American Academy of Pediatrics
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POLICY STATEMENT

Prevention of Influenza: Recommendations for Influenza Immunization of Children, 2007–2008

Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of All Children

Committee on Infectious Diseases

ABSTRACT

The American Academy of Pediatrics recommends annual influenza immunization for all children with high-risk conditions who are 6 months of age and older, for all healthy children ages 6 through 59 months, for all household contacts and out-of-home caregivers of children with high-risk conditions and of healthy children younger than 5 years, and for all health care professionals.

To more fully protect against the morbidity and mortality of influenza, increased efforts are needed to identify and immunize all children at high risk and all healthy children ages 6 through 59 months and to inform their parents when annual immunizations are due. Previously unimmunized children who are at least 6 months of age but younger than 9 years should receive 2 doses of influenza vaccine, given 1 month apart, beginning as soon as possible on the basis of local availability during the influenza season. If children in this cohort received only 1 dose for the first time in the previous season, it is recommended that 2 doses be administered in the current season. This recommendation applies only to the influenza season that follows the first year that a child younger than 9 years receives influenza vaccine. A child who then also fails to receive 2 doses the next year should be given only 1 dose per year from that point on. Influenza vaccine should also continue to be offered throughout the influenza season, even after influenza activity has been documented in a community.

On the basis of global surveillance of circulating virus strains, the influenza vaccine may change from year to year; indeed, 1 of the 3 strains in the 2007–2008 vaccine is different from the previous year's vaccine. All health care professionals, influenza campaign organizers, and public health agencies should develop plans for expanding outreach and infrastructure to immunize all children for whom influenza vaccine is recommended. Appropriate prioritization of administering influenza vaccine will also be necessary when vaccine supplies are delayed or limited. Because the influenza season often extends into March, immunization against influenza is recommended to continue through late winter and early spring. Lastly, it is recommended that for the 2007–2008 season, and likely beyond, health care professionals do not prescribe amantadine or rimantadine for influenza treatment or chemoprophylaxis, because widespread resistance to these antiviral medications now exists among influenza A viral strains. However, oseltamivir and zanamivir can be prescribed for treatment or chemoprophylaxis, because influenza A and B strains remain susceptible.

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Key Words
influenza, immunization, live-attenuated influenza vaccine, trivalent inactivated influenza vaccine, vaccine, children, pediatrics

Abbreviations
AAP—American Academy of Pediatrics
CDC—Centers for Disease Control and Prevention
LAIV—live-attenuated influenza vaccine
TIV—trivalent inactivated influenza vaccine
ILI—influenza-like illness
HAI— hemagglutinin-inhibition
GBS—Guillain-Barré syndrome

PURPOSE OF RECOMMENDATIONS AND RATIONALE

The purpose of this statement is to update the current recommendations for routine use of influenza vaccine in children, which were originally published in a condensed format in April 2007.[1] Highlights include (1) harmonization of the recommendation of the American Academy of Pediatrics (AAP) and the Centers for Disease Control and Prevention (CDC) that children younger than 9 years receive 2 doses of influenza vaccine in their second season of immunization if they only received 1 dose in the previous season; and (2) additional detail on the recommended storage, dosage, and administration of live-attenuated influenza vaccine (LAIV), including the recent licensure of LAIV for children as young as 2 years.

The continued expansion of the recommendations on influenza vaccine use among children in the United States is based on several considerations. Young children are at serious risk of influenza infection, hospitalization, and complications. The risk of influenza-associated hospitalization in healthy children younger than 24 months has been shown to be equal to or greater than the risk in previously recognized high-risk groups. Young children are at higher

TABLE 1 **Estimated Influenza-Associated Hospitalization Rates, Selected Studies**

Study Years	Population	Age Group	Hospitalization Rates (Per 100 000 People)	
			In Previously Recognized High-Risk Group	Not in Previously Recognized High-Risk Group
1973–1993[7,35]	Tennessee Medicaid	0–11 mo, 1–2 y, 3–4 y, 5–14 y	1900, 800, 320, 93	496 (6–11 mo) to 1038 (0–5 mo), 186, 86, 41
1974–1999[16]	Vaccine clinic	<2 y	—	200–300
1992–1997[8]	Health maintenance organizations	0–23 mo, 2–4 y, 5–17 y	—	144–187, 0–25, 8–12
1968–1973[35]	Health maintenance organization	15–44 y, 45–64 y, ≥65 y	56–110, 392–635, 399–518	23–25, 13–23
1969–1995[90]	National hospital discharge data	<65 y, ≥65 y	—	20–42, 125–228
2000–2001[39]	Two counties	<1 y, 1 y, 2 to <5 y	—	170, 50, 20
2001–2004[39,40]	Large children's hospital	≤6 mo, 6–11 mo, 1 to <2 y, 2 to <3 y	—	253, 113, 96, 36
2000–2004[8]	Three counties	≤6 mo, 6–23 mo, 24–59 mo	—	240, 60, 20
2003–2004[41]	9 States	≤6 mo, 6–23 mo	311, 118	—
1994–2000[100]	Health maintenance organization	6–23 mo, 2–4 y	213, 142	51, 32
2000–2004[98,106]	Large children's hospital	0–23 mo, 2–4 y, 5–11 y, 12–17 y	—	416, 70, 19, 18

— indicates data not available.

(Adapted with permission from Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices, 2007. *MMWR Recomm Rep*. 2007;56[RR-6]:6).

risk of hospitalization for influenza infection than are healthy 50- to 64-year-old adults, for whom routine immunization has been recommended since 2000.[2] High rates of hospitalization of infants and young children during influenza seasons have been appreciated for decades[3–5] (Table 1), but it has been difficult to determine the proportion of hospitalizations during influenza season attributable to respiratory syncytial virus and other respiratory tract viruses. Several studies have attempted to separate the relative contributions of respiratory syncytial virus and influenza to the hospitalization rate.[6–8] Influenza hospitalization rates vary among studies (190–480 per 100 000 population) because of differences in methodology and severity of influenza seasons. However, children younger than 24 months are consistently at substantially higher risk of hospitalization than are older children, and the risk of hospitalization attributable to influenza infection is highest in the youngest children. Children 24 through 59 months of age experience increased morbidity attributable to influenza illness, with increased rates of outpatient visits and use of antibiotics.[7–12]

