Influenza: A Global Perspective

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KEYWORDS

• Influenza • Influenza vaccines • Children • Vaccine policy • Antiviral medications

KEY POINTS

- The influenza virus circulates annually and causes global epidemics and occasional pandemics because of its ability to mutate via antigenic drift and shift, respectively.
- Children have high attack rates of influenza.
- Children younger than 5 years are at increased risk for severe or complicated influenza infections.
- Vaccination is the most effective means of protection against influenza.

INTRODUCTION

Influenza, a common, highly contagious, acute, febrile respiratory disease, is caused by influenza virus, which circulates globally. Influenza virus causes annual outbreaks, with or without seasonality, which are likely related to climate and other factors that influence transmission. The influenza virus undergoes frequent antigenic mutations, known as antigenic drift, that contribute to variability from year to year and present challenges for annual vaccine design and production. In addition, influenza poses a unique potential to cause pandemics when a novel virus emerges through genetic reassortment, or antigenic shift, resulting in a virus with surface glycoproteins against which there is little preexisting immunity in the population.

Influenza virus affects people of all ages and causes mild to severe illness and even death in some cases. According to the World Health Organization (WHO), annual epidemics of influenza result in an estimated 3 to 5 million cases of severe illness and between 250,000 and 500,000 deaths worldwide,[1] although the cocirculation of other pathogens and lack of diagnostic testing in many settings makes it difficult to accurately estimate the burden of influenza. As influenza is a vaccine-preventable illness, it is important from a global health standpoint to differentiate illnesses attributable to the influenza virus from influenza-like illnesses caused by other pathogens.

Those at increased risk for the most severe illness, or influenza-related complications, include the elderly, children younger than 5 years, and individuals of all ages,

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who are immunocompromised or have chronic underlying health conditions that predispose them to more severe disease, as well as pregnant women. Although health care workers are not at higher risk than the general population for influenza-related complications, they are a group that is often prioritized for vaccination to maintain the workforce and to prevent them from transmitting influenza to vulnerable patients.

Although treatment of influenza infection is available in certain settings, prevention is the better option. The best way to prevent influenza infection is by vaccination. Vaccination against influenza can prevent the primary influenza syndrome as well as complications, such as acute otitis media (AOM) or pneumonia.[2,3]

This article focuses on pediatric influenza and gives an overview of the influenza virus as well as the epidemiology of the disease. It includes information on influenza in children in low-resource settings, where available, and a discussion of influenza vaccines, treatments, and policy recommendations.

INFLUENZA IN CHILDREN: CLINICAL CHARACTERISTICS AND DISEASE BURDEN

In otherwise healthy children, influenza is typically a mild to moderate disease and, in most children, resolves without complications.[4] The most common signs and symptoms of influenza in children are sudden onset of fever, cough, and rhinorrhea. Influenza is most severe in younger children.[5–7] Symptoms, such as sore throat, headache, myalgia, and fatigue, are reported less commonly in children than adults.[8] This difference may be due in part to the inability of young children to describe these complaints. Because the signs and symptoms of influenza are not unique to this disease and the presentation of certain signs and symptoms varies among individuals, it can be difficult to diagnose influenza by clinical presentation alone; thus, a firm diagnosis generally requires laboratory confirmation.

Clinical attack rates and morbidity from influenza infection vary considerably from year to year and across geographies. When compared with adults, influenza attack rates are consistently higher in children and may reach 30% or more during selected seasons.[7,9] Data from the United States show the importance of laboratory testing in fully understanding the burden of influenza illness. Among young children, few influenza infections are recognized by clinical signs and symptoms alone; in one population-based US study of children younger than 5 years, only 17% of outpatient and 28% of inpatient cases of laboratory-confirmed influenza (LCI) received a clinical diagnosis of influenza from their health care provider before laboratory results were known.[4]

Although influenza-related hospitalization and death, discussed later, do occur, outpatient visits are far more common for all age groups. With increasing age, more children with influenza can be managed as outpatients, whereas with younger children, influenza tends to be more severe and more often requires hospitalization. In one population-based study in the United States, annual influenza-attributable outpatient visit rates were approximately 10-, 100-, and 250-fold greater than the rates of hospitalization for children younger than 5 months, 6 to 23 months, and 24 to 59 months, respectively.[4] Antibiotic use also increases as a result of influenza infections. A retrospective cohort study of children younger than 15 years over 19 influenza seasons in the United States estimated that for every 100 children, an average of 6 to 15 outpatient visits and 3 to 9 courses of antibiotics were attributable to influenza every year.[10]

LCI-related hospitalization rates are high among young children, ranging from 0.58 to 2.4 hospitalizations per 1000 children younger than 5 years per year in the United States.[4,11,12] Children younger than 6 months consistently have high rates of hospitalization, and about 80% to 85% of pediatric influenza-attributable hospitalizations are accounted for by children younger than 24 months.[4,10–14] Hospitalizations due to LCI

are likely underestimated for several reasons, including lack of diagnostic testing, insensitive diagnostic methods, and influenza virus being in the causal pathway to the hospitalization but no longer present at time of testing (eg, influenza virus leading to bacterial pneumonia or asthma exacerbation).[13,15]

Influenza infections can be complicated by other secondary infections, which add considerably to the burden of influenza. Clinically, AOM is the most frequent influenza-associated syndrome. Another significant, though less common, complication of influenza is pneumonia. Although pneumococcal and *Haemophilus influenzae* type B (Hib) infections were commonly identified pathogens preceding or concomitant to influenza infection in children, such secondary infections are less frequent now that pneumococcal and Hib vaccines are routinely administered to children.[5–7,16] Hospitalized children with influenza-associated bacterial pneumonia are more likely to have a severe and complicated clinical course than those hospitalized for influenza without associated pneumonia. Influenza-associated pneumonia can be particularly dangerous in children with underlying conditions and can be fatal.[17,18] In a mortality study in children hospitalized with LCI in the United States from 2004 to 2007, *Staphylococcus aureus* was the most common bacterial infection identified in children with influenza.[19]

Although death due to influenza is rare in an individual child, the annual outbreaks and high attack rates of the disease lead to demonstrable mortality at the population level. Influenza-related pediatric deaths became reportable to the US Centers for Disease Control and Prevention in 2004. From 2004 to 2016, between 37 (in the 2011–2012 influenza season) and 288 (in the 2009–2010 influenza season) annual deaths due to LCI were reported in children younger than 18 years in the United States.[20,21] These deaths are undoubtedly an underestimate given that health care workers do not routinely test for influenza, that the tests are imperfectly sensitive, and that influenza virus may initiate the sequence of events leading to death but may no longer be detectable at the time of testing. Studies in the United States have shown that among children who died of influenza, the illness progressed rapidly to death, often within 72 hours of clinical onset, further emphasizing the importance of prevention. Although children with underlying medical conditions are at increased risk for death from influenza, a substantial proportion of influenza-attributable pediatric mortality occurs in otherwise healthy children, many of whom die before they are admitted to the hospital.[19,22]

Although global surveillance for influenza is extensive, limited data are available that specifically address influenza burden in children in low-resource settings. Outside of research studies conducted in these areas, few clinical diagnoses of influenza are confirmed in the laboratory. Nevertheless, the available data show an important and disproportionately high burden of influenza among young children in low-resource settings compared with children of a similar age in more developed areas. As in temperate settings, influenza attack rates vary from year to year in tropical settings. Recent studies in young children in Bangladesh and Senegal during the 2013 season reported laboratory-confirmed clinical influenza attack rates of 24.5% and 18.0%, respectively, for all circulating strains of influenza.[23,24] Although these rates are high, comparable attack rates in young children in the United States in other nonpandemic years have been reported.[25–28] Even if attack rates of influenza are similar in young children in low- and high-resource settings, morbidity and mortality of influenza are likely to be higher in low-resource settings, given population characteristics (eg, malnutrition), reduced or delayed access to health care, and less extensive use of pneumococcal and Hib vaccines.

