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OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Recommendations for Influenza Immunization of Children

Committee on Infectious Diseases

Pediatrics 2004;113:1441-1447

DOI: 10.1542/peds.113.5.1441

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American Academy of Pediatrics

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POLICY STATEMENT

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

Committee on Infectious Diseases

Recommendations for Influenza Immunization of Children

ABSTRACT. Epidemiologic studies indicate that children of all ages with certain chronic conditions and otherwise healthy children younger than 24 months of age are hospitalized for influenza infection and its complications at high rates similar to those experienced by the elderly. Annual influenza immunization is recommended for all children with high-risk conditions who are 6 months of age and older. Young, healthy children are at high risk of hospitalization for influenza infection; therefore, the American Academy of Pediatrics recommends influenza immunization for healthy children 6 through 24 months of age, for household contacts and out-of-home caregivers of all children younger than 24 months of age, and for health care professionals. To protect these children more fully against the complications of influenza, increased efforts are needed to identify all high-risk children and inform their parents when annual immunization is due. The purposes of this statement are to update recommendations for routine use of influenza vaccine in children and to review the indications for use of trivalent inactivated influenza vaccine and live-attenuated influenza vaccine. *Pediatrics* 2004; 113:1441–1447; *influenza, vaccine, immunization, children.*

ABBREVIATIONS. AOM, acute otitis media; TIV, trivalent inactivated influenza vaccine; LAIV, live-attenuated influenza vaccine; GBS, Guillain-Barré syndrome; HIV, human immunodeficiency virus; CI, confidence interval.

BACKGROUND INFORMATION

In community studies, school-aged children have had the highest rates of influenza infection. Prospective surveillance of influenza illness demonstrates annual attack rates of between 15% and 42% in preschool- and school-aged children.^{1,2} During various influenza seasons, rates of annual outpatient visits attributable to influenza vary from 6 to 29 per 100 children.^{2,3} Influenza also may be important in the pathogenesis of acute otitis media (AOM) during influenza seasons⁴; 3% to 5% of children annually are estimated to experience AOM associated with influenza.^{2,5,6} 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.⁷ Antecedent influenza infection is sometimes associated with development of severe pneumococcal and staphylococcal pneumonia in children.⁸

The risk of influenza-associated hospitalization in healthy children younger than 24 months of age has

been shown to be equal to or greater than the risk in previously recognized high-risk groups. Young children also seem to be at higher risk of hospitalization for influenza infection than are healthy 50- to 64-year-old adults, for whom routine immunization has been recommended since 2000 (Table 1). High rates of hospitalization of the young during influenza seasons have been appreciated for decades,^{3,9,10} 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 published studies have made reasonable attempts to separate the relative contributions of respiratory syncytial virus and influenza to the hospitalization rate.^{2,7,11} 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 of age 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. Of 182 patients hospitalized at Montreal Children's Hospital with laboratory-proven influenza between 1999 and 2002, 34% were younger than 6 months of age.¹² Seventy percent of these 182 children had no underlying medical disorder. Suspected sepsis was the admission diagnosis for 31% of these hospitalized children.

Although serious morbidity and mortality can result from influenza infection in any person, the risk of complications is increased among pregnant women,¹³ individuals with underlying chronic cardiopulmonary conditions,^{14,15} and immunocompromised persons.^{16,17} Persons with renal, metabolic, and hematologic diseases are presumed to be at higher risk of severe influenza and its complications.