Community studies indicate that school-aged children have had the highest rates of influenza infection, with annual attack rates as high as 42% demonstrated in prospective surveillance studies.[6,13] During various annual influenza seasons, rates of outpatient visits attributable to influenza vary from 6 to 29 per 100 children.[5] Influenza is also important in the pathogenesis of acute otitis media during influenza seasons.[14] Annually, 3% to 5% of children are estimated to experience acute otitis media associated with influenza.[6,15,16] Influenza and its complications have been reported to result in a 10% to 30% increase in the number of antimicrobial courses prescribed to children during the influenza season.[5,6] Antecedent influenza infection is sometimes associated with development of pneumococcal and staphylococcal pneumonia in children.[17,18] Methicillin-resistant staphylococcal community-acquired pneumonia, with a rapid clinical progression and a high fatality rate, has been reported in previously healthy children and adults with concomitant influenza infection.[18] This, combined with the aforementioned high rates of influenza-associated hospitalization among children ages 6 through 23 months, indicates a need to include more young healthy children in annual immunization efforts.[5,12]

Well-designed studies support the recommendation of giving 2 doses rather than 1 to vaccine-naïve children who are at least 6 months of age but younger than 9 years (strong recommendation; evidence grade B [see Appendices 1 and 2 for definitions of evidence grades]).[19–21] Among children younger than 9 years who have never received influenza vaccine previously and who receive only 1 dose of influenza vaccine in their first year of vaccination, vaccine effectiveness is lower compared with children who receive 2 doses in their first year of being vaccinated. Unfortunately, the proportion of children who are fully immunized in their first year of influenza vaccination is low. In the 2005–2006 influenza season, only 1 of 5 children 6 through 23 months of age was fully immunized, and only 1 of 10 children needing 2 doses received both doses.[22] More recent coverage data from 6 immunization information system sentinel sites (vaccine registries) indicated that coverage levels for the 2006–2007 influenza season did not increase at 5 of 6 sites compared with the 2005–2006 influenza season and remained below 28% at all 6 sites. Among 24- to 59-month-olds at the 6 sites, 1.9% to 18.1% were fully immunized during the 2006–2007 influenza season,[23] the first season during which routine immunization of 24- to 59-month-olds was recommended.

Two recent, large retrospective studies of previously unimmunized children who had received 1 dose of trivalent inactivated influenza vaccine (TIV) determined that no substantial decrease had occurred in office visits related to influenza-like illness (ILI) compared with unimmunized children.[21,24] Similar results were reported in a case-control study of children 6 to 59 months of age.[25]

Although the efficacy of TIV and LAIV vary depending on recipient age, dosage, and antigenic similarity

between circulating and vaccine strains, both vaccines are cost-effective strategies for preventing influenza among children and their families when circulating and vaccine strains are identical. Both TIV and LAIV have been demonstrated to be effective in children and adults, but data directly comparing the efficacy or effectiveness of these 2 types of vaccines are limited, with studies having been conducted in a variety of settings and populations using several different clinical end points. Limited data suggest that LAIV, which has recently been approved for healthy individuals 2 years and older, provides greater protection than TIV for young children: LAIV provided 52% increased protection among children 6 to 71 months of age with recurrent respiratory tract infections.[26] Another study conducted among children 6 to 59 months of age during the 2004–2005 influenza season demonstrated a 55% reduction in cases of culture-confirmed influenza among children who received LAIV, compared with those who received TIV.[27]

Although immunization against influenza early in life may not prevent all cases of infection, the current policy is expected to further decrease morbidity and mortality associated with this virus.[28] It is hoped that broader routine influenza immunization will also reduce the financial costs attributable to influenza among people of all ages while improving the health of all children and families. Many consider this paradigm to represent a step toward universal annual influenza immunization in the United States.

EPIDEMIOLOGY OF INFLUENZA

Influenza is spread from person to person primarily by droplets of respiratory secretions expelled by coughing or sneezing but can also be spread by direct contact with influenza virus-contaminated surfaces. During community outbreaks of influenza, the highest attack rates occur among school-aged children. Secondary spread to adults and other children within a family is common. Incidence depends in part on immunity developed by previous experience (with natural disease) or recent influenza immunization with the circulating strain or a related strain. Immunity to the virus' surface antigens (hemagglutinin and neuraminidase) reduces the likelihood of infection and severity of disease if infection occurs.[29] Antibody against 1 influenza virus type or subtype confers limited or no protection against another type or subtype of influenza. Furthermore, antibody to 1 antigenic variant of influenza virus might not completely protect against a new antigenic variant of the same type or subtype.[30] Antigenic drift in the circulating strain(s) is a minor change in structure and is associated with seasonal epidemics. In temperate climates, seasonal epidemics usually occur during winter months. Antigenic shift (major changes in antigenic structure) is often associated with worldwide pandemics, because infection with previously circulating strains confers virtually no protection against the new strain of circulating virus.

Once influenza activity begins, community outbreaks can last 4 to 8 weeks or longer. People can spread infection 24 hours before symptoms manifest, peaking in viral shedding through nasal secretions during the first 3 days of the illness. Viral shedding directly correlates with the level of fever, however, and can be significantly prolonged in younger children and immunodeficient people.[31] Because of the highly contagious nature of influenza, infected children easily spread the disease to adults and other children within a family or a community.[28,31]

Rates of infection are highest among children, but rates of serious illness and death are highest among people 65 years and older, children younger than 2 years, and people of any age who have medical conditions that place them at increased risk of having complications from influenza.[3,32–34] The attack rate among children has been estimated at 10% to 40% annually, with approximately 1% of infections resulting in hospitalization.[6,14,35–37] Rates of emergency department visits and hospitalizations attributable to influenza infection are especially high for otherwise healthy children younger than 5 years, with rates for children younger than 2 years substantially greater than rates for children 2 years and older.[12,13,35] From 1979 to 2001, the estimated rate of influenza-associated hospitalizations in the United States among children younger than 5 years was approximately 108 per 100 000 person-years.[11] Recent population-based studies that have measured hospitalization rates for laboratory-confirmed influenza in young children have been consistent with studies that analyzed medical discharge data.[6,9,38–40] Annual hospitalization rates for laboratory-confirmed influenza in these studies decreased with age, ranging from 240 to 720 per 100 000 healthy children younger than 6 months to 17 to 45 per 100 000 for children 2 to 5 years of age. [6,38–41] Estimated hospitalization rates for children with high-risk medical conditions are approximately 500 per 100 000 children, and in 1 study, 37% of admissions occurred in children with medical conditions.[7,8,11,40] Population-based studies among hospitalized children with laboratory-confirmed influenza have demonstrated that although the majority of hospitalizations are brief (≤2 days), 4% to 15% of children hospitalized with laboratory-confirmed influenza required treatment in the ICU, and 3% required mechanical ventilation.[38,41] Among 1308 hospitalized children in 1 study, 80% were younger than 5 years, and 27% were younger than 6 months.[41]

There is also a high incidence of outpatient visits for influenza illness for children 23 to 59 months of age, with visit rates of 80 to 150 per 1000 children each year.[7–12] Otitis media, nausea, and vomiting also are commonly associated with influenza illness.[6,42,43] Influenza virus infections can cause primary influenza viral pneumonia; exacerbate underlying medical conditions (eg, pulmonary or cardiac disease); lead to secondary bacterial pneumonia, sinusitis, otitis, croup, or wheezing; or contribute to coinfections with other viral or bacterial pathogens.[39,41,44] These specific complications have occurred at a rate between 0.2% and 25% in past years.[35] The risks of hospitalization and morbidity associated with these complications are increased if children also have serious and chronic illnesses, such as hemoglobinopathies, bronchopulmonary dysplasia, asthma,

cystic fibrosis, malignancy, diabetes mellitus, chronic renal disease, or congenital heart disease.