A worldwide meta-analysis of data collected between 1995 and 2010 reported that the number of new episodes of influenza-associated severe acute lower respiratory infections (ALRIs) in children younger than 5 years was 15-fold greater in developing countries than in developed countries.[29] That same meta-analysis estimated between

28,000 and 111,500 deaths occurred in children younger than 5 years from influenza-related ALRIs in 2008. It was estimated that up to 99% of these deaths occurred in low-income countries.[29] A study in Bangladesh between 2008 and 2010 found that children younger than 5 years are hospitalized for influenza-associated illness at substantially higher rates than adults. The study estimated that 113,000 of 19,331,302 (0.6%) children younger than 5 years are hospitalized annually for influenza, compared with 16,000 of 132,920,875 (0.01%) persons at least 5 years of age. The study also reported that rates of hospitalization for influenza among young children in Bangladesh are disproportionately high when compared with influenza hospitalization rates among children of the same age in the United States.[30]

Influenza infection in children has consequences beyond the direct medical outcomes outlined earlier. Children shed influenza virus longer and in larger amounts than adults and, thus, play a major role in the transmission of influenza in families and society.[7,9,31–37] Influenza places a high medical and societal burden on children, their families, and communities. This burden is evident in school absenteeism, parents' missed days from work, and wages lost as a result.[4,11,16] In one study in Finland, school and day-care absenteeism is highest among children younger than 3 years, and parental days missed from work are higher as well.[16] A US-based study showed a similar trend, with parents of influenza-infected children missing an average of 1 day of work for every 3 days of school missed by a child attributable to influenza.[38] These numbers are likely an underestimate of the burden of influenza, as they reflect only those children who sought medical care for their illness and do not account for illnesses that occurred on non-school days.

VACCINES

Vaccination is the leading approach for the prevention of influenza, and many influenza vaccines are available on the global market. These vaccines fall into 2 broad categories: parenterally administered nonreplicating vaccines and intranasally (IN) administered live-attenuated vaccines. Current vaccines are all designed with the same goal of inducing immunity to the hemagglutinin (HA) and/or neuraminidase (NA) surface glycoproteins of the influenza virus. As the HA and NA of the virus undergo frequent antigenic drift, the seasonal influenza vaccine is reformulated as often as twice annually to match the strains projected to circulate in the following influenza season. The WHO recommends influenza strains that should be included in the seasonal influenza vaccines (for both the Northern and Southern hemispheres' vaccine compositions) based on global epidemiologic and virologic surveillance, which has been undertaken by the Global Influenza Surveillance and Response System (GISRS) for more than 50 years. The GISRS tracks the evolution of influenza viruses as well as the emergence of influenza strains with the potential to cause pandemics.[39]

Currently marketed influenza vaccines for nonpandemic use are trivalent or quadrivalent. Trivalent vaccines contain 3 total strains: 2 influenza A strains (one H1N1 and one H3N2) as well as 1 influenza B lineage strain; quadrivalent influenza vaccines contain an additional B lineage influenza strain. It has proven difficult to predict which B lineage will circulate in a given year, and in some years both B lineages circulate concurrently.[40,41] Thus, quadrivalent influenza vaccines were developed to include both influenza B lineages (Victoria and Yamagata) that currently circulate in humans. Quadrivalent vaccines were first licensed in the United States for use in the 2013 to 2014 influenza season.

There are 2 categories of seasonal influenza vaccine currently available on the global market. Intramuscularly (IM) or intradermally (ID) injected, nonreplicating influenza virus vaccines, which can be further classified based on production substrate (egg based or

cell culture based); types of preparation (whole virus, split-virion, subunit, or fully re-combinant vaccines); dose (0.25-mL pediatric, 0.5-mL adult), and by presence or absence of adjuvant (MF59). The other category of approved influenza vaccine is the live-attenuated influenza vaccine (LAIV), which is administered IN. Because of the time required for influenza vaccine manufacturing, testing, packaging, and distribution, seasonal vaccines are generally available only by late summer or early fall.

This section focuses on seasonal influenza vaccines (as opposed to pandemic vaccines), licensed primarily in the United States for children, defined here as individuals younger than 18 years. Influenza vaccines are not currently licensed anywhere in the world for infants younger than 6 months. For children 6 to 23 months old, the only available vaccines are inactivated influenza vaccines (IIVs). Nonadjuvanted inactivated vaccines are the only approved option for children younger than 2 years, except in Canada where an MF59-adjuvanted trivalent IIV was approved for children 6 to 23 months of age in 2015.[42,43] For children older than 2 years, an LAIV is also approved in many countries. For a summary of seasonal influenza vaccines licensed for children in the United States see **Table 1**.

INACTIVATED INFLUENZA VACCINES
Safety

Clinical trials and postlicensure surveillance have shown IIVs to be highly safe. The most common adverse events associated with IIVs in all age groups are injection site reactions. In children, injection site reactions as well as fever are the most common safety concerns of IIVs and tend to be mild and short-lived.[44–51] In 2010, a trivalent IIV produced by an Australian pharmaceuticals company was strongly correlated with increased rates of febrile seizures in children in Australia.[52] Subsequent enhanced surveillance for febrile seizures in the United States and elsewhere showed a slight increase in the rates of febrile seizures among children who had received IIVs. The febrile seizure risk among children in the United States was noted to be elevated in some years and not others and more so when IIV was coadministered with 13-valent pneumococcal conjugate vaccines or diphtheria, tetanus, and pertussis vaccines. In all cases the risk for febrile seizures in the United States was determined to be substantially lower than observed in 2010 in Australia.[45,52–54]

Although for most children IIVs are very safe, they may pose a safety risk to individuals with severe egg allergies. Residual egg protein may remain in most influenza

Table 1
Categories of pediatric vaccines licensed for prevention of seasonal influenza

	Live Attenuated	Nonreplicating Vaccines			
		Standard Inactivated	Recombinant	Intradermal Inactivated	Adjuvanted Inactivated
Route	IN	IM	IM	ID	IM
Frequency	Annual	Annual	Annual	Annual	Annual
Approved ages[a]	2–49 y	≥6 mo	≥18 y	18–64 y	6–23 mo, ≥65 y
HA (mcg/strain)	15	15	45	9	15
Substrate for production	Eggs	Eggs, cell culture	Cell culture	Eggs	Eggs, cell culture

