Invited Review

# Overview of Influenza Vaccines in Children

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Received April 8, 2013; accepted June 6, 2013; electronically published September 24, 2013.

Prevention of influenza infection through vaccination is the best strategy to reduce its disease burden; however, annual revaccination is required to provide protection from circulating virus strains. Currently available influenza vaccines are trivalent inactivated influenza vaccines (IIV) or live-attenuated influenza vaccines (LAIV); however, quadrivalent formulations of IIV and LAIV are expected to be available for the 2013–2014 influenza season. Among children 6 months through 8 years of age receiving their first influenza vaccination, 2 doses of vaccines are required to provide adequate protection. Because of the wide range of circulating influenza viruses and host immune responses, estimates of vaccine effectiveness vary widely by year, age group, and vaccine studied. We summarize the evidence base for pediatric influenza vaccination, and we describe the challenges and limitations of protecting this population with currently available vaccines.

**Key words.** Influenza Vaccines; LAIV; Inactivated Influenza Vaccines; Quadrivalent Vaccines



## INFLUENZA DISEASE BURDEN IN CHILDREN

Influenza is an important cause of medical visits and hospitalizations in children. In the United States, 10%–15% of children seek medical care for influenza-associated disease each year [1–6]. Rates of hospitalization among preschool children [3, 7] are comparable to those observed for persons 50–64 years of age [8], and children <2 years of age are at even higher risk. In 1 study, the average annual hospitalization rate among infants <6 months old was 450 per 100 000 children, compared to 90 per 100 000 among children 6–23 months of age, and 30 per 100 000 among children 24–59 months of age [6]. Influenza-associated hospitalization rates are also higher among children with cardiac and pulmonary conditions [7, 9].

Deaths from influenza among children are uncommon in the United States (Figure 1). From 2004 to 2010, mortality due to laboratory-confirmed influenza in children <18 years of age ranged from 45 to 268 deaths per year [10]. Although children with underlying diseases are more likely to die than those without, many deaths in the United States occur among children with no identifiable risk factors [11].

Influenza among school-aged children can lead to high rates of school absenteeism and lost days of work among parents. In 1 US study, 28 illnesses resulted in 68 missed school days for every 100 children followed during an influenza season, as well as 20 missed work days by parents and 22 secondary illnesses among household members [12]. Pediatric influenza infection also has a substantial economic burden—an estimated $106–$442 million in direct costs per year in the United States for emergency department visits and hospitalizations among children <5 years of age [13].

## LANDSCAPE OF INFLUENZA VACCINATION IN THE UNITED STATES

The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) has recommended universal influenza vaccination since 2010. During the 50 years between the first US influenza immunization policy in 1960 and universal recommendation in 2010, vaccination programs targeted specific groups known to be at high risk of severe complications, and those who might spread influenza viruses to high-risk persons, such as their caregivers [14, 15]. Although influenza vaccines have been licensed for use in children for decades, ACIP and the American Academy of Pediatrics (AAP) Committee on Infectious Diseases had issued only permissive