Deaths attributable to influenza are far less common in children than in the elderly. A study that modeled influenza-related deaths estimated that each year during the 1990s, an average of 92 deaths (0.4 deaths per 100 000) occurred among children younger than 5 years, compared with 32 651 deaths (98.3 per 100 000) among adults 65 years or older.[45] For both chronically ill and otherwise healthy children, however, fatal outcomes can occur. Of 153 laboratory-confirmed influenza-related pediatric deaths reported from 40 states during the 2003–2004 influenza season, 96 (63%) were children younger than 5 years and 61 (40%) were children younger than 2 years. Among the 149 children who died and for whom information on underlying health status was available, 100 (67%) did not have an underlying medical condition that was an indication for immunization at that time.[46] In California during the 2003–2004 and 2004–2005 influenza seasons, 51% of children with laboratory-confirmed influenza who died and 40% of those who required admission to an ICU had no underlying medical conditions.[10] These data indicate that although deaths are more frequent among children with risk factors for influenza complications, most pediatric deaths occur among children with no known high-risk conditions. In a single center throughout 3 consecutive influenza seasons, the mortality rate for children hospitalized with laboratory-confirmed influenza was 0.6% (2 of 325) and for all laboratory-confirmed influenza was 0.1% (2 of 1176).[40]

The annual number of influenza-related deaths among children reported to the CDC for the past 3 influenza seasons has ranged from 44 during 2004–2005 to 68 during 2006–2007.[47] During the 2006–2007 season, among people younger than 18 years, of 53 patients 6 months or older for whom immunization status was known, 50 (94%) had not been immunized against influenza. Although influenza-related deaths are not common, it is felt that many of them are potentially preventable by immunization.

Although serious morbidity and mortality can result from influenza infection in any person, the risk of complications is increased among pregnant women,[48] individuals with underlying chronic cardiopulmonary conditions,[37,49] individuals with certain neuromuscular conditions,[50] and immunocompromised people.[51,52] Viral shedding can last for weeks or months, a much longer period of time than the average child or adult might experience. These groups are also more likely to experience symptoms on a more severe level and for a prolonged period of time.[48,53–55]

CLINICAL MANIFESTATIONS OF INFLUENZA

The influenza virus generally requires an incubation period of 1 to 4 days, with an average of 2 days.[56] When symptoms of the disease manifest, the typical influenza patient experiences a sudden onset of fever, chills or rigors, headache, malaise, diffuse myalgia, and nonproductive cough. Other common signs of the disease involve the respiratory tract, ranging from sore throat and nasal congestion to rhinitis and prominent coughing. More infrequently, conjunctival infection, abdominal pain, nausea, vomiting, and diarrhea have been reported in relation to influenza illness.[35] Young children are less likely to report typical influenza symptoms. Adults who are infected with influenza virus can be contagious from the day before symptoms begin through the sixth day after onset of symptoms.[56] Uncomplicated influenza illness typically resolves after 3 to 7 days for the majority of people, although cough and malaise can persist for more than 2 weeks.

Young children can also be infectious before symptoms begin and for as many as 10 days after onset of symptoms. Influenza is commonly characterized in children by otitis media, nausea, and vomiting in addition to the other general symptoms described above.[6,42,43] In some children, influenza may appear as an upper respiratory tract infection or febrile illness with few respiratory tract symptoms. In infants, the disease can initially present signs similar to those of bacterial sepsis, high fever, or febrile seizures; studies have reported that up to 20% of children who are hospitalized for influenza infection experience febrile seizures.[38,43,44,57] In addition, influenza illness has been known to occasionally develop into croup, bronchiolitis, or pneumonia.[35] Although uncommon, other events that have been associated with influenza infection in children include encephalopathy, transverse myelitis, myositis, myocarditis, pericarditis, and Reye syndrome.[43,44,58,59] Respiratory illnesses caused by influenza viruses are difficult to distinguish from illnesses caused by other respiratory pathogens on the basis of signs and symptoms alone. Sensitivity (ie, amount of false-negative results) and predictive value of clinical definitions can vary, depending on the extent of other respiratory pathogens circulating in the community at the same time and the local level of influenza activity.[60] These results highlight the challenges of identifying influenza illness in the absence of laboratory confirmation.

VACCINES

Description

Tables 2 and 3 summarize information on the 2 types of influenza vaccine used to immunize both children and adults (LAIV and TIV) and the age group in which each available preparation is licensed to be used. Both contain strains of influenza A subtypes H1N1 and H3N2 and influenza B, which are selected annually on the basis of the viruses anticipated for circulation during the upcoming influenza season. The 2007–2008 vaccine virus strains are A/Solomon Islands/3/2006 (H1N1)-like (new for this season), A/Wisconsin/67/2005 (H3N2)-like, and B/Malaysia/2506/2004-like antigens.[47]

TIV is an inactivated vaccine that contains killed viruses and, therefore, cannot produce an active virus infection. However, hypothetically, this killed vaccine might produce mild influenza-like symptoms by inducing some of the same cytokines associated with the

TABLE 2 **Comparison of LAIV and TIV**

Element	LAIV	TIV
Route of administration	Intranasal spray	Intramuscular injection
Type of vaccine	Live virus	Killed virus
Product	Attenuated, cold-adapted	Inactivated subvirion or surface antigen
No. of included virus strains	3 (2 influenza A, 1 influenza B)	3 (2 influenza A, 1 influenza B)
Vaccine virus strains updated	Annually	Annually
Frequency of administration[a]	Annually	Annually
Approved age and risk groups	Healthy people 2–49 y of age	People ≥6 mo
Interval between 2 doses in children	4 wk	4 wk
Can be simultaneously administered with other vaccines	Yes[b]	Yes[c]
If not simultaneously administered,		
Can be administered within 4 wk of another live vaccine	No, prudent to space 4 wk apart	Yes
Can be administered within 4 wk of an inactivated vaccine	Yes	Yes

