preliminary pharmacokinetic data and limited safety data, oseltamivir can be used to treat influenza in both term and preterm infants from birth because benefits of therapy are likely to outweigh possible risks of treatment. Of note, the CDC recommends 3 mg/kg per dose twice daily for all infants <12 mo old; the Infectious Diseases Society of America guidelines[88] include both AAP and CDC recommendations.

[d] Oseltamivir dosing for preterm infants: the wt-based dosing recommendation for preterm infants is lower than that for term infants. Preterm infants may have lower clearance of oseltamivir because of immature renal function, and doses recommended for term infants may lead to high drug concentrations in this age group. Limited data from the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group provide the basis for dosing preterm infants by using their postmenstrual age (gestational age + chronological age). For extremely preterm infants (<28 wk), please consult a pediatric infectious disease physician.

[e] The duration of treatment with zanamivir is 5 d. Zanamivir is administered by inhalation by using a proprietary "Diskhaler" device distributed together with the medication. Zanamivir is a dry powder, not an aerosol, and should not be administered by using nebulizers, ventilators, or other devices typically used for administering medications in aerosolized solutions. Zanamivir is not recommended for people with chronic respiratory diseases, such as asthma or chronic obstructive pulmonary disease, which increase the risk of bronchospasm.

reduce the risk of certain influenza complications, including hospitalization and death.[99–103] The number of published RCTs in children is limited, and interpretation of the results of these studies needs to take into consideration the size of the study (the number of events might not be sufficient to assess specific outcomes in small studies), the variations in the case definition of influenza illness (clinically diagnosed versus laboratory confirmed), the time of treatment administration in relation to the onset of illness, and the child's age and health status as important variables. A Cochrane review of 6 RCTs involving treatment of 2356 children with clinically diagnosed

influenza, of whom 1255 had laboratory-confirmed influenza, showed that in children with laboratory-confirmed influenza, oral oseltamivir and inhaled zanamivir reduced the median duration of illness by 36 hours (26%; $P < .001$) and 1.3 days (24%; $P < .001$), respectively.[98] Among the studies reviewed, one trial of oseltamivir in children with asthma who had laboratory-confirmed influenza showed only a nonsignificant reduction in illness duration (10.4 hours; 8%; $P = .542$). Oseltamivir significantly reduced acute otitis media in children 1 to 5 years of age with laboratory-confirmed influenza (risk difference, −0.14; 95% CI, −0.24 to −0.04).[98] Another Cochrane review of RCTs in adults and children, which included 20 oseltamivir (9623 participants) and 26 zanamivir trials (14 628 participants),[95] found no effect of oseltamivir in reducing the duration of illness in children with asthma, but in otherwise healthy children, there was a reduction by a mean difference of 29 hours (95% CI, 12 to 47 hours; $P = .001$). No significant effect was observed with zanamivir. Regarding complications, this review did not find a significant effect of NAIs on reducing hospitalizations, pneumonia, bronchitis, otitis media, or sinusitis in children.[95] More recently, a meta-analysis of 5 new RCTs that included 1598 children with laboratory-confirmed influenza showed that treatment with oseltamivir significantly reduced the duration of illness in this population by 17.6 hours (95% CI, −34.7 to −0.62 hours).[96] When children with asthma were excluded, this difference was larger (−29.9 hours; 95% CI, −53.9 to −5.8 hours). The risk of otitis media was 34% lower in this group as well. Similarly, a meta-analysis conducted by Tejada et al[103] showed a statistically significant reduction in the risk of acute otitis media occurrence among treated children over placebo recipients (odds ratio, 0.48; 95% CI, 0.30 to 0.77). Overall, efficacy outcomes are best demonstrated in patients with laboratory-confirmed influenza. All these studies confirmed vomiting as an occasional adverse effect of oseltamivir, occurring in approximately 5% of treated patients. The balance between benefits and harms should be considered when making decisions about the use of NAIs for either treatment or chemoprophylaxis of influenza.