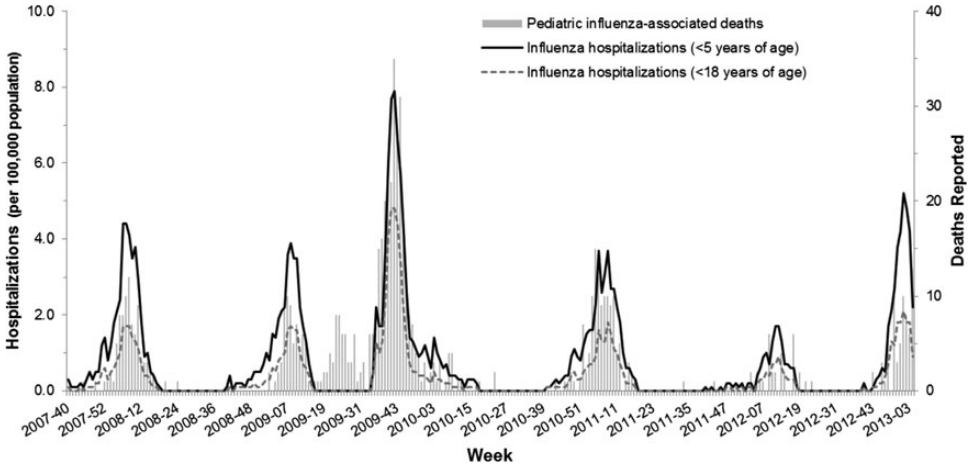


**Figure 1.** Pediatric influenza-associated hospitalizations and deaths in the United States[a], 2007–2013[b].
[a]Data sources: Influenza-Associated Pediatric Mortality Surveillance and the Emerging Infections Program. Data available at http://www.cdc.gov/flu/weekly/.
[b]Data as of January 29, 2013.

recommendations for non-high risk children until 2004 [16, 17]. The severe influenza A(H3N2) season during the fall and winter of 2003 resulted in increased mortality and hospitalizations among children and led to the first inclusion of healthy children among the high-risk groups targeted by CDC and AAP [11, 17–19]. Initially, these policies targeted children 6–23 months of age and their caregivers [17]. However, research published in 2006 identified an increased risk for children 24–59 months of age for influenza-associated illnesses in both inpatient and outpatient settings [6]; these data were used to support the 2006 recommendation to expand vaccination efforts to include children 6–59 months of age [20]. In 2008 and 2009, older children 5–18 years of age were added to the ACIP recommendation, although the vaccination of younger children was emphasized. The decision to recommend vaccination of all children was driven by evidence of the morbidity of influenza infection in children and their contacts, as well as school absenteeism and parental work loss. In addition, the rationale for vaccinating older children included the expectation that the simplified recommendations would improve coverage among children with medical conditions that put them at high risk for influenza-related complications. Potential benefits of immunizing children would also include the reduction of influenza virus transmission to contacts of children and in the community overall [15, 21]. The expansion of influenza vaccine recommendations among children has resulted in increased vaccine coverage in this age group over recent years, with an estimated 49% of children <18 years of age receiving at least 1 dose during the 2010–2011 season [22].

Two types of influenza vaccines are licensed for use in children in the United States: live-attenuated influenza vaccine (LAIV) and inactivated influenza vaccine (IIV). As of the 2012–2013 season, both vaccines contained 3 influenza viruses and must be administered annually. Live-attenuated influenza vaccine is composed of live-attenuated influenza viruses and is administered intranasally. Inactivated influenza vaccine contains purified protein of inactivated (killed) viruses and is administered via intramuscular injection. Currently, inactivated vaccine preparations are licensed for use in children ≥6 months of age, whereas LAIV is licensed for those ≥2 years of age. Persons at higher risk for complications of influenza infection because of underlying medical conditions, including children with asthma or those on long-term aspirin therapy, should not receive LAIV. Children <9 years of age who have not previously received influenza vaccine require 2 doses of vaccine, to help ensure that they generate a protective immune response [23, 24]. Several new vaccines have been licensed in the last 2 years but are currently not available to children, including high-dose IIV, cell culture-derived IIV, and recombinant hemagglutinin vaccines.

## INFLUENZA VACCINE SAFETY

Influenza vaccine is well tolerated by most children. Fever is a common adverse event reported following influenza vaccination in children, and it has been reported in up to 7%–14% of children after receipt of IIV [25, 26]. However, fever is commonly documented in children immunized with routine childhood vaccines, particularly when pneumococcal conjugate vaccine is coadministered with other vaccines including influenza vaccine [27, 28]. In children 5–9 years old who received only influenza vaccine, rates of fever >37.8°C were only 1%–2% after each of 2 doses [24]. Likewise, rates of fever due to influenza vaccine given alone to toddlers have been reported at approximately 2% [27].