[a] Two doses may be needed for children <9 years of age, depending on individual circumstances.
[b] No data are available regarding effect on safety or efficacy.
[c] TIV coadministration has been evaluated systematically only among adults with pneumococcal polysaccharide vaccine.

known symptoms of influenza disease. TIV is administered intramuscularly to individuals who are 6 months and older, including those who are healthy and those with chronic medical conditions. LAIV is a live-attenuated vaccine that is administered intranasally and is currently licensed by the Food and Drug Administration for use in healthy individuals 2 through 49 years of age. LAIV has the potential to produce mild signs or symptoms related to influenza virus infection. Because viruses for both vaccines are grown in eggs, neither should be administered to anyone with known allergic reactions (ie, hives, angioedema, allergic asthma, and systemic anaphylaxis) to chicken, egg proteins, or any other component of the vaccines. Less severe or local manifestations of allergy to egg or feathers are not contraindications to administration of influenza vaccine.[35]

Immunogenicity

It has been consistently shown that seroconversion rates to TIV increase with the age of the child receiving immunization, ranging from 70% to 100% by adolescence.[61,62] In 1 study in which 2 doses of TIV were administered to children between 6 and 24 months of age in 2 different influenza seasons, between 89% and 97% of the children in the 2 cohorts were considered seroprotected, as measured by a hemagglutinin-inhibition (HAI) titer of more than or equal to 1:40 and/or a fourfold increase in antibody to influenza A(H1N1), A(H3N2), and B.[63] Positive results have been similarly shown with the use of LAIV. Because LAIV is a live-attenuated vaccine, the resulting immune response is more likely to achieve a level of immunity that would be

TABLE 3 **Influenza Vaccines Licensed for Use in Different Age Groups—United States, 2007–2008 Season**

Vaccine	Trade Name	Manufacturer	Dose/Presentation	Thimerosal Mercury Content (μg of Hg/0.5-mL dose)	Age Group
Inactivated					
TIV	Fluzone	Sanofi Pasteur	0.25-mL prefilled syringe	0	6–35 mo
			0.5-mL prefilled syringe	0	≥36 mo
			0.5-mL vial	0	≥36 mo
			5.0-mL multidose vial	25	≥6 mo
TIV	Fluvirin	Novartis (formerly Chiron) (Cambridge, MA)	0.5-mL prefilled syringe	<1.0	≥4 y
TIV	Fluvirin	Novartis (formerly Chiron) (Cambridge, MA)	5.0-mL multidose vial	24.5	≥4 y
TIV	Fluarix	GlaxoSmithKline (Rixensart, Belgium)	0.5-mL prefilled syringe	<1.25	≥18 y
TIV	FluLaval	GlaxoSmithKline	5.0-mL multidose vial	25	≥18 y
TIV	Afluria	CSL Limited (Parkville, Victoria, Australia)	0.5-mL prefilled syringe	0	≥18 y
			5-mL multidose vial	24.5	
Live-attenuated					
LAIV	FluMist	MedImmune	0.2-mL sprayer	0	2–49 y

Sources: American Academy of Pediatrics[1] and Afluria [package insert]. CSL Limited, Parkville, Victoria, Australia; 2007.

induced by natural influenza virus infection. Although studies have yet to determine precise humoral and cellular immunologic levels of protection by LAIV, HAI antibodies in serum, immunoglobulin A in nasal secretions, T-lymphocyte responses, and interferon production have all been correlated with LAIV protection from influenza infection.[29,64]

For immunocompromised patients, response to TIV varies depending on the degree of immunosuppression. Most HIV-infected children and adults produce increased levels of antibody after immunization with TIV, but their absolute antibody concentrations are lower than those seen in healthy, immunized individuals.[65,66] Children with cancer who are not receiving chemotherapy frequently, and children who have sickle cell disease, have also been found to achieve adequate HAI response to TIV immunizations.[67,68]

Efficacy and Effectiveness

The efficacy (ie, prevention of illness among vaccine recipients in controlled trials) and effectiveness (ie, prevention of illness in populations receiving vaccine) of influenza vaccines depends primarily on the age and immunocompetence of the vaccine recipient, the degree of similarity between the viruses in the vaccine and those in circulation, and the outcome being measured. Influenza vaccine efficacy and effectiveness studies typically have multiple possible outcome measures, including the prevention of medically attended acute respiratory illness, prevention of laboratory-confirmed influenza illness, prevention of influenza or pneumonia-associated hospitalizations or deaths, seroconversion to vaccine strains, or prevention of seroconversion to circulating influenza virus strains.[50] For children 6 months and older, sufficient antibody levels against influenza are usually developed after receiving TIV.[69–76] Antibody response may be lower among children who are already at risk of developing complications from influenza infection.[77,78] One study involving children 6 to 24 months of age found that 89% of children seroconverted to all 3 vaccine strains given in the years during which the study took place. Vaccine efficacy was 67% against culture-confirmed influenza in these children, with vaccine strains matching the circulating influenza virus strains well.[63] Another study performed with children 1 to 15 years of age also demonstrated the effectiveness of TIV, with subjects exhibiting effectiveness rates of 77% and 91% during years which included H3N2 and H1N1, respectively.[62] Vaccine efficacy of 56% against influenza illness was documented among healthy children 3 to 9 years of age,[49] and another study determined vaccine efficacy against influenza type B and A infections of 22% to 54% and 60% to 78% among children with asthma 2 to 6 years of age and 7 to 14 years of age, respectively.[79] TIV has also been found to considerably decrease the incidence of influenza-attributable otitis media among young children,[80–82] although another study contradicts this finding.[63]

Results have also shown the efficacy and effectiveness of LAIV. One study conducted with healthy children 15 to 71 months of age found that when vaccine and circulating strains were well matched, efficacy rates were 93% for participants who received 2 doses of LAIV. Even when vaccine and circulating strains were not well matched, efficacy rates remained high at 85%. LAIV was also found to be 92% efficacious in preventing culture-confirmed influenza during this two-season study. Additional results of this study include a 27% reduction in febrile otitis media and a 28% reduction in otitis media with concomitant use of antibiotics.[83] In a study that compares live-attenuated vaccines versus inactivated influenza vaccines in infants and young children, LAIV shows significantly better efficacy and safety than TIV for children between 12 and 59 months of age without a recent history of wheezing or severe asthma.[27] Available studies suggest that LAIV shows better efficacy than TIV in young children against both strains contained within the vaccine and for drifted strains.

Safety

TIV

The most common symptoms associated with TIV administration are soreness at the injection site and fever. Fever, usually occurring 6 to 24 hours after immunization, affects approximately 10% to 35% of children younger than 2 years.[84] Mild systemic symptoms, such as nausea, lethargy, headache, muscle aches, and chills can also occur with TIV injection.