Although prospective comparative studies to determine the efficacy of influenza antiviral medications in hospitalized patients or pediatric patients with comorbidities have not been conducted, and prospectively collected data to determine the role of antiviral agents in treating severe influenza are limited, on the basis of information obtained from retrospective observational studies and meta-analyses conducted to date in both adults and children, most experts support the use of antiviral medications as soon as possible to treat pediatric patients with severe influenza, including hospitalized patients.[97,99–102,104] In an observational epidemiological study conducted in adult patients hospitalized with severe laboratory-confirmed influenza in Spain over 6 influenza seasons (2010–2016), the authors evaluated the effectiveness of NAIs, concluding that when started early after the onset of symptoms (≤48 hours or ≤5 days), NAI treatment was associated with a reduction in influenza-associated deaths (adjusted odds ratio, 0.37 [95% CI, 0.22 to 0.63]; and adjusted odds ratio, 0.50 [95% CI, 0.32 to 0.79], respectively).[99] However, treatment initiation more than 5 days after the onset of influenza symptoms was not associated with reduction in mortality in hospitalized adults.

Importantly, and despite limited evidence from prospectively conducted trials, treatment with oseltamivir for children with serious, complicated, or progressive disease presumptively or definitively caused by influenza, irrespective of influenza vaccination status (the circulating strains may not be well matched with vaccine strains) or whether illness began greater than 48 hours before admission, is recommended by the AAP, CDC, Infectious Diseases Society of America,[88] and Pediatric Infectious Diseases Society. Earlier treatment provides better clinical responses. However, treatment after 48 hours of symptoms in adults and children with moderate to severe disease or with progressive disease has been shown to provide some benefit and should be offered.[105–107] In a retrospective study of 653 PICU admissions from 2009 to 2012, the estimated risk of death was reduced in NAI-treated cases (odds ratio 0.36; 95% CI, 0.16 to 0.83).[105] No additional benefit exists for double-dose NAI therapy on reduction of mortality or virological clearance compared with standard-dose therapy on the basis of a recent systematic review and meta-analysis of 10 published studies[108] (4 RCT and 6 observational studies) involving 20 947 adult and pediatric patients.

Children younger than 2 years are at an increased risk of hospitalization and complications attributable to influenza. The FDA has approved oseltamivir for treatment of children as young as 2 weeks of age. Given preliminary pharmacokinetic data and limited safety data, the CDC and AAP support the use of oseltamivir to treat influenza in both term and preterm infants from birth because benefits of therapy of neonatal

influenza are likely to outweigh possible risks of treatment.

Oseltamivir is available in capsule and oral suspension formulations. The available capsule doses are 30, 45, and 75 mg, and the commercially manufactured liquid formulation has a concentration of 6 mg/mL in a 60-mL bottle. If the commercially manufactured oral suspension is not available, the capsule may be opened and the contents mixed with simple syrup or Ora-Sweet SF (sugar free) by retail pharmacies to a final concentration of 6 mg/mL.

In adverse event data collected systematically in prospective trials, vomiting was the only adverse effect reported more often with oseltamivir compared with a placebo when studied in children 1 to 12 years of age (ie, 15% of treated children versus 9% receiving a placebo). In addition, after reports from Japan of oseltamivir-attributable neuropsychiatric adverse effects, a review of controlled clinical trial data and ongoing surveillance has failed to establish a link between this drug and neurologic or psychiatric events.[109,110]

Clinical judgment (based on underlying conditions, disease severity, time since symptom onset, and local influenza activity) is an important factor in treatment decisions for pediatric patients who present with influenzalike illness. Antiviral treatment should be started as soon as possible after illness onset and should not be delayed while waiting for a definitive influenza test result because early therapy provides the best outcomes. Influenza diagnostic tests vary by method, availability, processing time, sensitivity, and cost (Table 5), all of which should be considered in making the best clinical decision. Positive and negative predictive values of influenza test results are influenced by the level of influenza activity in the population being tested, the characteristics of a test compared to a gold standard, pretest probability, whether the influenza virus is actively replicating in the person, proper collection and transport of specimens, and proper test procedures. Testing should be performed when timely results will be available to influence clinical management or infection-control measures. Although decisions on treatment and infection control can be made on the basis of positive rapid test results, particularly when influenza is known to be circulating, negative results should not always be used in a similar fashion because of the suboptimal sensitivity and potential for false-negative results. An updated list of rapid influenza diagnostic tests is available at https://www.cdc.gov/flu/professionals/diagnosis/table-ridt.html. Positive results of rapid influenza diagnostic tests are helpful because they may reduce additional testing to identify the cause of the child's influenzalike illness and