Rhinorrhea or nasal stuffiness is the most common adverse event following LAIV administration [29]. This symptom may be more common in children than adults, although the presence of circulating respiratory viruses at the time influenza vaccine is typically administered may also result in symptomatic disease, and rhinorrhea has been frequently observed after receipt of intranasal placebo [30].

In the United States, ongoing routine surveillance for adverse events is conducted through 2 systems: the Vaccine Safety Datalink, which utilizes electronic data from large healthcare organizations, and the Vaccine Adverse Event Reporting System, a nationwide passive surveillance system. Through these systems, no increase in clinically important medical events has been observed after receipt of IIV, with the exception of febrile seizures in 2010 [31]. Serious adverse events are rarely reported even in the youngest (6–23 months) children [32, 33]. Analyses looking specifically at the risk of Guillain-Barre Syndrome, a putative adverse outcome of IIV, found no elevated risk among children <18 years of age [34]. After undertaking a detailed review of the adverse effects of influenza and other vaccines, the Institute of Medicine concluded that anaphylaxis (due to allergy to 1 of the contents of the influenza vaccine) was the only serious adverse event with sufficient evidence to support a causal association [35].

Because most of the currently available vaccine formulations contain residual egg proteins, additional precautions are needed in administering vaccine to those with egg allergy. Egg allergies can be screened for by asking individuals if they can eat eggs without adverse effects; those who are able to eat eggs without reaction are unlikely to be allergic. However, egg allergy alone is not a contraindication for receipt of vaccine, and persons who have experienced only hives after exposure to egg can receive IIV, if administered by a healthcare provider familiar with the potential manifestations of egg allergy and with a 30-minute observation period after vaccination [36]. Those who report severe reactions to egg, involving symptoms such as cardiovascular changes or respiratory distress, or who have required epinephrine or another emergency medical intervention, are more likely to have a serious reaction upon re-exposure to egg proteins and should be referred to a physician with expertise in the management of allergic conditions for risk assessment.

One large multicenter clinical study identified an increased risk of wheezing for young children with asthma who receive LAIV and an increased risk of wheezing and all-cause hospitalizations (primarily due to gastrointestinal and respiratory tract infections) among children aged 6–23 months [37]. Because of these findings, LAIV is not licensed in the United States for use in children <2 years of age, and includes a warning for children with asthma, or those 2–4 years of age with a history of wheezing in the previous 12 months [38]. The association between LAIV and an increased risk of wheezing has not been found among older children (6–17 years) with asthma [39]. Additional studies have not replicated this increased risk in children <5 years of age with or without asthma [40, 41]; these findings and evidence of higher LAIV efficacy in this age group has led to suggestions to consider lowering the licensed age limit of LAIV [41].

Although influenza vaccines have a long history of safety in children, recent findings for 2 specific vaccines demonstrate the need for continued vigilance for potential adverse events. In 2010, the Southern Hemisphere formulation of trivalent IIV produced by CSL (Victoria, Australia) was associated with an increased risk for febrile seizures in Australian and New Zealand children <5 years of age, and its use in this age group was suspended by the Australian Therapeutic Goods Authority [31]. The CSL IIV vaccine has now been recommended for use in Australia again, but only for children ≥9 years of age [42]. Enhanced surveillance for febrile seizures following vaccination in the United States also identified an elevated risk among children 6 months through 4 years of age during the first day postvaccination with IIV; this risk was higher among children receiving 13-valent conjugated pneumococcal vaccine concomitantly [43, 44]. Upon review of these data, together with the results of a risk-benefit analysis, ACIP determined that the health risks for the remaining unvaccinated children outweighed those at risk for febrile seizures after receiving vaccine, and it did not change the recommendation for children in this age range [36]. However, ACIP recommends the use of the CSL vaccine product only for children ≥9 years of age [45].