[a] Approved ages may differ by manufacturer and country.
Adapted from Neuzil KM, Ortiz JR. Influenza vaccines and vaccination strategies. In: Bloom BR, Lambert PH, editors. The Vaccine Book. Cambridge (MA): Academic Press. p. 429; with permission.

vaccines as the virus for the vaccine is grown in embryonated hens' eggs. Eggs are not used in the production of cell culture-based vaccines; however, these vaccines may still contain trace amounts of egg proteins. There is currently one cell culture-based vaccine on the market for children at least 4 years of age. The recombinant trivalent vaccine is the only entirely egg-free vaccine, but it is not licensed for use in individuals younger than 18 years.[45,55] Nonetheless, individuals with egg allergy should receive influenza vaccines (including egg-based vaccines) unless they have had a severe reaction to a prior influenza immunization. For individuals with severe egg allergy, egg-based vaccines should be administered by a physician trained to recognize and manage allergic responses. For more detailed instructions, see **Fig. 1**.

Immunogenicity

Nonreplicating vaccines elicit an immune response primarily against the HA component of the influenza virus. HA is one of the glycoproteins on the surface of the influenza virus and functions in the attachment of the virus to the host cells. Neutralizing antibodies specific to HA are the predominant means by which IIVs confer immunity
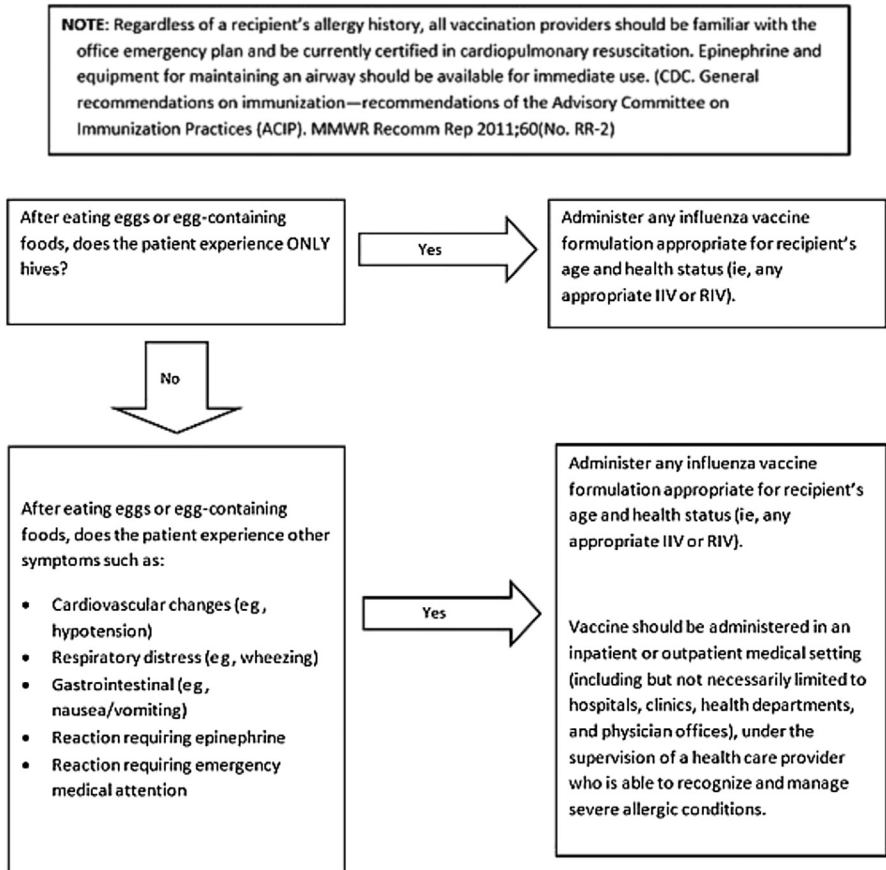

Fig. 1. Recommendations regarding influenza vaccination of persons who report allergy to eggs: Advisory Committee on Immunization Practices, United States, 2016 to 17 Influenza season. (*Data from* CDC. Flu vaccine and people with egg allergies. Available at: https://www.cdc.gov/flu/protect/vaccine/egg-allergies.htm. Accessed April 17, 2017.)

against influenza, although antibodies to the NA and other antibodies also play a role that is not as well understood.[46,47]

The immunogenicity of IIVs in children varies by influenza strain, the formulation of the vaccine, and the underlying condition and prior exposure of the recipient to similar viruses or vaccines. Depending on the degree to which the vaccine strains match the circulating strains, seasonal influenza vaccines will confer more or less protection, as antibody against influenza is for the most part strain specific. Therefore, antibody against one type or subtype of influenza may provide modest to no protection against other types or subtypes of influenza.[47]

Older children tend to have a strong antibody response, and just one dose of IIV is enough to confer protective immunity. Children younger than 9 years may have reduced antibody responses and should receive 2 doses of IIV at least 4 weeks apart the first time they are vaccinated against influenza. Once children have been primed with 2 doses of IIV, they are recommended to receive a single dose of vaccine in subsequent years. A young child may also be primed with 2 single doses of influenza vaccine across 2 influenza seasons.[47,56] For more information on vaccine priming and appropriate dosing for children, refer to **Fig. 2**.[57]

Efficacy and Effectiveness

IIVs have demonstrated efficacy and effectiveness across broad age groups and among different populations over many influenza seasons. Vaccine efficacy generally refers to the performance of a vaccine in protecting against a previously defined clinical or
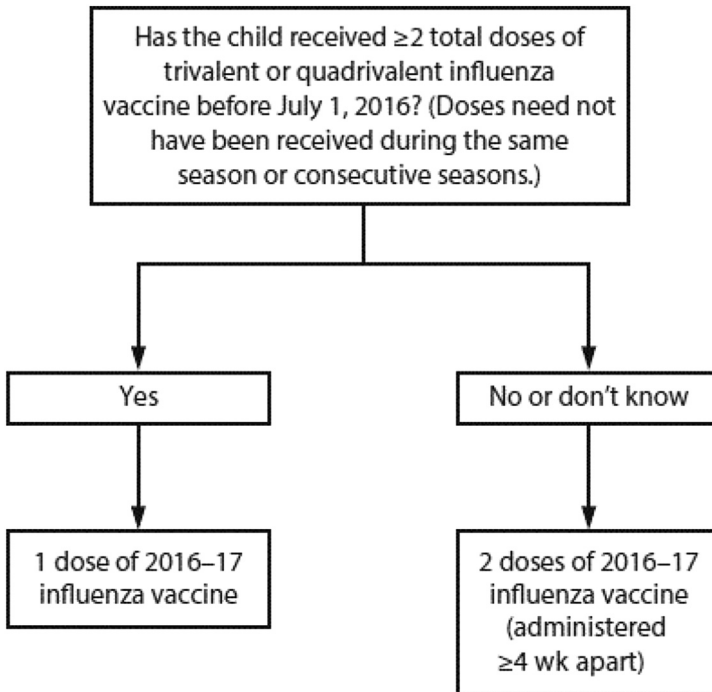