TABLE 5 Comparison of Types of Influenza Diagnostic Tests[a]

Testing Category	Method	Influenza Viruses Detected	Distinguishes Influenza A Virus Subtypes	Time to Results	Performance
Rapid molecular assay	Nucleic acid amplification	Influenza A or B viral RNA	No	15–30 min	High sensitivity; high specificity
Rapid influenza diagnostic test	Antigen detection	Influenza A or B virus antigens	No	10–15 min	Low to moderate sensitivity (higher with analyzer devise); high specificity
Direct and indirect immunofluorescence assays	Antigen detection	Influenza A or B virus antigens	No	1–4 h	Moderate sensitivity; high specificity
Molecular assays (including RT-PCR)	Nucleic acid amplification	Influenza A or B viral RNA	Yes, if subtype primers are used	1–8 h	High sensitivity; high specificity
Multiplex molecular assays	Nucleic acid amplification	Influenza A or B viral RNA, other viral or bacterial targets (RNA or DNA)	Yes, if subtype primers are used	1–2 h	High sensitivity; high specificity
Rapid cell culture (shell vial and cell mixtures)	Virus isolation	Influenza A or B virus	Yes	1–3 d	High sensitivity; high specificity
Viral culture (tissue cell culture)	Virus isolation	Influenza A or B virus	Yes	3–10 d	High sensitivity; high specificity

Source: Uyeki.[88]

[a] Negative results may not rule out influenza. Respiratory tract specimens should be collected as close to illness onset as possible for testing. Clinicians should consult the manufacturer's package insert for the specific test for the approved respiratory specimen(s). Specificities are generally high (>95%) for all tests compared to reverse transcriptase-polymerase chain reaction (RTP CR). FDA-cleared rapid influenza diagnostic tests are Clinical Laboratory Improvements Act (CLIA)-waived; most FDA-cleared rapid influenza molecular assays are CLIA-waived, depending on the specimen.

promote appropriate antimicrobial stewardship. Available FDA-approved rapid molecular assays based on nucleic acid detection are highly sensitive and specific diagnostic tests that can provide rapid results. An updated list of these tests is available at https://www.cdc.gov/flu/professionals/diagnosis/table-nucleic-acid-detection.html. Molecular assays are preferred in hospitalized patients because they are more sensitive compared with antigen detection. Early detection, prompt antiviral treatment, and infection-control interventions can lead to improved individual patient outcomes and allow for effective cohorting and disease containment.

People with suspected influenza who are at higher risk of influenza complications should be offered treatment with antiviral medications (Table 2). Efforts should be made to minimize treatment of patients who are not infected with influenza. Otherwise healthy children who have suspected influenza with an uncomplicated presentation at times when influenza viruses are known to be circulating in the community should be considered for antiviral medication, particularly if they are in contact with other children who either are younger than 6 months (because they are not able to receive influenza vaccine) or have high-risk conditions (including age <5 years) that predispose them to complications of influenza. If there is a local shortage of antiviral medications, local public health authorities should be consulted to provide additional guidance about testing and treatment.

INFLUENZA CHEMOPROPHYLAXIS

Randomized placebo-controlled studies showed that oral oseltamivir and inhaled zanamivir were efficacious when administered as chemoprophylaxis to household contacts after a family member had laboratory-confirmed influenza.[88] Baloxavir received FDA approval in November 2020 for influenza chemoprophylaxis.[93,111] When compared with a placebo as a preventive treatment of adults and children, the proportion of household members 12 years and older who developed influenza was 1% in participants treated with a single dose of baloxavir within 48 hours of exposure to a symptomatic household contact with influenza and 13% in the placebo-treated group.[93] Baloxavir was well tolerated in this randomized study conducted in Japan during the 2018–2019 influenza season. There are no data on IV peramivir for chemoprophylaxis.