A second product-specific adverse event was identified in 2010, when an increase in incidence of narcolepsy was detected among children 4–19 years of age who received an AS03-adjuvanted monovalent pandemic A(H1N1) vaccine (Pandemrix, GSK) in Finland. The increased incidence in this population was small in magnitude (9 per 100 000 person-years) but indicated a large relative risk compared to unvaccinated children [46]. Similar results were subsequently reported in Sweden [47], although findings in other European countries were less conclusive [48]. Additional research in Finnish children identified a shared human leukocyte antigen mutation among children who suffered this rare but serious and long-lasting adverse event [49]. These findings are limited to a single monovalent adjuvanted vaccine produced in Europe, and they have not been associated with adjuvanted pandemic vaccines produced in other locations such as Canada [50] or with adjuvanted trivalent vaccines. Other types of

adjuvanted IIV, including vaccines adjuvanted with MF-59, are under clinical evaluation but have a safety profile similar to that of unadjuvanted IIV in clinical trials. Compared to IIV, adjuvanted IIV induces slightly higher rates of systemic and local reactions such as mild fever in older children, but analyses have not revealed any immediate serious adverse events for adjuvanted trivalent products [51]. However, adjuvanted influenza vaccines are not currently licensed for use in the United States.

## INFLUENZA VACCINE EFFICACY AND EFFECTIVENESS

Prospective studies have evaluated the efficacy and immunogenicity of influenza vaccines in children [26, 52–54]. In general, children >2 years of age respond well to influenza vaccine, with a significant increase in antibody response in children <9 years of age after the second dose of vaccine [24]. By contrast, fewer immunogenicity data from clinical trials are available in children <2 years of age [27, 55]. Studies have demonstrated that children 2–6 years old who lack detectable baseline anti-influenza antibody levels (measured through hemagglutination inhibition assay) have lower antibody responses to influenza vaccine [52]. Furthermore, antibody responses in children to influenza B antigens in vaccine [56] or after wild-type influenza B virus infection [4] can be substantially lower than responses to influenza A antigens. Low serum antibody responses to influenza B, both vaccine-induced and infection-induced, are relatively common in young children.

The clinical effectiveness of influenza vaccines varies by year and setting. This variability can be challenging to interpret and is driven by a number of factors. It is related in part to virus dynamics, including both vaccine match to circulating viruses and the overall influenza attack rate in the study population during the study period. Elements in the study design including the specificity of the outcome measured and the sensitivity of any diagnostic tests used also play important roles in the final effectiveness estimate. Overall, vaccines are most effective in reducing laboratory-confirmed influenza infection versus outcomes such as nonspecific respiratory illness or school absenteeism. There may also be different patterns of effectiveness against severe (ie, hospitalizations) versus mild infections, although these patterns are not well understood. A number of meta-analyses have attempted to systematically review and summarize these disparate findings [57–62]. These reviews found evidence of improved protection from LAIV versus IIV in pediatric populations >2 years of age, but they also cited the need for better data, particularly from randomized controlled trials, in the youngest age groups.

The estimated efficacy of trivalent IIV in children, derived from randomized controlled trials (RCTs) with laboratory-confirmed influenza outcomes, generally ranges from 43% to 91%, although no significant effect has been observed in some years with low influenza attack rates, such as during 2000–2001 [63] (Table 1). Because IIV is now recommended for all children in the United States, placebo-controlled RCTs of IIV are no longer feasible in this country, and assessment of effectiveness of vaccines has relied heavily on observational studies. In particular, case-control studies from the 2003–2004 influenza season demonstrated the impact of poor match between vaccine and circulating strains in a year with high rates of influenza disease when no RCT data were available. During that year, overall vaccine effectiveness (VE) estimates were lower, with notable decreased effectiveness among children 6–23 months of age versus those aged 24–59 months [64–67].