Control of fever with acetaminophen or other appropriate antipyretics may be important in young children, because fever and other symptoms of influenza could exacerbate underlying chronic conditions. Children and adolescents with influenza should not receive aspirin or any salicylate-containing products because of the resulting increased risk of developing Reye syndrome.[35] Parents need to be warned about proper use of all antipyretics.

LAIV

Prelicensure studies found no significant difference in rates of fever, rhinitis, or nasal congestion between LAIV immunization and placebo administration. Postlicensure studies indicate that among children immunized for the first time, fever and stuffy nose are more common in recipients of LAIV than among recipients of TIV. An increase in fever, runny nose, and nasal congestion was shown after the first dose, but not after the second dose when administered to children 15 to 71 months of age.[85] However, researchers have observed a statistically significant increase in asthma or reactive airway disease in children 12 to 59 months of age after the first dose with LAIV.[83] In another study, medically significant wheezing was more common within 42 days after the first dose of LAIV compared with TIV among previously unimmunized children 6 to 24 months of age, and hospitalization for any cause within 180 days of immunization was significantly more common among LAIV recipients 6 to 11 months of age.[27] An additional study was conducted among more than 11 000 children 18 months to 18 years of age, in which 18 780 doses of vaccine were administered for 4 years. For children 18 months to 4

years of age, no increase was reported in asthma visits 0 to 15 days after immunization, compared with the pre-immunization period. A significant increase in asthma events was reported 15 to 42 days after immunization, but only in vaccine year 1.[86]

LAIV shedding can occur after immunization, although the amount of detectable virus is less than occurs during natural influenza infection. In the rare instance when shed vaccine virus is transmitted to a nonimmunized contact, illness has not occurred. However, inactivated influenza vaccine is preferred for close contacts of very severely immunosuppressed people[50] (recommendation; evidence grade D) rather than LAIV.

Guillain-Barré Syndrome

If there is an association between seasonal influenza vaccine and Guillain-Barré syndrome (GBS), the risk is very minimal, at no more than 1 to 2 cases per million doses. Although an increase in the number of cases of GBS was reported during the "swine flu" vaccine program of 1976,[87] obtaining strong epidemiologic evidence for a possible limited increase in risk for a rare condition with multiple causes is difficult.[50] GBS has an annual incidence of 10 to 20 cases per 1 million adults,[88] and during the 1976 swine influenza vaccine program, 1 GBS case was reported per 100 000 people immunized. The risk of influenza vaccine-associated GBS was higher among people 25 years or older than among people younger than 25 years.[88] Whether influenza immunization specifically might increase the risk of recurrence of GBS is unknown. However, avoiding immunizing people who are not at high risk of severe influenza complications and who are known to have experienced GBS within 6 weeks after a previous influenza vaccine dose is prudent.[50]

HIV

Because past reports are conflicting, the issue of safety of TIV immunization for children and adults with HIV infection is uncertain. However, experts generally believe that the benefits of TIV influenza immunization for children with HIV infection far outweigh the risks.

Allergies

Children with known allergic reactions (eg, hives, angioedema, allergic asthma, or systemic anaphylaxis) to chicken or egg proteins should not receive these vaccines, because both TIV and LAIV are developed with embryonated hen eggs (recommendation; evidence grade D). However, less severe or local manifestations of allergy to egg or feathers are not contraindications to administration of influenza vaccine.[35]

Cost-effectiveness

The hospitalization costs for influenza among children in the United States are estimated to be $55 million per year.[40] Several studies have suggested that the costs and benefits of immunizing children produce significant savings from health care and societal perspectives. In 1 study, the savings per immunized child ranged from $7.23 to $15.98 in any program of children up to 13 years of age, and an investment of $2 156 109 in immunization of children younger than 5 years was predicted to result in an estimated savings yield of $3 424 409 in health care costs, even with an assumed vaccine efficacy of only 60%.[89] Other cost analyses have documented the considerable cost burden of illness among children. In a study of 727 children at a single medical center during 2000–2004, the mean total cost of hospitalization for influenza-related illness was $13 159 ($39 792 for patients admitted to an ICU and $7030 for patients cared for exclusively on the wards).[90] Strategies that focus on immunizing children with medical conditions that confer a higher risk of influenza complications seem to be more cost-effective than a strategy of immunizing all children.[91] The expenses of immunizing children of varying ages were estimated, comparing the costs between using TIV with those of LAIV; costs per quality-adjusted life-year saved increased with age for both vaccines. In 2003 dollars per quality-adjusted life-year, costs for routine immunization using TIV were $12 000 for healthy children 6 to 23 months of age and $119 000 for healthy adolescents 12 to 17 years of age, compared with $9000 and $109 000 using LAIV, respectively.[92] Other studies demonstrated that influenza immunization of young children generates considerable savings from a societal perspective, especially if the total costs of immunization are less than $30 per child and if immunizations can be administered in after-hours or weekend group settings so as to help parents not miss work for their children's immunization.[93–96]

A recent review of research on the costs and benefits of immunizing children, household contacts, and those at high risk of morbidity and mortality from influenza complications[97] suggests that the immunization of children has the potential to protect others in their homes and communities. However, because of limitations in the design or execution of several analyzed studies, this finding remains inconclusive. Results from a public survey on the cost associated with influenza disease provided the following estimates: when asked about their willingness to pay to prevent a hypothetical child from having an uncomplicated case of influenza, the median willingness-to-pay amount was $100 for a child 14 years of age and $175 for a child 1 year of age.[98]

Vaccine Storage and Administration

TIV is a split-virus vaccine made up of inactivated, disrupted virus particles administered intramuscularly into the anterolateral thigh of infants and young children and into the deltoid muscle of older children and adults. The benefits of protecting children against the known risks of influenza far outweigh the hypothetical risks associated with the small amounts of thimerosal in some currently available forms of influenza vaccine. Certain types of TIV can be obtained free of thimerosal, including single-dose Fluzone (Sanofi Pasteur, Swiftwater, PA) and Fluvirin (Novartis, Emeryville, CA), but the latter vaccine is not licensed for use in children younger than 4 years.