More severe outcomes of influenza, such as encephalopathy and death, have not been well studied, although deaths attributable to influenza are far less common in children than in the elderly. The fatality rate in children has been estimated to be 3.8 per 100 000 population.⁹ Cases of encephalopathy and sudden unexplained death have been reported in US children,¹⁸ but population-based rates are not known. The Centers for Disease Control and Prevention began to actively solicit reports of influenza-associated deaths and encephalopathy in individuals younger than 18 years of age during the 2003–2004 influenza season.¹⁹

TABLE 1. Estimated Influenza-Associated Hospitalization Rates (Per 100 000 Persons) From Selected Studies

Study Years	Population	Age Group	Persons in Previously Recognized High-Risk Group	Persons Not in Previously Recognized High-Risk Group
1973–1993 ^{7,15}	Tennessee Medicaid	0–11 mo	1900	496 (0–5 mo) 1038 (6–11 mo)
		1–2 y	800	186
		3–4 y	320	86
		5–14 y	92	41
1974–1999 ²	Vaccine clinic	<2 y		200–300
1992–1997 ¹¹	Health maintenance organizations	0–23 mo		144–187
		2–4 y		0–25
		5–17 y		8–12
1968–1973 ⁶⁸	Health maintenance organization	15–44 y	56–110	23–25
		45–64 y	392–635	13–23
		≥65 y	399–518	—
1969–1995 ⁶⁹	National hospital discharge data	<65 y		20–42
		≥65 y		125–228

Adapted from *MMWR Recomm Rep.* 2001;50(RR-4):1–44.

VACCINES

The only influenza vaccine licensed for use in children younger than 5 years of age and for children 6 months of age and older with high-risk medical conditions is the trivalent inactivated influenza vaccine (TIV). A live-attenuated influenza vaccine (LAIV), which is administered intranasally, was licensed by the Food and Drug Administration for use in healthy individuals between 5 and 49 years of age. Current formulations of both these vaccines contain 3 virus strains representing influenza A subtypes H1N1 and H3N2 and influenza B. The strains to be included in the vaccine are selected annually on the basis of the viruses anticipated to be circulating during the upcoming influenza season.

TIV

Manufacturing, Handling, and Administration

TIV viruses are grown in embryonated hen eggs, inactivated, and then (in most instances) preserved with thimerosal (1:10 000). Manufacturers currently distributing TIV in the United States are Aventis Pasteur (Swiftwater, PA) (Fluzone) and Evans Vaccines (Liverpool, England) (Fluvirin). Fluzone and Fluvirin can be obtained thimerosal-preservative-free. Fluvirin is not licensed for children younger than 4 years of age, because efficacy has not been established in this age group. Removal of thimerosal from TIV results in wastage of one third of doses produced. Most experts view the protection of more children against the known risks of influenza more important than the theoretic risk of small amounts of thimerosal in influenza vaccine. Children younger than 9 years of age receiving any influenza vaccine for the first time should be given 2 doses 1 month apart. TIV vaccines licensed in the United States consist of disrupted virus particles and are termed split-virus vaccines.

Safety of 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, is more common in children younger than 2 years of age (10%–35% of recipients).^{20,21} Mild

systemic symptoms such as nausea, lethargy, headache, muscle aches, and chills are reported also. A retrospective “self-control” analysis of 251 000 children 6 months to 17 years of age who received influenza immunization in 1 of 5 managed care settings did not reveal any evidence of increased occurrence of important medically attended events associated with immunization.²² Immunization of children who have asthma with TIV does not increase bronchial hyperactivity.²³

During the “swine flu” vaccine program in 1976, an increase in the number of cases of Guillain-Barré syndrome (GBS) was reported in adults within 10 weeks after immunization. Additional investigations have revealed that there may be a slight increase in the risk of GBS (approximately 1 additional case of GBS per 1 million vaccine recipients) among adults after influenza immunization, at least in some years.^{24–27} It is unknown whether influenza immunization of individuals with a history of GBS increases the rate of recurrence of GBS. History of GBS is considered a relative contraindication to immunization with TIV. The Institute of Medicine evaluated the association of demyelinating diseases and influenza vaccine and concluded that there is no evidence bearing on a causal relationship between influenza vaccines and demyelinating neurologic disorders in children 6 to 23 months of age.²⁸ Health care professionals should promptly report all clinically significant adverse events after influenza immunization to the Vaccine Adverse Events Reporting System (www.vaers.org) even if it is uncertain that the vaccine caused the event. The Institute of Medicine has specifically recommended reporting of neurologic events.