Data published to date indicate that both LAIV and adjuvanted IIV may be more efficacious than IIV in healthy preschool- and school-aged children, even from a single dose and against drifted virus strains. Live-attenuated influenza vaccine efficacy estimates range from 64% to 93%, including years with mismatched strains (Table 1). This range suggests greater heterotypic protection from LAIV compared with IIV in children. Some data also suggest that a single dose of LAIV may provide sufficient protection in this immunologically naive population [30, 68]. However, there are a limited number of studies that directly compare IIV and LAIV in the same population (Table 2). These studies demonstrated up to a 55% reduction in laboratory-confirmed influenza among children receiving LAIV compared with IIV, including children with asthma or recurrent respiratory tract infections. The relative efficacy of LAIV versus IIV is less clear for less specific outcome measures such as school absenteeism. The data suggesting increased protection from LAIV in children are different from what is observed in adults, for whom available data suggest equal or slightly lower VE conferred by LAIV compared with IIV [69]. However, the age at which protection afforded by IIV outweighs that of LAIV remains unclear.

Adjuvanted vaccines, which are not licensed in the United States, have only limited efficacy data available. One RCT found that trivalent IIV containing the MF-59 adjuvant (an oil-in-water emulsion) was 86% effective in reducing influenza infections in children 6–72 months of age [51].

## SPECIAL PEDIATRIC POPULATIONS

Children <2 years of age are at high risk for severe influenza and complications, but they have fewer vaccine options

**Table 1.** Randomized Controlled Trials of Influenza Vaccine Effectiveness in Children, by Vaccine Type

| Reference | Time Frame | Age Range | Outcome Measured | VE Estimate | Comments |
|---|---|---|---|---|---|
| **Inactivated Influenza Vaccines** | | | | | |
| Gruber et al 1990 [96] | 1985–86 | 3–18 years | Culture-confirmed influenza[a] | 62% | Single dose of vaccine given. B-only year. Study also had bivalent LAIV arm. Outcomes assessed by seroconversion are a possible source of bias. |
| Clover et al 1991 [97] | 1986–87 | 3–18 years | Culture-confirmed influenza[a] | 62% | Single dose of vaccine given. A-only year. Year 2 of Gruber et al 1990 [96]. Outcomes assessed by seroconversion are a possible source of bias. |
| Neuzil et al 2001 [26] | 1985–90 | 1–16 years | Culture-confirmed influenza | 91% (H1N1-pred. years)<br>77% (H3N2-pred. years) | VE increased by age group. Influenza A bivalent vaccines used Year 1. |
| Khan et al 1996 [98] | 1991–92 | 9–12 years | School absenteeism | 56% (absenteeism) | No laboratory confirmation of influenza. Study also had LAIV arm. |
| Colombo et al 2001 [99] | 1995–96 | 1–6 years | ILI | 67% (ILI) | No laboratory confirmation of influenza. ILI data collected during influenza season. |
| Hoberman et al 2003 [63] | 1999–2000<br>2000–01 | 6–24 months | Culture-confirmed influenza (AOM) | 66% (1999–2000)<br>– 7% (2000–01) | Low influenza attack rate in both study arms in Year 2. |
| Jansen et al 2008 [28] | 2003–05 | 18–72 months | PCR-confirmed influenza | 51% (IIV + PCV)<br>52% (IIV alone) | Study of IIV + PCV, IIV alone, or placebo. Also looked at reduction in febrile respiratory illness. |
| Vesikari et al 2011 [51] | 2007–08<br>2008–09 | 6–72 months | PCR-confirmed influenza | 43% (overall)<br>45% (strain-matched) | H3N2-predominant. Study also had adjuvanted IIV arm. |
| Loeb et al 2010 [88] | 2008–09 | 36 months – 15 years | PCR-confirmed influenza | 59% | Cluster randomized. Study population of Hutterite communities. |
| **Adjuvanted Inactivated Influenza Vaccines** | | | | | |
| Marchisio et al 2002 [100] | 1999–2000 | 1–5 years | AOM and respiratory illness (among children with recurrent AOM) | 13% (respiratory illness)<br>39% (AOM) | Virosomal-adjuvanted intranasal IIV. H3N2-predominant season. |
| Esposito et al 2003 [89] | 2000–01 | 6 months–9 years | URIs, hospitalizations, and school absenteeism | 27% (URIs)<br>60% (hospitalizations)<br>61% (school absenteeism) | Virosomal-adjuvanted intranasal IIV. H1N1-predominant season. Also VE of 39% in reducing medical visits among household contacts. |
| Principi et al 2003 [101] | 2001–02 | 6 months–5 years | URIs, hospitalizations, and school absenteeism | 33% (URIs)<br>50% (hospitalizations)<br>48% (school absenteeism) | Virosomal-adjuvanted intramuscular IIV. Indirect effects also reported. |
| Vesikari et al 2011 [51] | 2007–08<br>2008–09 | 6–72 months | PCR-confirmed influenza | 86% | H3N2-pred. Study also had unadjuvanted IIV arm. |
| **Live-Attenuated Influenza Vaccines** | | | | | |
| Khan et al 1996 [98] | 1991–92 | 9–12 years | School absenteeism | 47% (absenteeism) | No laboratory confirmation of influenza. Study also had unadjuvanted IIV arm. |
| Belshe et al 1998 [30] | 1996–97 | 15–71 months | Culture-confirmed influenza | 93% (overall)<br>89% (1 dose)<br>94% (2 doses) | High VE in all age groups. Also 30% VE in reducing acute otitis media. |