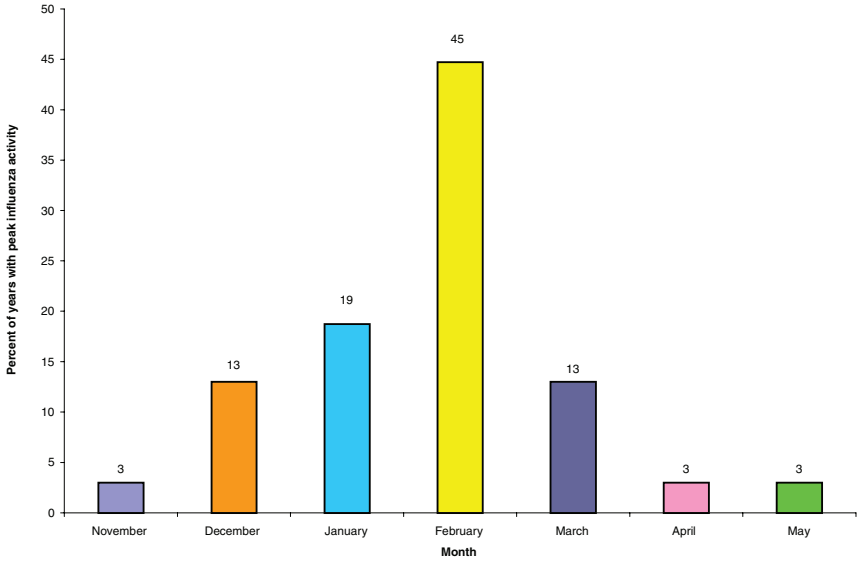


FIGURE 1
Month of peak influenza activity (%) from 1976 to 2007.

Note: The peak week of influenza activity was defined as the week with the greatest percentage of positive respiratory specimens for influenza. The number of peak weeks in each month was then summed and a percentage calculated.

Source: US World Health Organization Collaborating Laboratory (CDC, unpublished data, 1976–2007).

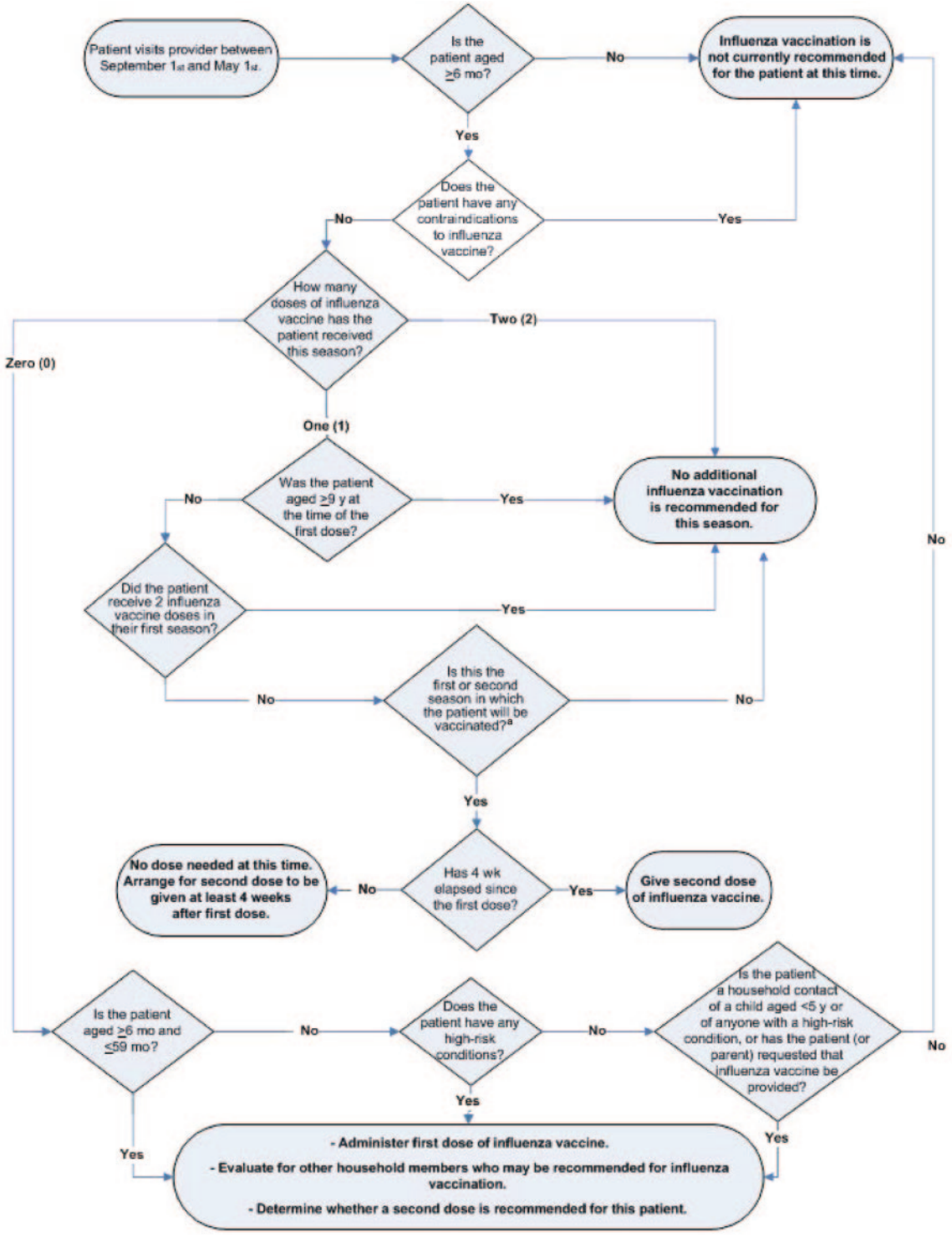
The cold-adapted LAIV formulation that is currently licensed in the United States must be shipped and stored at 2°C to 8°C.[50,99] LAIV doses are administered intranasally, in a prefilled, single-use sprayer containing 0.2 mL of vaccine. A removable dose-divider clip is attached to the sprayer to administer 0.1 mL separately to each nostril. Although information on how concurrent administration of LAIV with other vaccines affects the safety or efficacy of either LAIV or the simultaneously administered vaccine has not been well studied, it is generally recommended that inactivated or live vaccines be administered simultaneously with LAIV. After administration of a live vaccine, at least 4 weeks should pass before another live vaccine is administered. LAIV does not contain thimerosal.

TIMING OF INFLUENZA VACCINE ADMINISTRATION

To ensure the development of sufficient protection against influenza, influenza vaccine should be given during the autumn of each year before the onset of influenza season, at the time specified in the yearly recommendations of the CDC's Advisory Committee on Immunization Practices (www.cdc.gov/flu). Traditionally, the recommended time ranges from the beginning of October to the end of January, unless vaccine supplies are available and sufficient to immunize people earlier in September. Influenza vaccine administration throughout the entire season is now recommended, as the influenza season extends well into March (recommendation; evidence grade C). Immunization throughout the season may still protect some individuals against late outbreaks of influenza (Fig 1). In addition, there may be more than 1 peak of activity during an influenza season, so later immunization may still help protect from a later peak caused by a different strain of influenza virus that same season.