Fig. 2. Influenza vaccine dosing algorithm for children aged 6 months through 8 years: Advisory Committee on Immunization Practices, United States, 2016 to 17 influenza season. (*Data from* Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and control of seasonal influenza with vaccines. MMWR Recomm Rep 2016;65(5):1–54.)

laboratory outcome during clinical trials. Vaccine effectiveness describes a vaccine's performance against the same outcomes in nonrandomized settings, as observed after licensure. Estimates of vaccine efficacy and effectiveness may vary between studies depending on the vaccine match, population (age and comorbid conditions), and study outcome. It is, therefore, difficult to systematically compare point estimates of vaccine efficacy across trials, unless the studies define the outcome in the same way and administer the same vaccine in the same study season. Efficacy and effectiveness tend to be greater when the vaccine virus strains more closely match the circulating virus strains.[57]

A meta-analysis of randomized controlled trials of influenza vaccine efficacy over 12 influenza seasons showed IIV had a pooled efficacy of 59% (95% confidence interval [CI], 51%–67%) among those aged 18 to 65 years.[58] Although no trials in children 2 to 17 years of age met inclusion criteria for this particular meta-analysis at the time of publication, many clinical trials have been conducted on the efficacy of seasonal influenza vaccine in children (Table 2). Among children aged 1 to 16 years in a multiyear study in Nashville, Tennessee, efficacy against culture-confirmed clinical influenza was 91.4% and 77.3%, respectively, during H1N1 and H3N2 years. There were too few laboratory-confirmed episodes to evaluate by narrower age strata.[59] In a randomized controlled trial in healthy children aged 6 to 23 months, vaccine efficacy was 66% (95% CI, 34%–82%) against culture-confirmed clinical illness in the first year but could not be assessed in the second year because of low influenza attack rates.[27] A clinical trial in Europe in 2007 to 2008 and 2008 to 2009 randomized healthy influenza vaccine-naïve children aged 6 months to less than 72 months to receive IIV, MF59 adjuvanted IIV, or a noninfluenza control vaccine. Vaccine efficacy was 43% and 86%, respectively, for IIV and adjuvanted IIV versus the noninfluenza control vaccine against all LCI illness across both influenza seasons.[51] In a multinational study among children 3 to 8 years of age, vaccine efficacy of a quadrivalent IIV was 55.9% against polymerase chain reaction–confirmed clinical illness of any severity.[60]

Although most studies of influenza vaccines focus on LCI illness of any severity, it is also important to look at the efficacy of influenza vaccine against more severe disease. In the multinational study of quadrivalent vaccine mentioned earlier, vaccine efficacy among children 3 to 8 years of age was 73.1% against all strains for moderate to severe LCI.[60] As severe outcomes of influenza are rare in children, they may be difficult and costly to identify in prospective studies. A case-control study design examined the effectiveness of influenza vaccine in preventing admissions to the pediatric intensive care unit (PICU). In this study, influenza vaccination reduced children's risk of life-threatening influenza and/or influenza-related admission to the PICU by 74% during influenza seasons from 2010 to 2012. In this study, there was no effectiveness demonstrated among children receiving influenza vaccine for the first time who did not receive the recommended 2 doses.[61] In a case-cohort analysis of children aged 6 months through 17 years during the 2010–2014 influenza seasons, overall influenza vaccine efficacy against death was 65% (95% CI, 54%–74%).[62]

Adjuvanted Vaccines

An adjuvant is a substance that can be formulated as a component of a vaccine to improve the immune response to the vaccine antigens. Most seasonal influenza vaccines are unadjuvanted; the only adjuvanted seasonal influenza vaccine approved for use in many countries, including the United States, uses MF59, an oil-in-water emulsion of squalene. Adjuvanted influenza vaccines are primarily licensed for individuals 65 years and older, as the adjuvant helps their weakened immune systems mount a stronger antibody response. In 2015, Canada became the first country to approve the MF59-adjuvanted influenza vaccine for use in children 6 to 23 months of age.

Table 2
Individually randomized controlled trials of influenza vaccines in children, 1985 to 2013 influenza seasons

Study Years	Study Location	Age Group	Influenza Vaccine	Vaccine Strains	Number of Doses of Vaccine	Control Vaccine	Clinical Outcome Measure	Laboratory Outcome Measure	N	Circulating Strain	Vaccine Efficacy (95% CI)	Attack Rate of Control Group (%)
Trials with non-influenza vaccine control group												
1985–1990[59]	United States (Nashville, Tennessee)	1–16 y	*Study y 1*: bivalent inactivated vaccine[a] *Study y 2–5*: trivalent inactivated vaccine[a] *All y*: bivalent cold adapted[a]	*Study y 1*: A/Dunedin/6/83, A/Chile/1/83, A/Korea/1/82, A/Philippines/2/82 *Study y 2*: A/Texas/1/85, A/Chile/1/83, A/Bethesda/1/85, A/Mississippi/1/85 *Study y 3*: A/Kawasaki/9/86, A/Taiwan/1/86, A/Bethesda/1/85, A/Leningrad/360/86 *Study y 4*: A/Kawasaki/9/86, A/Taiwan/1/86, A/Los Angeles/2/87, A/Sichuan/2/87 *Study y 5*: A/Kawasaki/9/86, A/Taiwan/1/86, A/Los Angeles/2/87, A/Shanghai/11/87	1 dose of vaccine either IN or injected IM	Double control intranasal: placebo IM injection: placebo (y 1), monovalent influenza B vaccine (y 2–5)	Influenza-like illness or other upper respiratory illness	Culture	791	H1N1 y H3N2 y	*Cold-adapted*: 95.5 (66.7–99.4) *IIV*: 91.4 (63.8–98.0) *Cold-adapted*: 67.7 (1.1–89.5) *IIV*: 77.3 (20.3–93.5)	7.1 4.3

