

AMERICAN ACADEMY OF PEDIATRICS

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

Reduction of the Influenza Burden in Children

ABSTRACT. Epidemiologic studies indicate that children with certain chronic conditions, such as asthma, and otherwise healthy children younger than 24 months are hospitalized for influenza and its complications at high rates similar to those experienced by the elderly. Currently, annual influenza immunization is recommended for all children 6 months and older with high-risk conditions. To protect these children more fully against the complications of influenza, increased efforts are needed to identify and recall high-risk children for annual influenza immunization. In addition, immunization of children 6 through 23 months of age and their household contacts and out-of-home caregivers is now encouraged to the extent feasible. The ultimate goal is a universal recommendation for influenza immunization. Issues that need to be addressed before institution of routine immunization of healthy young children include education of physicians and parents about the morbidity caused by influenza, adequate vaccine supply, and appropriate reimbursement of practitioners for influenza immunization.

ABBREVIATIONS. AOM, acute otitis media; TIV, trivalent inactivated influenza vaccine; T-CAIV, trivalent live-attenuated, cold-adapted influenza vaccine; FDA, Food and Drug Administration; 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} Depending on the influenza season, rates of annual outpatient visits attributable to influenza vary from 6 to 29 per 100 children.^{2,3} There is evidence that influenza may be important in the pathogenesis of acute otitis media (AOM) during influenza seasons.⁴ It is estimated that 3% to 5% of children experience influenza-associated AOM annually.^{2,5} In addition, concurrent infection of the middle ear with both viruses and bacteria can significantly worsen the course of AOM.⁶ Influenza and its complications lead to a 10% to 30% increase in the number of antimicrobial courses prescribed to children during influenza season.⁷ Antecedent influenza infection also is associated with

development of severe pneumococcal pneumonia in children.⁸

It recently has become clear that healthy children younger than 24 months are at as great a risk of influenza-associated hospitalization as are previously recognized high-risk groups. Young children also appear to be at higher risk of hospitalization for influenza than are healthy 50- to 64-year-olds, for whom routine immunization has been recommended since 2000 (Table 1). One study in Japan demonstrated that among hospitalized children, influenza A infection was associated with a higher incidence of febrile seizures and repeated seizures in the same febrile illness than were adenovirus or parainfluenza infections.⁹ Deaths attributable to influenza are far less common in children than they are in the elderly. The fatality rate in children has been estimated to be 3.8 per 100 000.¹⁰

High rates of hospitalization of the young during influenza seasons have been appreciated for decades,^{3,10,11} but it has been difficult to distinguish the proportion of hospitalizations during influenza season that were attributable to respiratory syncytial virus and other respiratory viruses. Recently published studies have made reasonable attempts to separate the relative contributions of respiratory syncytial virus and influenza.^{2,7,12} Rates vary greatly among studies because of differences in methodology and severity of influenza seasons. However, it has been shown consistently that children younger than 24 months are at substantially higher risk of hospitalization than are older children and that the risk of hospitalization attributable to influenza infection is highest in the youngest 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 those with immunocompromising diseases.^{16,17} Persons with renal, metabolic, and hematologic diseases are presumed to be at higher risk of severe influenza and its complications.

LABORATORY DIAGNOSIS

Rapid diagnostic assays for influenza can be used in an office setting. Currently, 5 kits are available, and 2 are waived under the Clinical Laboratory Im-

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 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 ¹² | Health maintenance organizations | 0–23 mo | | 144–187 |
| | | 2–4 y | | 0–25 |
| | | 5–17 y | | 8–12 |
| 1968–1973 ⁵⁷ | Health maintenance organization | 15–44 y | 56–110 | 23–25 |
| | | 45–64 y | 392–635 | 13–23 |
| | | ≥65 y | 399–518 | — |
| 1969–1995 ⁵⁸ | National hospital discharge data | <65 y | | 20–42 |
| | | ≥65 y | | 125–228 |

Adapted from Centers for Disease Control and Prevention. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep.* 2001;50(RR04):1–46.

provement Amendments of 1988 (Public Law 100-578). Some of these assays detect only influenza A, and others detect influenza A or B. The optimal use of rapid tests remains uncertain because of their relatively low sensitivity and because testing of all patients with respiratory illness is impractical. However, rapid and accurate diagnosis of influenza has become more relevant since active agents against influenza A and B have been licensed. Rapid diagnosis also may decrease nosocomial transmission and unnecessary antimicrobial use.