Decisions on whether to administer antiviral chemoprophylaxis should take into account the exposed person's risk of influenza complications, vaccination status, the type and duration of contact, recommendations from local or public health authorities, and clinical judgment. Optimally, postexposure chemoprophylaxis should only be used when antiviral agents can be started within 48 hours of exposure; the lower once-daily dosing for chemoprophylaxis with oral oseltamivir or inhaled zanamivir should not be used for treatment of children symptomatic with influenza.[112] Early full treatment doses (rather than chemoprophylaxis doses) should be used in high-risk symptomatic patients without waiting for laboratory confirmation.

Chemoprophylaxis should not be considered a substitute for vaccination. The influenza vaccine should always be offered before and throughout the influenza season when not contraindicated. Antiviral medications are important adjuncts to influenza vaccination for control and prevention of influenza disease. Toxicities may be associated with antiviral agents, and indiscriminate use might limit availability. Pediatricians should inform recipients of antiviral chemoprophylaxis that risk of influenza is lowered but still remains while taking the medication, and susceptibility to influenza returns when medication is discontinued. Although antiviral use is not a contraindication to vaccination with IIVs, it is likely that LAIV effectiveness will be decreased for children receiving oseltamivir or other influenza antiviral agents.[112] Among some high-risk people, both vaccination with IIV and antiviral chemoprophylaxis may be considered.[112] Updates will be available at www.aapredbook.org/flu and at www.cdc.gov/flu/professionals/antivirals/index.htm.

ANTIVIRAL RESISTANCE

Antiviral resistance to any drug can emerge, necessitating continuous population-based assessment conducted by the CDC. During the 2019–2020 influenza season, >99% of influenza A(H1N1)pdm09 and B/Victoria viruses tested were susceptible to oseltamivir, peramivir, and zanamivir, and all were susceptible to baloxavir. All tested influenza A(H3N2) and B/Yamagata viruses were susceptible to these antiviral agents. Decreased susceptibility to baloxavir has been reported in Japan, where its use has been more common,[113–117] and surveillance for resistance among circulating influenza viruses is ongoing in Japan and the United States.[9,118,119] In contrast, high levels of resistance to amantadine and rimantadine persist among the influenza A viruses currently circulating. Adamantane medications are not recommended for use against influenza unless resistance patterns change.[88]

Viral surveillance and resistance data from the CDC and WHO

indicate that the majority of currently circulating influenza viruses likely to cause influenza in North America during the 2021–2022 influenza season continue to be susceptible to oseltamivir, zanamivir, peramivir, and baloxavir.[7] If a newly emergent oseltamivir- or peramivir-resistant virus is a concern, recommendations for alternative treatment will be available from the CDC and AAP. Resistance characteristics can change for an individual patient over the duration of a treatment course, especially in those who are severely immunocompromised. Up-to-date information on current recommendations and therapeutic options can be found on the AAP Web site (www.aap.org or www.aapredbook.org/flu), through state-specific AAP chapter Web sites, or on the CDC Web site (www.cdc.gov/flu/).

FUTURE DIRECTIONS

Safety and effectiveness data for influenza vaccines used during the 2020–2021 influenza season will be analyzed as they become available and reported by the CDC as they are each season. However, new data might not be available given the low levels of circulation of influenza during the COVID-19 pandemic. Continued evaluation of the safety, immunogenicity, and effectiveness of influenza vaccines, especially for at-risk and diverse populations, is important. The duration of protection, the potential role of previous influenza vaccination on overall VE, and VE by vaccine formulation, virus strain, timing of vaccination, and subject age and health status in preventing outpatient medical visits, hospitalizations, and deaths continue to be evaluated. For the 2021–2022 influenza season, it will be particularly important to understand the effect of SARS-CoV-2 and influenza virus cocirculation on the epidemiology and morbidity of influenza in the pediatric population. Understanding how to better educate parents about influenza symptoms and how to recognize when to seek medical attention would be informative. Additionally, with limited data on the use of antiviral agents in hospitalized children and in children with underlying medical conditions, prospective clinical trials to inform optimal timing and efficacy of antiviral treatment in these populations are warranted. This is particularly relevant as new antiviral agents or new indications for existing antiviral agents become available. At this time, the FDA has accepted supplemental new drug applications for baloxavir marboxil for the treatment of acute uncomplicated influenza in pediatric patients from 1 to 12 years of age.[120]