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|---|---|---|---|---|---|
| Belshe et al 2000 [68] | 1997–98 | 26–85 months | Culture-confirmed influenza | 87% | Protection provided by vaccine during mismatched year, H3N2 and B-predominant. Year 2 of Belshe et al 1998 [30]. |
| Tam et al 2007 [102] | 2000–03 | 12–36 months | Culture-confirmed influenza | 70% (Year 1)<br>64% (Year 2) | Protection against strain-matched infections: 73% (Year 1), 84% (Year 2). |
| Vesikari et al 2006 [74] | 2000–02 | 6–36 months | Culture-confirmed influenza | 85% (Year 1)<br>89% (Year 2) | Highest VE for both years against H1N1 and H3N2 (slightly lower for B). |
| Bracco Neto et al 2009 [103] | 2001–03 | 6–36 months | Culture-confirmed influenza | 74% (Year 1)<br>74% (Year 2) | VE for single dose was 58% (Year 1) and 65% (Year 2) in this age group. |

Abbreviations: AOM, acute otitis media; IIV, inactivated influenza vaccines; ILI, Influenza-like illness; LAIV, live-attenuated influenza vaccines; PCR, polymerase chain reaction; PCV, pneumococcal conjugate vaccine; pred., predominant; URI, Upper respiratory tract infection; VE, vaccine effectiveness.

[a]In absence of virus isolation, outcome of influenza infection was also assumed among individuals with a postseason serum antibody rise if no other virus was detected and if illness occurred either within 10 days of isolate from same household or during period of intense virus activity in community.