A newly described syndrome, oculorespiratory syndrome, was described during 2000–2001 among 3.4% of adult recipients of an influenza vaccine distributed in Canada by Shire Biologics (Fluviral S/F). Symptoms occurred within 24 hours of immunization and included bilateral red eyes and/or facial edema, respiratory complaints (coughing, wheezing, tightness of chest, difficulty breathing), difficulty swallowing, or sore throat. Symptoms were generally mild, and all resolved. The implicated vaccine

contained large clumps of unsplit virus particles as evidenced by electron microscopy.^{29,30} It is not known with certainty whether this reaction follows immunization with other influenza vaccines or whether it occurs in children. Only split-virus influenza vaccine is available in the United States.

Studies of the safety of TIV immunization of children and adults with human immunodeficiency virus (HIV) infection have yielded conflicting results. Some studies have demonstrated a transient (2- to 8-week) increase in HIV-1 replication and/or a decrease in CD4⁺ T-lymphocyte cell counts,³¹⁻³⁴ and other studies have reported no significant effects.³³⁻⁴⁰ Most experts believe that the benefits of influenza immunization with TIV far outweigh the risks in children with HIV infection.

Allergic Reactions to TIV

Because influenza vaccine is grown in embryonated hen eggs, children demonstrating anaphylactic reactions to chicken or egg proteins may rarely experience a similar reaction to influenza vaccine and therefore should not be given TIV unless they undergo desensitization. Inactivated influenza vaccine containing thimerosal should not be given to individuals with hypersensitivity to thimerosal. Urticarial reactions to TIV have been reported.

Efficacy of TIV

Efficacy estimates vary depending on the age group, season, degree of antigenic match between the circulating viruses and the vaccine strains, and end points studied. Protective efficacy against influenza illness confirmed by positive culture varies between 30% and 95% depending on season and population studied.⁴¹⁻⁴⁵ Studies in the United States and Japan raise the possibility that immunization of a high proportion of school-aged children may result in diminished incidence of disease in all age groups including the elderly.^{46,47}

Studies of the efficacy of influenza immunization against AOM have produced conflicting results. The incidence of AOM attributable to all causes in a group child care center was 36% less among 187 children immunized with TIV than among 187 children not immunized in other child care centers.⁴² In that same evaluation, there was an 83% decrease in influenza-associated AOM in immunized versus nonimmunized children. In a second child care center study, 186 children 6 to 30 months of age were assigned randomly to receive TIV or no influenza vaccine and then were followed biweekly by blinded observers. Influenza vaccine was slightly protective against AOM during the influenza season (odds ratio: 0.69; 95% confidence interval [CI]: 0.49-0.98).⁴⁸ However, a randomized, placebo-controlled study of TIV among more than 750 children 6 to 24 months of age failed to show decreases in the incidence of AOM or in duration of middle-ear effusion among vaccine recipients, compared with placebo recipients.⁴⁵

TIV Vaccine Coverage

Despite recommendations to immunize all children with asthma, only 10% to 31% of this popula-

tion receives the TIV vaccine each year.⁴⁹⁻⁵¹ In 4 health maintenance organizations, 40% of patients with asthma attending an allergy clinic were given influenza vaccine; however, only 1% of all children with asthma made a visit to an allergy clinic.⁴⁹ A survey of parents of all children hospitalized during the influenza season revealed that the most important determinant of immunization was the physician's recommendation for influenza vaccine.⁵¹

Costs of TIV Influenza Immunization

Whether universal immunization of young children would result in a net cost or a net savings to society depends on the influenza attack rate, the rates of health outcomes (ie, outpatient visits, hospitalizations, and deaths), and the cost of immunization. The attack rate and rates of health outcomes can vary considerably from year to year, and regional variation in both these factors is possible within a given season. These variations make it impossible to generate a single, precise estimate of the cost-effectiveness or cost-benefit of universal immunization of children.