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Table 2
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Study Years	Study Location	Age Group	Influenza Vaccine	Vaccine Strains	Number of Doses of Vaccine	Control Vaccine	Clinical Outcome Measure	Laboratory Outcome Measure	N	Circulating Strain	Vaccine Efficacy (95% CI)	Attack Rate of Control Group (%)
1996–1997[26]	United States	15–71 mo	LAIV (Aviron, Mountain View, California)	A/Texas/36/91-like (H1N1), A/Wuhan/359/95-like (H3N2), B/Harbin/7/94-like	1 or 2 IN doses; 2 doses given 60 d apart	Placebo	Symptomatic fever, runny nose or nasal congestion, sore throat, cough, headache, muscle aches, chills, vomiting, otitis media	Culture	*LAIV*: 189 *Control*: 99	*One-dose regimen* All strains H3N2 B	89 (65–96) 87 (47–97) 91 (46–99)	14.1 8.1 6.1
									LAIV: 849 *Control*: 410	*2-dose regimen* All strains H3N2 B	94 (88–97) 96 (90–99) 91 (78–96)	18.0 12.0 7.6
1996–1998[25]	United States	26–85 mo	LAIV (Aviron, Mountain View, California)	A/Shenzhen/227/95-like (H1N1), A/Wuhan/359/95 (H3N2), B/Harbin/7/94-like	1 IN dose	Placebo	Lower respiratory tract disease and/or otitis media with or without fever	Culture	*Study y 1* *LAIV*: 1070 *Control*: 532	*Study y 1* All strains H3N2 B	93 (87–96) 95 (88–97) 91 (79–96)	17.7 11.8 6.9
									Study y 2 *LAIV*: 917 *Control*: 441	*Study y 2* All strains H3N2 (matched) H3N2 (unmatched) B	87 (78–93) 100 (54–100) 86 (75–92) 100 (79–100)	12.7 0.9 11.6 0.2
1999–2001[27]	United States (Pittsburgh)	6–24 mo	IIV (Fluzone, Aventis Pasteur, Swiftwater, Pennsylvania)	*Study y 1*: A/Beijing/262/95 (H1N1), A/Sydney/15/97 (H3N2), B/Yamanashi/166/98 *Study y 2*: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Yamanashi/166/98	2 IM injections, 4 wk apart	Placebo	Upper respiratory tract infection accompanied by fever (≥38°C) and/or AOM	Culture	*Study y 1* *IIV*: 273 *Control*: 138 *Study y 2* *IIV*: 252 *Control*: 123	*Against influenza* All strains *Against AOM* All strains	*Study y 1*: 66 (34–82) *Study y 2*: −7 (−247–67) *Study y 1*: −0.28 *Study y 2*: −19.5	15.9 3.3 35.8 59.5

2000–2002[82]	Belgium, Finland, Israel, Spain, United Kingdom	6 to <36 mo	LAIV (Wyeth Vaccines Research, Marietta, Pennsylvania)	Study y 1: A/New Caledonia/20/99 (H1N1), A/Sydney/05/97 (H3N2), B/Yamanashi/166/98 Study y 2: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Victoria/504/2000	Study y 1: 2 IN doses, 35 ±7 d apart Study y 2: 1 IN dose	Placebo	Influenza-like illness, pneumonia, AOM	Study y 1: serology Study y 2: PCR	Study y 1 LAIV: 951 Control: 665 Study y 2 LAIV: 640 Control: 450	Study y 1 All strains	85.9 (76.3–92.0)	13.4
										All vaccine-matched strains	85.4 (74.3–92.2)	10.8
										H1N1	91.8 (80.8–97.1)	7.7
										H3N2	ND	0.2
										B	72.6 (38.6–88.9)	3.5
										Study y 2 All strains	85.8 (78.6–90.9)	30.9
										All vaccine-matched strains	88.7 (82.0–93.2)	29.1
										H1N1	90.0 (56.3–98.9)	3.1
										H3N2	90.3 (82.9–94.9)	22.4
										B	81.7 (53.7–93.9)	5.1

Table 2
(continued)

Study Years	Study Location	Age Group	Influenza Vaccine	Vaccine Strains	Number of Doses of Vaccine	Control Vaccine	Clinical Outcome Measure	Laboratory Outcome Measure	N	Circulating Strain	Vaccine Efficacy (95% CI)	Attack Rate of Control Group (%)
2000–2003[83]	China, Hong Kong, India, Malaysia, the Philippines, Singapore, Taiwan, Thailand	12 to <36 mo	LAIV (Wyeth Vaccines Research, Marietta, Pennsylvania)	*Study y 1:* A/New Caledonia/20/99 (H1N1), A/Sydney/05/97 (H3N2), B/Yamanashi/166/98 *Study y 2:* A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Yamanashi/166/98	*Study y 1:* 2 IN doses, 28 d apart *Study y 2:* 1 dose in study y 2	Placebo	Influenza-like illness as described in Belshe et al,[26] 1998	Culture	*Study y 1* *LAIV:* 1653 *Control:* 1111 *Study y 2* *Primed LAIV:* 881 *Unprimed LAIV:* 503 *Primed control:* 759 *Unprimed control:* 494	*Study y 1* All strains All vaccine-matched strains H1N1 H3N2 (unmatched) B (matched) *Study y 2* All strains All vaccine-matched strains H1N1 H3N2 B (unmatched)	70.1 (60.9–77.3) 72.9 (62.8–80.5) 80.9 (69.4–88.5) 90.0 (71.4–97.5) 44.3 (6.2–67.2) 64.2 (44.2–77.3) 84.3 (70.1–92.4) — 86.3 (71.4–94.1) —	16.4 12.5 7.3 2.4 3.2 11.9 9.9 N/R N/R N/R

| 2001–2002[84] | South Africa, Brazil, Argentina | 6 to <36 mo | LAIV (Wyeth Vaccines, Marietta, Pennsylvania) | Study y 1: A/New Caledonia/20/99-like (H1N1), A/Panama/2007/99-like (H3N2), B/Yamanashi/166/98-like, B/Victoria/504/00-like
Study y 2: A/New Caledonia/20/99-like (H1N1), A/Panama/2007/99-like (H3N2), B/Victoria/504/00-like | Study y 1: 1 or 2 intranasal doses
Study y 2: 1 dose | Placebo | Lower respiratory tract disease and/or otitis media with or without fever | Culture | Study y 1
LL: 944
PP: 474
Study y 2
LL/L: 339
PP/P: 342 | Study y 1[b]
LL vs PP
All strains

All vaccine-matched strains
H1N1
H3N2

B (matched)

Study y 2
LL/L vs PP/P
All strains

All vaccine-matched strains
H1N1

H3N2

B (matched) | 72.0 (61.9–79.8)
73.5 (63.6–81.0)

NC
72.7 (60.7–81.5)
81.4 (64.2–91.2)

46.6 (14.9–67.2)
73.6 (33.3–91.2)

94.0 (62.0–99.9)
49.4 (−253.0–95.4)
−102.4 (−2137.1–71.0) | N/R
N/R

N/R
N/R
N/R

N/R
N/R

N/R
N/R

N/R |

Table 2
(continued)

Study Years	Study Location	Age Group	Influenza Vaccine	Vaccine Strains	Number of Doses of Vaccine	Control Vaccine	Clinical Outcome Measure	Laboratory Outcome Measure	N	Circulating Strain	Vaccine Efficacy (95% CI)	Attack Rate of Control Group (%)
2007–2008[51]	Germany and Finland	6 to <72 mo	*Study y 1*: ATIV (Fluad, Novartis Vaccines), subunit TIV (Aggripal S1, Novartis Vaccines) *Study y 2*: ATIV and split TIV (Influsplit SSW, GlaxoSmithKline Biologicals)	*Study y 1*: A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), B/Malaysia/2506/2004 *Study y 2*: A/Brisbane/59/2007 (H1N1), A/Brisbane/10/2007 (H3N2), B/Florida/4/2006	2 doses, 28 d apart	Meningococcal C conjugate vaccine (Menjugate); 6 to <12 mo; tick-borne encephalitis vaccine (Encepur children); 12 to <72 mo	Influenza-like illness	rRT-PCR	*ATIV*: 1937 *TIV*: 1772 *Control*: 993	All strains ATIV	86 (74–93)[c]	4.7
										All strains TIV	43 (15–61)	4.7
										Vaccine-matched strains ATIV	89 (78–95)	4.1
										Vaccine-matched strains TIV	45 (16–64)	4.1
2009[85]	South Africa	6–60 mo; HIV-infected	TIV (VAXIGRIP, Sanofi-Aventis, Lyon, France)	A/Brisbane/59/2007(H1N1), A/Uruguay/716/2007(H3N2), B/Florida/4/2006	2 IM doses, 1 mo apart	Placebo	Influenza-like illness	Culture and RT-PCR	*TIV*: 203 *Control*: 200	All strains	24.7 (−64.7–66.4)	8.5