**Table 2.** Relative Effectiveness Studies of Inactivated and Live-Attenuated Influenza Vaccines in Children

| Reference | Time Frame | Age Range | Outcome Measured | Findings (Effectiveness) | Findings (Safety) |
|---|---|---|---|---|---|
| **Healthy Children** | | | | | |
| Khan et al 1996 [98] | 1991–92 | 9–12 years | School absenteeism | 18% reduction in absenteeism among IIV recipients (vs LAIV) | Minimal adverse reactions to both vaccines. |
| Belshe et al 2007 [37] | 2004–05 | 6–59 months | Culture-confirmed influenza | 55% reduction in laboratory-confirmed influenza among LAIV recipients (vs IIV) | Significant increase of medically attended wheezing among LAIV recipients <11 months. |
| **High-Risk Children** | | | | | |
| Ashkenazi et al 2006 [40] | 2002–03 | 6–71 months | Culture-confirmed influenza (children with recurrent respiratory infection) | 53% reduction in laboratory-confirmed influenza among LAIV recipients (vs IIV) | No significant difference between groups in incidence of wheezing after vaccination. |
| Fleming et al 2006 [39] | 2002–03 | 6–17 years | Culture-confirmed influenza (children with asthma) | 35% reduction in laboratory-confirmed influenza among LAIV recipients (vs IIV) | No significant difference between groups in risk of adverse pulmonary outcomes after vaccination. |

Abbreviations: IIV, inactivated influenza vaccines; LAIV, live-attenuated influenza vaccines.

than older children. Limited age-specific efficacy data for children 6–24 months or 6–36 months of age indicate that IIV provides comparable protection in this age group to that in older children during study years when the vaccine is well matched to circulating viruses. Hoberman et al [63] found IIV to be 66% efficacious among children 6–24 months, during study years with sufficient data to calculate an estimate. Vesikari et al [51] found a point estimate of 40% efficacy for IIV among those 6–35 months of age compared to 45% among those 36–71 months in the same study, but the study was not sufficiently powered to detect a significant difference. Additional data from observational studies demonstrated that although IIVs can be effective in this age group, VE is related to how closely vaccines are matched against circulating strains [64–67, 70–73]. For example, during the mismatched 2003–2004 season in the United States, VE point estimates were 66% in children 24–59 months and 28% in children 6–23 months of age [64]. Limited data suggest that LAIV and adjuvanted IIV may provide better protection than IIV in younger children, although these vaccines are not currently available for use in this age group. In the same study that found IIV to have a VE of 40% among children 6–35 months [51], the MF-59 adjuvanted IIV was found to be 79% effective in preventing influenza infection in this age group. A single RCT in Europe examining LAIV in children 6–35 months of age reported an effectiveness of 84%–85% [74].

Currently available influenza vaccines are not licensed for use in infants <6 months of age, although safety and immunogenicity in infants as young as 2 months of age have been demonstrated [75]. However, young infants can potentially be protected from influenza infection via transplacentally acquired antibodies if their mothers are vaccinated during pregnancy. Observational data from the United States estimated that infants of vaccinated mothers are 41%–48% less likely to be hospitalized with laboratory-confirmed influenza than infants of unvaccinated mothers [76, 77]. An RCT in Bangladesh estimated that vaccinating pregnant women had an efficacy of 69% against laboratory-confirmed influenza in infants followed for 24 weeks after delivery [78]. The American College of Obstetricians and Gynecologists recommends that IIV be considered an essential element of prenatal care, based on the increased risk of serious influenza illness facing pregnant women [79]. Analyses of data from both IIV and adjuvanted IIV in pregnant women have consistently demonstrated safety for the pregnant woman and her infant, with protection against mortality noted in retrospective trials during the 2009 pandemic period [80, 81].

In children with underlying diseases, LAIV is not recommended despite data suggesting its safety in populations such as children with cancer [82]. In addition, RCTs of IIV are not generally conducted in high-risk children with chronic diseases or immunosuppression, because these children have long been recommended to receive influenza vaccine. However, limited available data suggest that both IIV and LAIV are effective in children with asthma or chronic respiratory illness, and that LAIV may provide superior protection (Table 2). Although serum antibody responses among children with asthma are similar to those of healthy children, including during acute exacerbations [83], antibody responses among very young children with other high-risk medical conditions may be decreased compared with children without high-risk medical conditions [84].