VACCINES

Currently, the only influenza vaccine licensed for use in children in the United States is the trivalent inactivated influenza vaccine (TIV). A biologic licensing application for a trivalent live-attenuated, cold-adapted influenza vaccine (T-CAIV) administered intranasally was submitted to the Food and Drug Administration (FDA) in October 2000 and is currently under review. Current formulations of these vaccines contain 3 virus strains: influenza A(H1N1), A(H3N2), and B.

Manufacturing, Handling, and Administration

TIV virus is grown in embryonated hen eggs, inactivated, and then in most instances preserved with thimerosal (1:10 000). The removal of thimerosal from routine childhood vaccines has decreased the amount of thimerosal children receive in immunizations. The benefits of influenza immunization are considered to outweigh the theoretical risk of adverse effects, if any, from the small volume of thimerosal in TIV. Currently, the manufacturers distributing TIV in the United States are Aventis Pasteur, Swiftwater, Pennsylvania (Fluzone), Evans Vaccines, Liverpool, England (Fluvirin), and Wyeth-Lederle Vaccines, Philadelphia, Pennsylvania (FluShield). Fluvirin, which can be obtained thimerosal-free, is not licensed for children younger than 4 years, because safety and efficacy have not been established in this age group. A limited number of doses of thimerosal-free Fluzone will be available for the 2002–2003 season. Children younger than 9 years receiving TIV for the first time should be given 2 doses 1 month apart.

Safety

The most common symptoms associated with TIV administration are soreness at the injection site and fever. More subjective symptoms, such as nausea, lethargy, headache, muscle aches, and chills, also are reported. Fever, usually occurring 6 to 24 hours after immunization, is more common in children younger than 2 years (10%–35% of recipients).¹⁸ Immunization of children with asthma does not increase bronchial hyperactivity.¹⁹ After the “swine flu” vaccine program in 1976, an increase in the number of cases of Guillain-Barré syndrome (GBS) was reported. Additional investigations have revealed that there may be a very 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.^{20–23} It is unknown whether influenza immunization of individuals with a history of GBS increases the recurrence rate.

Studies of the safety of TIV immunization of children and adults with human immunodeficiency virus (HIV) infection have yielded conflicting results. Some have demonstrated a transient (2- to 8-week) increase in HIV-1 replication and/or a decrease in CD4⁺ T-lymphocyte cell counts,^{24–27} and others have reported no significant effect.^{28–33} Most experts believe that the benefits of influenza immunization outweigh the risks in children with HIV infection.

Allergic Reactions to TIV

Because influenza vaccine is grown in embryonated hen eggs, children demonstrating anaphylactic reaction to chicken or egg proteins rarely can experience a similar reaction to influenza vaccine and, therefore, should not be given TIV. Inactivated influenza 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 influ-

enza illness confirmed by positive culture varies between 60% and 95% when vaccine strains match the predominant circulating strains.^{34–38} Studies in the United States and Japan raise the possibility that immunization of schoolchildren results in diminished incidence of disease in all age groups, including the elderly.^{39,40}

Studies of the efficacy of influenza vaccine against AOM have produced conflicting results. The overall incidence of AOM in a group child care center was 36% lower among 187 children immunized with TIV compared with 187 children not immunized in other child care centers.³⁵ In that evaluation, there was an 83% decrease in influenza-associated AOM. In a second child care center study, 186 children 6 to 30 months of age were randomly assigned to receive TIV or no vaccine and then were followed biweekly by blinded observers. Influenza vaccine was protective against AOM during the influenza season (odds ratio: 0.69; 95% confidence interval [CI]: 0.49–0.98).⁴¹ 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.³⁸

Vaccine Coverage

Despite recommendations to immunize all children with asthma, only 10% to 31% of this population receive the TIV vaccine each year.^{42–44} 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.⁴² According to parents surveyed, the most important determinant of immunization was physician recommendation.⁴⁴

Costs of 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 of these factors is possible within a given season. These variations make it impossible to generate a single precise estimate of the cost-effectiveness or the 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, 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.^{45–47} A subcommittee of the Advisory Commit-

tee on Immunization Practices, after a review of the major economic studies of influenza immunization,^{45–49} concluded that it is unlikely that universal influenza immunization of young children will generate savings, from a societal perspective, unless the total costs of immunization are less than \$20 to \$25 per child immunized (M. Meltzer, oral presentation at Advisory Committee on Immunization Practices Influenza Workshop, Atlanta, GA, September 11, 2001).