Flu vaccine administration should ideally begin before the start of influenza season (Figs 1 and 2) (recommendation; evidence grade D). Influenza vaccine-naïve children who are 9 years and older need only 1 dose for their first time (recommendation; evidence grade B). In contrast, any child younger than 9 years receiving TIV or LAIV for the first time should receive a second dose at least 4 weeks after the first (recommendation; evidence grade B).[19–21] The CDC and AAP are now harmonized in their 2007–2008 recommendations for the child younger than 9 years who received only 1 dose in the first year influenza vaccine was given; both recommend that the child receive 2 doses of influenza vaccine if he or she received only 1 dose the previous season (recommendation; evidence grade B). This recommendation applies only to the influenza season that follows the first year that a child younger than 9 years receives influenza vaccine. No data are available for other influenza vaccine administration scenarios. Although data are limited, recently published studies indicate that young children who receive only 1 dose of TIV in each of the first 2 seasons have lower antibody levels and are significantly less likely to have protective antibody titers when the vaccine antigen changes than are children who receive their first 2 doses of vaccine in the same season. Studies have documented a lower efficacy against ILI after a single dose of TIV in the second season for children who received only 1 dose during the first season.[21,24,25]

Compared with a regimen of 2 doses in the fall, spring-fall priming of young children engenders similar antibody responses when vaccine antigens are unchanged from 1 season to the next.[21] Priming in this



(Adapted with permission from the American Academy of Pediatrics, Committee on Infectious Diseases. Prevention of influenza: recommendations for influenza immunization of children, 2006–2007. *Pediatrics* 2007; 119:846–51 and Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56(RR06):1–54.

[a]If children aged < 9 years of age received their first influenza vaccine last year and got only 1 dose, it is recommended that 2 doses be administered in the current season. This recommendation applies for this season only. No data are available for other influenza vaccine administration scenarios.

FIGURE 2
Algorithm for determining recommended influenza immunization actions for children.

fashion does provide a degree of protection against ILI but with substantially lower efficacy compared with a regimen that provides 2 doses in the fall. One study conducted over 2 consecutive seasons in which the vaccine antigens did not change estimated 62% effectiveness against ILI for healthy children who had received 1

dose in the spring and a second the following fall, compared with 82% for those who received both doses in the fall.[24] A study assessing protective antibody responses after 1 and 2 doses of vaccine among children 5 to 8 years of age who never were immunized previously indicated that children who received 2 doses were substantially more likely than those who received 1 dose to have a protective antibody response.[20] The proportion who had a protective antibody response against the H1N1 antigen and the H3N2 antigen increased from 67% and 92%, respectively, after the first dose to 93% and 97%, respectively, after the second dose. However, 36% of children who received 2 doses did not have a protective antibody response to the influenza B antigen.[20]

When vaccine antigens do change in consecutive years, young children who receive only 1 dose of vaccine in their first year of immunization are less likely to have protective antibody responses when administered only a single dose during their second year of immunization, compared with children who receive 2 doses in their first year of immunization.[101,102] An open-label, nonrandomized study compared children 6 to 23 months of age who had received 1 dose of vaccine during the 2003–2004 influenza season and a second dose of a different vaccine during the 2004–2005 season with children who received 2 doses of the same vaccine during the 2004–2005 season. The proportion that had protective antibody levels against the H3N2 antigen (changed during the second year) or the H1N1 antigen (unchanged) was similar. However, 27% of children who had received only 1 dose of influenza vaccine during the 2003–2004 season had a protective antibody response to a single dose of the 2004–2005 vaccine influenza B virus antigen (changed from the previous year), compared with 86% of children who received 2 doses of the 2004–2005 vaccine in their first year of immunization.[101]

Annual immunization against influenza is the preferred strategy for prevention of infection, but certain situations exist in which the use of antiviral agents is beneficial.[35]

Two classes of antiviral medications are currently available and felt to be safe and effective in children for the treatment or prophylaxis of influenza infections: the adamantanes (amantadine and rimantadine) and the neuraminidase inhibitors (oseltamivir and zanamivir).[103] However, because recent studies have shown that the overwhelming majority (92%) of influenza A virus isolates are resistant to the adamantanes in the United States, using amantadine or rimantadine is not recommended for treatment or chemoprophylaxis of the influenza A strain until data are available on susceptibility of this year's influenza isolates (recommendation; evidence grade C).[50,103] However, oseltamivir and zanamivir are antiviral therapies that can be prescribed (recommendation; evidence grade C), if necessary, because surveillance data indicate that influenza A and B strains have not shown clinically important levels of resistance. These topics are covered in greater detail in the recently published AAP clinical report "Antiviral Therapy and Prophylaxis for Influenza in Children."[103]

CONTRAINDICATIONS AND PRECAUTIONS

Children Who Should Not Be Immunized With TIV

- Children younger than 6 months.
- Children who have a moderate-to-severe febrile illness. Minor illnesses, with or without fever, do not contraindicate its use, particularly among children with mild symptoms of upper respiratory tract infection or allergic rhinitis.
- Children who have a history of hypersensitivity, including anaphylaxis, to eggs; to any previous influenza vaccine dose; or to any of the vaccine components.
- Children who have a history of GBS (recommendation; evidence grade C).
- Children Who Should Not Be Immunized With LAIV.
- Children younger than 2 years (recommendation; evidence grade B).
- Children who have a moderate-to-severe febrile illness.
- Children who received other live vaccines within the last 4 weeks.
- Children who have asthma, reactive airways disease, or other chronic disorders of the pulmonary or cardiovascular systems.
- Children who have underlying medical conditions, including metabolic disease, such as diabetes, renal dysfunction, and hemoglobinopathies.
- Children who have known or suspected immunodeficiency disease or are receiving immunosuppressive therapies.
- Children who are receiving aspirin or other salicylates.
- Children who have a history of GBS (recommendation; evidence grade C).
- Adolescents who are pregnant.
- Children who have a history of hypersensitivity, including anaphylaxis, to eggs; to any previous influenza vaccine dose; or to any of the vaccine components.

Precautions

Consideration should be given to the potential risks and benefits of administering influenza vaccine to any child with known or suspected immunodeficiency. Precaution should also be taken when considering LAIV administration to people with minor acute illness, such as a mild upper respiratory tract infection with or without fever. Although the vaccine can most likely be given in this case, LAIV should not be delivered if nasal congestion will impede the delivery of the vaccine to the nasopharyngeal mucosa, until the congestion-inducing illness is resolved.[64] In addition, TIV is the influenza vaccine of choice for any child living with a family member or household contact who is severely immunocompromised (ie, in a protected environment). The preference of TIV over LAIV for these individuals is because of the theoretic risk of infection in an immunocompromised

contact of a LAIV-immunized child. As a precautionary measure, recently immunized people should restrict contact with severely immunocompromised (ie, in a protected environment) patients for 7 days after LAIV immunization, although there have been no reports of LAIV transmission between these 2 groups.