## IMPACT OF VACCINATING CHILDREN

Vaccinating children can reduce influenza-related illnesses at the community, school, or household level, due to indirect effects or herd immunity [85–89]. In Canada, vaccinating children 3–15 years of age resulted in a community-level VE of 59% against polymerase chain reaction (PCR)–confirmed influenza, compared with communities where children received hepatitis A vaccine as a control [88]. In a US study, provision of LAIV to all eligible children, resulting in a school-wide vaccine coverage of 48%, was associated with significant decreases in medically attended acute respiratory illness rates among adults in the community, despite a mismatch between vaccine and circulating strains [85]. These findings have been replicated over several years [86, 87], and they are consistent with early studies suggestive of the role of children in transmitting influenza in the community [90]. School-based immunization with LAIV has led to reductions in influenza in both vaccinated children and members of their households as well as decreased illness-associated expenditures and adult work-days lost [91]. At the household level, Esposito et al [89] detected significant declines in respiratory tract infections, medical visits, and school or work absenteeism among parents and siblings of children vaccinated with IIV compared with a control group.

The economic impacts of vaccinating children vary by study, age group, and vaccine type. An analysis from the United States using an outcome measure of Quality-Adjusted Life Years identified vaccination of high-risk children as cost-saving, and it found that vaccinating children 6–23 months of age was more cost-effective than vaccinating older children. Because lost productivity due to vaccine-related medical visits can impact cost-effectiveness, additional studies have suggested improving the cost-effectiveness of vaccination by using group-based vaccination approaches or flexible-schedule vaccination clinics [92, 93]. In Canada,

LAIV demonstrated improved cost-effectiveness versus IIV; these data were used to support the preference for LAIV in eligible children in that country [94].

## FUTURE OF INFLUENZA VACCINES IN CHILDREN

Both inactivated and live-attenuated quadrivalent vaccines will be introduced in the 2013–2014 influenza season. These vaccines contain 2 influenza B viruses instead of 1 (representing each of the 2 circulating antigenic lineages of influenza B viruses). Modeling studies suggest that this change alone could result in a modest reduction of influenza-associated disease burden [95].

At this time, adjuvanted vaccines are not widely available, but limited data suggest potentially enhanced antibody response and effectiveness compared with unadjuvanted IIV. The potential for adjuvanted IIV to provide longer duration of protection compared with IIV could offer additional benefits to children in tropical countries, where influenza viruses circulate year-round or have multiple epidemic peaks each year.

Future directions for influenza vaccination include the development of "universal" vaccines that can provide protection against multiple virus strains, potentially with only 1 dose or with protection over multiple years. Vaccines containing a common antigen should provide broader protection against a wider array of influenza viruses.

In addition to improvements related to vaccine products, research that addresses key knowledge gaps in VE is essential. These gaps include the relative VE of LAIV and adjuvanted IIV in young children versus older children, a better estimate of VE among children with high-risk medical conditions, and improved standard methods for classifying "matched" and "mismatched" virus strains. Increased use of PCR-based influenza diagnostics allows researchers the opportunity to use highly specific laboratory-confirmed influenza outcomes, versus culture- or serology-based influenza diagnostics. This expanded diagnostic capacity generates an opportunity for new studies as well as broader collaborations that can generate comparable estimates of VE, both to refine existing vaccine products and to determine the relative benefits of new vaccines in the United States and other settings.

Increasing vaccine coverage in children with currently available vaccines offers the best opportunity for improved influenza control at this time. In addition, protection of young children below the recommended age for vaccination will continue to depend on vaccination programs for pregnant women and other household members of infants, to prevent transmission to this especially vulnerable group of children.

## Acknowledgments

We acknowledge the Influenza-Associated Pediatric Mortality Surveillance System and the Influenza Hospitalizations Surveillance Network (FluSurv-NET) for their surveillance efforts and data contribution. The FluSurv-NET is a collaboration of state health departments, academic institutions, and local partners, and is funded by the CDC.

***Disclaimer.*** The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

***Financial support.*** J. A. E. received research support from Novartis, Gilead, and Chimerix; and provided consulting services to GlaxoSmithKline.

***Potential conflicts of interest.*** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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