The total cost of immunizing a single child includes direct and indirect costs. The direct costs include supplies (eg, syringe and vaccine), personnel, and administrative expenses. Indirect costs can be a significant component of the total cost of immunization. One of the most important factors is the time lost from work by caregivers of children to be immunized. Three studies have suggested that universal childhood immunization may be cost-saving if immunizations could be performed in a group-based setting such as an after-hours or weekend immunization clinic that would not require a parent to miss work.⁵²⁻⁵⁴ A subcommittee of the Advisory Committee on Immunization Practices, after a review of the major economic studies of influenza immunization,⁵²⁻⁵⁶ concluded that universal influenza immunization of young children may generate savings, from a societal perspective, if the total costs of immunization are less than \$30 per child immunized (M. Meltzer, oral presentation at Advisory Committee on Immunization Practices Influenza Workshop, October 15, 2003, Atlanta, GA).

Public and private insurers should be responsible for payment of costs for the influenza vaccine for children. Transferring financial responsibility to intermediate risk-bearing entities such as independent practice associations or other physician groups, individual physicians, or hospitals will result in children not being immunized and should not be allowed. Physicians incur significant administrative expenses associated with ensuring that children are fully immunized in a timely fashion, including explaining the benefits and risks of immunization to parents; ordering, purchasing, storing, and administering vaccines; recording immunizations in patients' charts; tracking immunization schedules and notifying patients; and other activities. Therefore, they should receive reimbursement for the expenses associated with these tasks for each vaccine administration.

It has been estimated that between 46% and 74% of

children 6 to 23 months of age will require at least 1 additional visit to a health care professional to receive influenza immunization. Suggested strategies to minimize the strain on practices include 1) beginning immunization as early in the season as possible, 2) using all visits (not just well-child visits) for immunizations, and 3) scheduling specific clinic times for influenza immunizations.⁵⁷

Availability of TIV

In recent years, approximately 70 to 90 million doses of TIV, which generally meet national vaccine demands, have been available annually. Vaccine demand may be increasing, and therefore preordering of vaccine is recommended. If vaccine supplies are limited, visit the American Academy of Pediatrics web site (www.aap.org) for suggestions for prioritization of use.

LAIV

Viral Strains and Manufacturing

Cold-adapted, live-attenuated influenza A and B strains were developed by passaging the viruses at successively lower temperatures in tissue culture.⁵⁸ These LAIV strains grow at 25°C, and their replication is restricted at 38°C to 39°C. LAIV strains, similar to influenza A strains contained in TIV, are produced through genetic reassortment. Because LAIV is grown in embryonated hen eggs, it should not be given to anyone who has had an anaphylactic reaction to chicken or egg proteins. The LAIV licensed for use in the United States (FluMist) is manufactured by MedImmune Inc (Gaithersburg, MD).

Storage, Administration, and Schedule of LAIV

The current LAIV formulation licensed in the United States must be stored frozen (refer to the FluMist package insert for specific requirements of each lot of vaccine). Once the vaccine is warmed to room temperature, it must be used within 30 minutes. Each 0.5-mL dose of vaccine contains approximately 10⁷ tissue culture infectivity doses of influenza strains A subtype H1N1, A subtype H3N2, and B. It is administered intranasally (0.25 mL in each nostril) by a Becton Dickinson (Franklin Lakes, NJ) AccuSpray device, which resembles a tuberculin syringe. Children younger than 9 years of age being immunized against influenza for the first time should receive 2 doses of LAIV given 6 weeks apart before the start of the influenza season.