Year	Study	Age	Vaccine	Strains	Dose	Control	Outcome	Method	N		
2010–2011[60]	Multinational study, 15 sites in Bangladesh, Dominican Republic, Honduras, Lebanon, Panama, the Philippines, Thailand, and Turkey	3–8 y	QIV (GlaxoSmithKline Vaccines)	A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), B/Florida/4/2006 (Yamagata lineage)	1 or 2 IM injections depending on priming	Hepatitis A vaccine (Havrix, GSK Vaccines)	Influenza-like illness	rRT-PCR	QIV: 2379 Control: 2398	*Any severity*	
										All strains	55.9 (39.1–67.3)	4.67
										All vaccine-matched strains	45.1 (9.3–66.8)	2.34
										H1N1	55.6 (21.3–74.9)	1.58
										H3N2	57.6 (28.5–74.9)	1.96
										B/Yamagata (matched)	100 (— to 100)	0.08
										B/Victoria (matched)	47.2 (12.4–68.2)	1.79
										Moderate-severe		
										All strains	73.1 (47.1–86.3)	2.17
										H1N1	76.5 (30.3–92.1)	0.71
										H3N2	82.4 (49.1–93.9)	0.96
										B/Yamagata (matched)	100.0 (— to 100.0)	0.04
										B/Victoria (matched)	42.1 (47.1–77.2)	0.5
2013[23]	Bangladesh	24–59 mo	LAIV (Nasovac-S, SIIL, Pune, India; lot 167E2002)	A/California/7/2009 (H1N1)-like, A/Victoria/361/2001 (H3N2)-like, B/Wisconsin/1/2010 (Yamagata lineage)-like	1 IN dose	Placebo	Symptomatic fever (≥38.0°C), upper respiratory illness, AOM, meningitis, or sepsis	rRT-PCR	LAIV: 1174 Control: 587	All strains	41.0 (28.0–51.6)	24.5
										All vaccine-matched strains	57.6 (43.6–68.0)	15.8
										H1N1	50.0 (9.2–72.5)	3.6
										H3N2	60.4 (44.8–71.6)	12.3
										B (matched)	0.0 (−1001–90.9)	0.2
										B (unmatched)	6.5 (−43.0–38.8)	5.3

Table 2
(*continued*)

Study Years	Study Location	Age Group	Influenza Vaccine	Vaccine Strains	Number of Doses of Vaccine	Control Vaccine	Clinical Outcome Measure	Laboratory Outcome Measure	N	Circulating Strain	Vaccine Efficacy (95% CI)	Attack Rate of Control Group (%)
2013[24]	Senegal	2 to <5 y	LAIV (Nasovac- STM, SIIL, Pune, India; lot 167E2002)	A/California/7/ 2009 (H1N1)- like, A/ Victoria/361/ 2001 (H3N2)- like, B/ Wisconsin/1/ 2010 (Yamagata lineage)-like	1 IN dose	Placebo	Fever (>37.5°C), cough, sore throat	rRT-PCR	*LAIV*: 1174 *Control*: 587	All strains	0.0 (−26.4– 20.9)	18.0
										All vaccine- matched strains	−6.1 (−50.0– 25.0)	8.0
										H1N1	−9.7 (−62.6– 26.1)	6.2
										H3N2	—	0.0
										B (matched)	9.5 (−88.9– 56.6)	1.7
										B (unmatched)	7.3 (−26.3, 31.9)	10.6

Comparative trials of influenza vaccines; no noninfluenza vaccine control group

Study Years	Study Location	Age Group	Influenza Vaccine	Vaccine Strains	Number of Doses of Vaccine	Control Vaccine	Clinical Outcome Measure	Laboratory Outcome Measure	N	Circulating Strain	Vaccine Efficacy (95% CI)	Attack Rate of Control Group (%)
2002[69]	145 sites in Belgium, Finland, Germany, Greece, Israel, Italy, the Netherlands, Norway, Poland, Portugal, Spain, Switzerland, the United Kingdom	6–17 y	LAIV (Wyeth Vaccines Research, Marietta, Pennsylvania) TIV split virion (Aventis Pasteur, Lyon, France)	*LAIV*: A/New Caledonia/20/ 99 (H1N1), A/ Panama/2007/ 99 (H3N2), B/ Hong Kong/ 330/01 *TIV*: Caledonia/ 20/99—IVR-116, A/ Panama/2007/ 99—RESVIR-17, B/ Shanghai/7/97	1 dose IN or IM injection	None	Influenza-like illness, pneumonia, AOM	rRT-PCR	*LAIV*: 1111 *TIV*: 1109	All strains	31.9 (1.1– 53.5)[d]	6.6[e]
										All vaccine- matched strains	34.7 (3.9–56.0)	6.4
										H1N1	100 (−8.4– 100.0)	0.5
										H3N2	0.6 (−141.8– 59.2)	1.1
										B	36.3 (0.1–59.8)	4.8

2002[71]	Belgium, Czech Republic, Finland, Germany, Italy, Poland, Spain, Switzerland, the United Kingdom	6–71 mo	LAIV (Wyeth Pharmaceuticals, Marietta, Pennsylvania) TIV split virion (Aventis Pasteur, Lyon, France)	*LAIV*: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Hong Kong/330/01 *TIV*: A/Panama/2007/99 (H3N2), A/New Caledonia/20/99 (H1N1), B/Shangdong/7/97	*LAIV*: 2 IN doses, 35 ±7 d apart *TIV*: 1 IM injection	None	At least 1: fever (≥38.0°C rectal or 37.5°C axillary), shortness of breath, pulmonary congestion, pneumonia, AOM, or wheezing 2 or more: rhinorrhea, pharyngitis, cough, muscle aches, chills, headache, irritability, decreased activity, or vomiting	Serology and PCR	*LAIV*: 1050 *TIV*: 1035	All strains	52.4 (24.6–70.5)[d]	5.8[e]
										All vaccine-matched strains	52.7 (21.6–72.2)	4.8
										H1N1	100.0 (42.3–100.0)	0.8
										H3N2	−97.1 (−540.2–31.5)	0.6
										B	68.0 (37.3–84.8)	3.6
2004[70]	249 sites in the United States, 12 countries in Europe and the Middle East, and 3 countries in Asia	6–59 mo	LAIV (FluMist, MedImmune) TIV (United States and Asia: Fluogen, Aventis Pasteur; Europe and Middle East: Fluzone, Aventis Pasteur)	A/New Caledonia/20/99 (H1N1), A/Wyoming/3/2003 (H3N2)-like, B/Jilin/20/2003	1 or 2 IN (LAIV) or IM injection (TIV) doses (28–42 d apart if 2 doses)	Placebo	Protocol-defined influenza symptoms	Culture	*LAIV*: 4179 *TIV*: 4173	All strains	54.9 (45.4–62.9)[d]	8.6[e]
										All vaccine-matched strains	44.5 (22.4–60.6)	2.4
										H1N1 (matched)	89.2 (67.7–97.4)	0.7
										H3N2 (matched)	—	0
										H3N2 (unmatched)	79.2 (70.6–85.7)	4.5
										B	27.3 (−4.8–49.9)	1.7