RECOMMENDATIONS

Influenza immunization is recommended for the following groups (Fig 2)

- Healthy children 6 through 59 months of age (recommendation; evidence Grade B).
- Children at high risk and adolescents with underlying medical conditions, including:
- Asthma or other chronic pulmonary diseases, such as cystic fibrosis (recommendation; evidence grade B).
- Hemodynamically significant cardiac disease.
- Immunosuppressive disorders or therapy.
- HIV infection.
- Sickle cell anemia and other hemoglobinopathies.
- Diseases requiring long-term aspirin therapy, such as juvenile idiopathic arthritis or Kawasaki disease (TIV only).
- Chronic renal dysfunction.
- Chronic metabolic disease, such as diabetes mellitus.
- Any condition that can compromise respiratory function or handling of secretions or can increase the risk of aspiration, such as cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders.
- Household contacts and out-of-home caregivers of children younger than 5 years and children who are at risk of all ages. Immunization of close contacts of children younger than 6 months may be particularly important, because these infants cannot be immunized (recommendation; evidence grade B).
- Children who required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases, such as diabetes mellitus; renal dysfunction; hemoglobinopathies; or immunodeficiency caused by medication or by HIV infection.
- Any female who will be pregnant during influenza season (TIV only).

In addition, immunization with either TIV or LAIV is recommended for the following individuals to prevent transmission of influenza to those at risk, unless contraindicated:

- Individuals 5 years and older.
- Healthy contacts and caregivers of other children or adults at high risk of developing complications from influenza infection (recommendation; evidence grade B).
- Close contacts of immunosuppressed individuals (TIV only if severely immunosuppressed).
- Health care workers or volunteers.
- Information about influenza surveillance is available through the CDC Voice Information System (influenza update, 888-232-3228) or at www.cdc.gov/flu.

FUTURE NEEDS AND RESEARCH

Influenza vaccine schedules and effectiveness depend a great deal on how well vaccine strains match circulating virus strains each year. Research to further enhance the methods currently used to predict potential antigenic changes each year is important. Evaluations of the impact of influenza immunization programs must account for year-to-year variations in influenza attack rates, illness severity, hospitalization costs and rates, and vaccine effectiveness.

The AAP continues to review new immunization strategies to protect against influenza, including the possibility of expanding routine influenza immunization recommendations toward universal immunization or other approaches that will help greatly reduce the transmission of influenza. Despite the implementation of a universal influenza immunization campaign in Ontario and the subsequent increase of vaccine distribution and financial resources for this promotion, the incidence of influenza in this Canadian province has not decreased after the introduction of this program.[104] Others feel these data are susceptible to various biases and have suggested that to evaluate universal influenza immunization program effectiveness, other established and available measures used in previous studies describing the epidemiology of influenza should be used instead of laboratory data.[105] Additional analyses on the cost-effectiveness of expanding influenza immunization programs are indicated to better clarify and specify the economic and societal effects associated with immunization. This is especially prudent with the recommendation to immunize healthy children through 18 years of age, as is being proposed to decrease transmission and burden of disease to the entire population at risk of influenza morbidity and mortality. Any move toward universal annual influenza immunization in the United States increases the demand and potentially could reduce the cost to produce more influenza vaccine, which should also stabilize the market and give incentive for increased production capacities by vaccine manufacturers.

In addition, health care professionals and the public will benefit from continued education about annual influenza illness and vaccines. Research is necessary in identifying gaps in proposed plans for executing large-scale immunization programs. Particular attention must be paid to vaccine supply, distribution, implementation, and financing so as to determine and achieve realistic immunization goals for children and society each year.

Efforts should be dedicated toward building outreach and infrastructure to ensure an optimal distribution of vaccine so that more people are immunized. All health care professionals, influenza campaign organizers, and public health agencies should develop and refine their

plans for expanding outreach and infrastructure to improve immunization rates of children with high-risk conditions for whom the vaccine is recommended and all healthy children 6 through 59 months of age. In addition, more support for programs that increase uptake of vaccine in pregnant women is needed. Appropriate prioritization of recipients of influenza vaccine should always be considered, especially when local vaccine supplies are delayed or limited.

Continued investigation of the safety, immunogenicity, and effectiveness of LAIV for young children is important. Additional studies of other special populations, such as patients who are receiving mild-to-moderate immunosuppression (eg, methotrexate, low-dose corticosteroids) also warrant additional consideration. Development of a safe, immunogenic vaccine for infants younger than 6 months would also be valuable. Lastly, efforts are being explored to improve the vaccine development process so as to allow for a shorter interval between identification of vaccine strains to be included each year and vaccine production. For example, the development of a tissue culture-based vaccine could increase production capacity and eliminate the contraindication for those with known allergic reactions to egg proteins.

ACKNOWLEDGMENTS

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APPENDIX 1 Guideline Definitions for Evidence-Based Statements

Statement Type	Definition	Implication
Strong recommendation	The subcommittee believes that the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (grade A or B).[a]	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recommendation	The subcommittee believes that the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (grade B or C). In some clearly identified circumstances, recommendations may be made on the basis of lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.	Clinicians also should generally follow a recommendation but remain alert to new information and sensitive to patient preferences.
Option	Either the quality of evidence that exists is suspect (grade D) or well-performed studies (grade A, B, or C) show little clear advantage to one approach versus another.	Clinicians should be flexible in their decision making in regards to appropriate practice, although they may set boundaries on alternatives; patient preference should play a substantial influencing role.
No recommendation	There is both a lack of pertinent evidence (grade D) and an unclear balance between benefits and harms.	Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should play a substantial influencing role.

[a] See Appendix 2 for the definitions of evidence grades.

Source: American Academy of Pediatrics, Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. *Pediatrics*. 2004;114(3):874 – 877.

APPENDIX 2 **Definitions Grades of Evidence**

Grade	Evidence Quality
A	Well-designed randomized, controlled trials or diagnostic studies performed on a population similar to the guideline's target population
B	Randomized, controlled trials or diagnostic studies with minor limitations; overwhelmingly consistent evidence from observational studies
C	Observational studies (case-control and cohort design)
D	Expert opinion, case reports, or reasoning from first principles (bench research or animal studies)

Source: American Academy of Pediatrics, Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. *Pediatrics*. 2004;114(3):874–877.

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