Safety of LAIV in Healthy Children

An analysis of solicited events combined across the 4 placebo-controlled trials in the subset of healthy children 60 to 71 months of age was performed (see the FluMist package insert). The largest absolute differences between LAIV and placebo after dose 1 were increases in headache (18% with FluMist vs 12% with placebo) and runny nose or nasal congestion (48% with LAIV vs 44% with placebo). These differences were not statistically significant. No differences were observed for fever. After dose 2, the largest absolute differences between FluMist and placebo were runny nose or nasal congestion (46%

with FluMist vs 32% with placebo) and cough (39% with FluMist vs 31% with placebo). A randomized (vaccine to placebo, 2:1), double-blind trial in healthy children 1 to 17 years of age was conducted in the Northern California Kaiser Permanente health maintenance organization to assess the rate of medically attended events within 42 days of immunization. In an unplanned retrospective analysis, a statistically significant increase in asthma or reactive airway disease was observed for children 12 to 59 months of age after dose 1 (relative risk: 3.53; 90% CI: 1.1, 15.7). There was no clustering of wheezing events. However, because of this finding, FluMist currently is not licensed by the Food and Drug Administration for children younger than 60 months of age. Additional evaluation of safety data within this age group is needed.

Efficacy of LAIV in Healthy Children

All prelicensure studies were performed in healthy children. There are no data on the effectiveness of LAIV when given to children with rhinitis attributable to infection or allergy. Vaccine efficacy against influenza A (H3N2) and B outbreaks was demonstrated in a US pediatric, multicenter trial of FluMist.⁵⁹ The wild-type strains that circulated the first season after immunization were influenza A (H3N2) and B. Efficacy of 2 doses of LAIV against influenza illness confirmed by positive culture was 96.0% (95% CI: 89.4–98.5) for influenza A (H3N2) and 90.5% (95% CI: 78.0–95.9) for influenza B. Protective efficacy in children who received only 1 dose of vaccine also was high; it was 86.9% (95% CI: 46.6–96.8) against influenza A (H3N2) and 91.3% (95% CI: 45.6–98.6) against influenza B. Eighty-five percent of the children who participated in the US multicenter study returned for reimmunization before the next influenza season and received vaccine or placebo as they had previously. The influenza A/Sydney/H3N2 that circulated in year 2 was a drifted strain that did not match the vaccine strain influenza A/Wuhan. Despite the strain differences, the LAIV was 85.9% (95% CI: 75.3–91.9) efficacious in preventing influenza illness confirmed by positive culture attributable to influenza A/Sydney, indicating good heterotypic protection against this strain.⁶⁰ The efficacy of LAIV against influenza A (H1N1) infection could not be determined in the multicenter US trial, because influenza A (H1N1) did not circulate during either season. Therefore, a challenge study with the influenza H1N1 vaccine strain was performed in 222 randomly chosen previous vaccine and placebo recipients. Previous immunization was 82.9% (95% CI: 60.2–92.7) efficacious in preventing shedding of influenza A (H1N1) vaccine strain virus after challenge.⁶¹

Efficacy of LAIV Against AOM

In the US multicenter LAIV efficacy study, vaccine efficacy against otitis media associated with influenza illness confirmed by positive culture was 97.5% (95% CI: 85.5–99.6). The decrease in all episodes of otitis media attributable to all causes during the influenza season among vaccine recipients compared

with placebo recipients was 8.7% (95% CI: -5.5-20.8), and the decrease in episodes of febrile otitis media attributable to any cause was 30.1% (95% CI: 11.3-45.0).⁶⁰

Transmissibility of LAIV

Studies of transmission of LAIV strains to nonimmunized contacts have included nasal secretion cultures and serologic evaluation. Several studies have failed to document transmission.⁶² However, in a child care trial in which 80% of 98 vaccine recipients shed vaccine virus, 1 of 99 placebo recipients shed type B vaccine virus on a single day.⁶³

The proposed explanation for the uncommon occurrence of transmission is that the vaccine virus is shed for a shorter duration and in a much smaller quantity than are wild-type strains. In seronegative children, virus shedding usually occurs from day 2 to day 9 after immunization, and the average peak virus titers approach 10^3 plaque-forming units/mL. The maximal virus shedding observed has been 10^4 to 10^5 plaque-forming units/mL, which is 10- to 100-fold less than that typically seen with natural infection.⁶⁴

Coadministration of LAIV With Other Vaccines

No data about concurrent administration of LAIV and recommended childhood vaccines are available currently. According to the general recommendations on immunization, inactivated vaccines can be given simultaneously with LAIV. Live vaccines also can be administered at the same time. However, if live vaccines are not administered on the same day, they should be separated by 4 weeks.