Abbreviations: ATIV, adjuvanted trivalent inactivated influenza vaccine; HIV, human immunodeficiency virus; L, one dose of live attenuated influenza vaccine; LL, two doses of live attenuated influenza vaccine; NC, not calculated; N/R, not reported; P, one dose of placebo; PCR, polymerase chain reaction; PP, two doses of placebo; QIV, quadrivalent inactivated influenza vaccine; rRT, real time Reverse Transcription; RT, Reverse Transcription; TIV, trivalent inactivated influenza vaccine; Y, years.

[a] Manufacturer not listed.
[b] Data for study years 1 and 2 for other treatment groups are available in the full publication.
[c] Study results are mainly from study year 1.
[d] Relative efficacy of LAIV compared with TIV.
[e] Attack rate is of TIV group, as there was no placebo control group in this study.
Courtesy of Kathleen Neuzil, MD, MPH, Baltimore, MD.

Recent studies on the safety, immunogenicity, and efficacy of the MF59-adjuvanted IIV in young children has shown them to be highly immunogenic and efficacious. There is evidence that the adjuvanted IIV may elicit greater reactogenicity, although adverse events associated with MF59-adjuvanted IIV vaccination were mild and transient and rates were relatively low in the clinical trial setting. One study conducted in Argentina, Australia, Chile, the Philippines, and South Africa between 2011 and 2012 showed that the adjuvanted trivalent inactivated vaccine induced significantly higher antibody titers after 2 doses than did the unadjuvanted vaccine. This superior antibody response persisted through 6 months after vaccination against both homologous and heterologous influenza strains.[63] As mentioned earlier, a study in Germany and Finland in 2007 to 2008 and 2008 to 2009 reported efficacy data for the adjuvanted trivalent inactivated vaccine. In this study, the adjuvanted trivalent IIV had absolute and relative efficacies, respectively, of 86% and 75% against all circulating influenza strains and 89% and 80%, respectively, against vaccine-matched strains when compared with unadjuvanted trivalent IIV.[51] The same study showed local and systemic reactions to vaccination to be similar in younger children vaccinated with adjuvanted trivalent IIV and trivalent IIV, although in older children the rates of systemic, but not local, reactions were higher after vaccination with adjuvanted trivalent IIV. Serious adverse events were evenly divided between the treatment groups.[51] A large trial of adjuvanted quadrivalent IIV is ongoing (NCT01964989).

LIVE-ATTENUATED INFLUENZA VACCINES

Worldwide, there are 2 types of LAIVs: one developed in the former Union of Soviet Socialist Republics and the other in the United States. The Leningrad-based LAIVs have been approved in Russia for children 3 years of age and older for many decades. More recently, a Leningrad-based LAIV has been manufactured and licensed in India for children aged 2 years and older. In the United States, an LAIV based on the Ann Arbor strain and approved under the trade name FluMist was first licensed for use in persons 5 to 49 years of age in 2003; in 2007, the age range was expanded to include children beginning at 2 years of age. LAIV is administered IN as a spray. LAIVs induce a rapid immune response in the mucosal linings of the upper respiratory tract that depend on viral replication and, initially, on activation of local immune responses. The LAIVs are based on attenuated influenza A and B vaccine viruses, called master donor viruses (MDV-A and MDV-B), which are temperature sensitive and have been rendered cold adapted, such that the virus replicates efficiently only at lower temperatures, such as in the mucosal linings of the nasopharynx, but not in the lower respiratory tract, where temperatures are relatively higher. Similar to IIVs, LAIVs are either trivalent (H1N1, H3N2, B) or quadrivalent (H1N1, H3N2, 2 B strains) according to the most recent strain recommendations. This article focuses predominantly on the US LAIV.

Safety

LAIV administration has been associated most commonly with mild upper respiratory tract reactions, such as runny nose, nasal congestion, and fever in children younger than 8 years. In clinical studies, an increased risk for wheezing illness was observed in LAIV/Ann Arbor backbone recipients aged less than 24 months (3.8% LAIV vs 2.1% IIV). An increase in hospitalizations was also observed in children aged less than 12 months after vaccination with LAIV/Ann Arbor. For these reasons, LAIV/Ann Arbor is approved for use beginning at 24 months of age. Postlicensure surveillance data from North America and Europe have not demonstrated an increased frequency

of wheezing illness after administration of LAIV/Ann Arbor among healthy children older than 2 years.[44,46]

Immunogenicity

Several studies have assessed various mucosal and systemic immune responses following vaccination with LAIV.[64] Studies have also demonstrated the greater breadth of antibodies produced in response to LAIV as compared with IIV.[65] In general, when compared with IIV, LAIV induces better mucosal antibody responses and IIV induces stronger serum antibody responses.[47,66]

Overall, LAIV immunogenicity data do not correlate well with vaccine efficacy.[65–68] As there is no generally accepted correlate of immunity for LAIV, manufacturers and regulatory agencies must rely primarily on efficacy or effectiveness data for vaccine development and policy decisions.

Efficacy and Effectiveness

The efficacy of LAIV has been studied extensively. A pivotal study during the 1996 to 1997 influenza season in children 15 to 71 months of age examined the absolute efficacy of one versus 2 doses of LAIV. The one-dose regimen was 89% effective at preventing LCI illness from all influenza strains. When 2 doses of LAIV were administered 60 days apart, LAIV was 94% effective against all influenza strains.[26] Several trials comparing the efficacy of LAIV and trivalent IIV have also been conducted in children. These studies have shown LAIV to be 31.9% to 54.9% more effective against all influenza virus strains than IIV.[69–71] These head-to-head comparative trials, demonstrating superiority of LAIV to trivalent IIV in young children, led to preferential recommendations for LAIV over IIV in many countries, including the United States.

For children in low-resource countries, LAIVs are promising options given the efficacy demonstrated in comparative trials with IIV and the ease of administration. In 2013, 2 prospective placebo-controlled clinical trials were conducted on the efficacy of a single dose of the Russian-backbone LAIV in young children in Bangladesh and Senegal. In Bangladesh, LAIV was 57.6% effective against vaccine-matched influenza strains, which had an attack rate of 15.8% in the placebo group. In Senegal during the same influenza season, LAIV had zero efficacy against vaccine-matched influenza strains, despite being sufficiently powered (an attack rate of 18.0% in the placebo group) to show such an effect.[23,24] The differences in the results from these two studies are poorly understood; however, inconsistent results for the Ann Arbor backbone LAIV have also occurred in recent years, as detailed later.