There is also a need for more systematic health services research on influenza vaccine uptake and refusal as well as identification of methods to enhance uptake. Developing influenza vaccination programs in nontraditional settings, including the pediatric emergency department, may also increase distribution.[121,122] Further investigation is needed concerning vaccine acceptance and hesitancy and methods to overcome parental concerns and improve coverage. This might be particularly relevant with the introduction of the COVID-19 vaccine for children and adolescents in 2021. Efforts may include evaluating the strategy of offering to immunize parents and adult child care providers in the pediatric office setting and understanding the level of family contact satisfaction with this approach; how practices handle the logistic, liability, legal, and financial barriers that limit or complicate this service; and most importantly, how this practice may affect disease rates in children and adults. Furthermore, ongoing efforts should include broader implementation and evaluation of mandatory HCP vaccination programs in both inpatient and outpatient settings.

Efforts should be made to create adequate outreach (eg, mobile integrated health care) and infrastructure to facilitate the optimal distribution of the vaccine so that more people are immunized. Given the experience with COVID-19, pediatricians have become more involved in pandemic preparedness and disaster planning efforts. A bidirectional partner dialogue between pediatricians and public health decision-makers assists efforts to address children's issues during the initial state, regional, and local plan development stages. Additional information on this topic can be found at https://pediatrics.aappublications.org/content/pediatrics/early/2017/05/11/peds.2016-3690.full.pdf.

Access-to-care issues, lack of immunization records, and questions regarding who can provide consent may be addressed by linking children (eg, those in foster care or the juvenile justice system or refugee, immigrant, or homeless children) with a medical home, using all health care encounters as vaccination opportunities, and more consistently using immunization registry data.

Development efforts continue for universal influenza vaccines that induce broader protection and eliminate the need for annual vaccination.[123] The success of mRNA and other novel technologies used in

the development of COVID-19 vaccines may accelerate the prospects of broad influenza vaccines. Understanding the establishment of immunity against influenza in early life and the development of a safe immunogenic vaccine for infants younger than 6 months are essential. Studies on the effectiveness and safety of influenza vaccines containing adjuvants that enhance immune responses to influenza vaccines or that use novel routes of administration are needed. Efforts to improve the vaccine development process to allow for a shorter interval between identification of vaccine strains and vaccine production continue. New antiviral drugs are in various development phases given the need to improve options for the treatment and chemoprophylaxis of influenza.

Pediatricians can remain informed of advances and other updates during the influenza season by following the CDC Influenza page (www.cdc.gov/flu) and the AAP *Red Book Online* Influenza Resource Page (www.aapredbook.org/flu).

ADDITIONAL RESOURCES

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ABBREVIATIONS

AAP: American Academy of Pediatrics
ACIP: Advisory Committee on Immunization Practices
ALRTI: acute lower respiratory tract infection
CDC: Centers for Disease Control and Prevention
CI: confidence interval
COVID-19: novel coronavirus disease 2019
FDA: US Food and Drug Administration
GBS: Guillain-Barré syndrome
HA: hemagglutinin
HCP: health care personnel
IIV: inactivated influenza vaccine
IIV4: quadrivalent inactivated influenza vaccine
IV: intravenous
LAIV: live attenuated influenza vaccine
LAIV3: trivalent live attenuated influenza vaccine
LAIV4: quadrivalent live attenuated influenza vaccine
NAI: neuraminidase inhibitor
RCT: randomized controlled trial
RIV4: quadrivalent recombinant influenza vaccine
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
VE: vaccine effectiveness
WHO: World Health Organization

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