Genetic Stability of LAIV

In multiple studies conducted over 20 years, no reversion of the LAIV strains to a virulent phenotype in vaccine recipients has been detected. The stability of LAIV is attributed to the fact that the donor strains contain attenuating mutations in at least 3 genes and that the overall replication of the vaccine virus in the human mucosa is low. Consequently, the probability of generating mutants that have lost the attenuated phenotype is small.^{65,66}

ANTIVIRAL MEDICATION

For a discussion of the use of antiviral medications in influenza illness, refer to the *Red Book*.⁶⁷

RECOMMENDATIONS

TIV Indications

1. Health care professionals should be diligent with their efforts, through tracking and reminder systems, to ensure that children traditionally considered at high risk of severe disease and complications from influenza infection receive annual influenza immunization. High-risk children and adolescents who should receive priority for influenza immunization are those with the following (evidence grade II-3 [see Appendix 1]):
 - Asthma or other chronic pulmonary diseases such as cystic fibrosis;

- Hemodynamically significant cardiac disease;
- Immunosuppressive disorders or therapy;
- HIV infection;
- Sickle cell anemia and other hemoglobinopathies;
- Diseases requiring long-term aspirin therapy, such as rheumatoid arthritis or Kawasaki disease;
- Chronic renal dysfunction;
- Chronic metabolic disease such as diabetes mellitus.

Other individuals who should receive priority for influenza immunization include:

- Women who will be in their second or third trimester of pregnancy during influenza season (evidence grade II-3), and
 - Persons who are in close contact with high-risk children, including 1) all health care professionals in contact with pediatric patients in hospital and outpatient settings and 2) household contacts and out-of-home caregivers of high-risk individuals of any age (evidence grade II-3).
2. Young, healthy children are at high risk of hospitalization for influenza infection; therefore, the American Academy of Pediatrics recommends influenza immunization of healthy children between 6 and 24 months of age (evidence grade II-3). This recommendation applies to any child who will be from 6 through 23 months of age at any time during the influenza season, which extends from the beginning of October through March. Children should not be immunized before they reach 6 months of age. Influenza immunization of household contacts and out-of-home caregivers of children younger than 24 months of age is recommended also (evidence grade III). Immunization of close contacts of children younger than 6 months may be particularly important, because these infants will not be immunized.
 3. TIV may be given to any person older than 6 months of age who (or whose parent) wishes to prevent influenza. Persons who should not receive TIV include individuals who have had anaphylactic reaction to chicken or egg proteins or any other component of the vaccine, such as thimerosal.

LAIV Indications

LAIV is indicated for healthy individuals 5 to 49 years of age who want to be protected against influenza. TIV is preferred for close contacts of immunosuppressed individuals.

Persons should not receive LAIV if any of the following criteria are present:

- Age <5 years;
- History of anaphylactic reaction to egg or chicken protein;
- Receiving salicylates;
- Known or suspected immunodeficiency;
- History of GBS;
- Reactive airway disease or asthma;
- Other conditions traditionally considered high risk for severe influenza (chronic pulmonary disorders

or cardiac disorders, pregnancy, chronic metabolic disease, renal dysfunction, hemoglobinopathies, immunodeficiency, or immunosuppressive therapy).

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APPENDIX 1. US Preventive Services Task Force Rating System of Quality of Scientific Evidence⁷⁰

I	Evidence obtained from at least 1 properly designed, randomized, controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomization
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferentially from >1 center or group
II-3	Evidence obtained from multiple time series with or without the intervention or dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s)
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

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Recommendations for Influenza Immunization of Children
Committee on Infectious Diseases
Pediatrics 2004;113;1441-1447
DOI: 10.1542/peds.113.5.1441

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