ANNUAL MONITORING OF VACCINE EFFECTIVENESS AND LIVE-ATTENUATED INFLUENZA VACCINE

The increasing number of influenza vaccines, and the inherent unpredictability of influenza strain circulation, necessitates a nimble system to monitor and evaluate the impact of individual vaccines and policy decisions. A growing number of surveillance systems in the United States, Canada, Australia, and Europe monitor influenza vaccine effectiveness annually and have the ability to produce early, in-season estimates of vaccine performance.[27,72,73] The US Influenza Vaccine Effectiveness Network has shown reduced effectiveness to LAIVs during 3 influenza seasons (2013 to 2014, 2014 to 2015, and 2015 to 2016) and better performance of IIVs compared with LAIVs in children. These data contradict the head-to-head randomized trials mentioned earlier, which favored LAIVs, and data from other countries where LAIVs continue to show effectiveness.[57]

The reasons for the overall poorer performance of LAIV compared with IIV in recent influenza seasons are not well understood and should be the subject of future studies. Possible explanations of the low efficacy include (1) the suboptimal performance of the specific (H1N1) HA vaccine component included in the vaccine; (2) potential interference among viruses in the quadrivalent vaccine (ie, the additional influenza B vaccine component may affect viral replication of the A(H1N1)pdm09 virus); and (3) evaluation in a more highly vaccinated population in recent years, as compared with populations of earlier studies, in which it is likely that a higher proportion of children were vaccine naïve.[74] In light of the low effectiveness against influenza A(H1N1)pdm09 in the United States during the 2013 to 2014 and 2015 to 2016 influenza seasons, the United States and Canada have altered their vaccine recommendations for children beginning in the 2016 to 2017 season.[57,75]

INFLUENZA VACCINE POLICY

In 2012, the WHO updated its recommendations on the use of influenza vaccine.[76] For countries considering the initiation or expansion of programs for seasonal influenza vaccination, the WHO recommends that pregnant women should have the highest priority for vaccine receipt. This recommendation was based on the risk of severe disease, evidence on the safety of the vaccine during pregnancy, the potential for benefit to women and infants, and the operational feasibility. Additional groups to be considered, in no particular order of priority, are children aged 6 through 59 months, the elderly, individuals with specific medical conditions, and health care workers. It is recommended that health care workers receive influenza vaccine in many countries both to limit transmission to vulnerable patients as well as to maintain the health care workforce during influenza outbreaks.

As no vaccines are approved for children younger than 6 months of age, protection of these vulnerable infants can only be achieved through vaccination of the mother during pregnancy and vaccination of close contacts to limit transmission.[76] Randomized controlled clinical trials in Bangladesh, South Africa, and Mali have demonstrated that vaccination of pregnant women can reduce the incidence of LCI in infants.[77–79]

In temperate countries with seasonal outbreaks, influenza vaccine is given annually, before the influenza season. Influenza vaccine programs are more challenging in tropical and subtropical countries. Given the varying influenza circulation patterns in the tropics, it is not yet clear if a Southern or Northern Hemisphere vaccine administered in annual campaigns would provide year-round protection against the diverse strains that may be seen in such countries. Further, the optimal formulation or timing of immunization is still uncertain in many countries with limited historical influenza surveillance.[46]

In the United States, routine annual influenza vaccination is recommended for all persons aged 6 months and older. Children receiving influenza vaccine for the first time require 2 doses of influenza vaccine. Special effort should be made to vaccinate children at high risk for complications of influenza, American Indian and Alaskan native children, all household and close contacts of children younger than 6 months of age, pregnant and breastfeeding women, all health care personnel, and childcare providers and staff.[54,57] Although vaccines are recommended primarily to reduce influenza and its complications in the recipient, it is acknowledged that administering vaccines to children may also reduce transmission and the incidence of influenza at the household and community level.

The Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) update their influenza vaccine recommendations annually.[54,57] In light of the low effectiveness against influenza A(H1N1)pdm09 in the

United States during the 2013 to 2014 and 2015 to 2016 influenza seasons, the ACIP and AAP recommended that LAIV not be used in the 2016 to 2017 influenza season.[57] Studies are ongoing to determine whether the interim recommendation in the United States that LAIV should not be used will continue for subsequent influenza seasons. In Canada, the use of LAIV was not preferentially recommended for the 2016 to 2017 influenza season, as it had been in the past.[75]

ANTIVIRAL MEDICATIONS

Antiviral medications with activity against influenza viruses are an important adjunct to influenza vaccine in the control of influenza. These medications can be used to treat or to prevent influenza. Three influenza antiviral medications approved by the US Food and Drug Administration are recommended for use in the United States during the 2016 to 2017 influenza season: oral oseltamivir, inhaled zanamivir, and intravenous peramivir. These drugs are chemically related antiviral medications known as NA inhibitors that have activity against both influenza A and B viruses. Amantadine and rimantadine, from the adamantane class of antivirals, are licensed in the United States for the treatment of influenza A viruses. However, the adamantanes are not currently recommended because they have no intrinsic activity against influenza B viruses and there are high levels of resistance among circulating influenza A viruses.[80] Antiviral resistance is monitored carefully, and information is updated on a frequent basis throughout the season.[81]

Antiviral medications are underused for children with influenza in the United States. Trials of antiviral medications in children have shown that early treatment can shorten the duration of illness and reduce complications, including AOM, and the duration of hospitalization. The AAP and the ACIP update antiviral recommendations on an annual basis, providing specific dosage information for treatment and prophylactic use.[54,80] When indicated, antiviral treatment should be started as soon as possible after illness onset. Decisions about starting antiviral treatment should not wait for laboratory confirmation of influenza.

The AAP recommends that health care providers offer treatment as soon as possible for any child (1) hospitalized with presumed influenza; (2) hospitalized for severe, complicated, or progressive illness attributable to influenza; or (3) with presumed illness of any severity if the child is at high risk of complications. Treatment should be considered as soon as possible for any healthy child with presumed influenza or healthy children with presumed influenza who live at home with a sibling or household contact that is younger than 6 months or has a medical condition that predisposes to complications.[54]

SUMMARY

Influenza is a common respiratory illness in children and accounts for substantial morbidity and mortality on an annual basis. Influenza vaccines, the mainstay of influenza prevention and control efforts, are safe and effective. The absolute effectiveness of vaccines varies by year and is influenced by circulating virus, vaccine type, and host characteristics. The reason for recent reduced performance of LAIVs in children in the United States and elsewhere is poorly understood, and active research is ongoing. Vaccination programs are less common in tropical and subtropical countries, where unique logistical and feasibility challenges exist related to vaccine availability and more prolonged periods of virus circulation. Antiviral medications for prevention and treatment of influenza in children are an important adjunct to vaccines.

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