CURRENT LOGISTIC CONSTRAINTS TO UNIVERSAL IMMUNIZATION OF HEALTHY CHILDREN

Limited Vaccine Quantity

In recent years, approximately 70 to 90 million doses of TIV have been available annually, which generally meets national vaccine demands. However, the national distribution of vaccine has been delayed during the past 2 influenza seasons. Currently, vaccine is recommended for more than 100 million persons traditionally considered to be at high risk of serious complications from influenza. Approximately half of all vaccine is used by persons not at high risk of complications. Vaccine demand among both groups has been increasing, and therefore, a larger, more dependable supply of vaccine is desirable before a universal recommendation for influenza immunization of young children is implemented.

Seasonal Vaccine Availability

Global surveillance of circulating influenza strains permits recommendation during spring of the strains to be included in vaccine for the following fall. Once the strains are selected, they must be adapted for growth in embryonated hen eggs, after which large-scale production begins. The size and number of lots of vaccine that can be grown at any one time in a production facility is limited, and the timing of vaccine lot release cannot be predicted accurately. The earliest that vaccine becomes available generally is September, and immunization needs to begin before widespread influenza outbreaks occur, most of which are in January and February. Consequently, immunizations must be completed in a 3- to 5-month period. This challenge is made more difficult by the need to deliver 2 doses of vaccine 1 month apart to immunologically naive children.

Multiple Injections

At this point, the only influenza vaccine licensed in the United States is administered intramuscularly. Until additional combination vaccines are available, US children already receive up to 20 separate injections of vaccine during the first 2 years of life. The addition of 2 or 3 more injections may not be well accepted by practitioners, parents, or children. Availability of an intranasally administered vaccine would obviate this issue in some children. However, safety and efficacy data on the intranasal T-CAIV are limited in children younger than 18 months, and thus, it

may not be licensed, at least initially, for use in young children.

Complicated Schedule

It generally is assumed that TIV can be administered at the same visit as other childhood immunizations, although studies of this practice are lacking.

Recall Systems

Currently, many practitioners lack the computerized tracking and recall systems necessary to efficiently and effectively identify children eligible for immunizations. More widespread availability and use of immunization registries will alleviate this problem.

Personnel Demands

Additional clerical, nursing, and physician time would be required during the fall months to provide universal influenza immunization to all children 6 to 24 months of age. Not all medical practices may have the flexibility and capacity to absorb this seasonal increased time demand. Investigators at the University of Rochester, in collaboration with the Centers for Disease Control and Prevention, are conducting feasibility and implementation studies. Such evaluations need to be performed in multiple settings before it is assumed that universal immunization can be implemented without undue hardship for practitioners, parents, and children. Cost-effectiveness studies have demonstrated that universal influenza immunization is more likely to be cost-beneficial if immunization is performed in group settings that do not require parents to take time from work. The feasibility of evening and weekend "immunization clinics" in the practice setting needs to be evaluated.

Reimbursement and Liability Issues

An important determinant of feasibility is whether practitioners will be fairly compensated for the widespread administration of influenza vaccine to young children. Adequate compensation should be determined before it can be assumed that the cost of additional work and expense of influenza vaccine can be absorbed. Practitioners should be aware that influenza vaccine for healthy children is unlikely to be covered under the Vaccine Injury Compensation Program until it receives a full recommendation from the Advisory Committee on Immunization Practices.

ANTIVIRAL MEDICATION

Amantadine and Rimantadine

The tricyclic amines amantadine hydrochloride and rimantadine hydrochloride inhibit the replica-

tion of influenza A virus (Table 2). Prophylaxis with either drug can prevent approximately 70% to 90% of influenza A illness.⁵⁰ The recommended dose for each drug in children younger than 10 years is 5 mg/kg of body weight per day in 1 or 2 doses, not to exceed 150 mg/day. For children 10 years and older, the dose is 100 mg twice a day. Both drugs decrease the severity and shorten the duration of influenza A illness in healthy subjects by approximately 1 day when therapy is started within 48 hours of onset of symptoms. Amantadine is licensed by the FDA for treatment of influenza in children 12 months or older, but rimantadine is licensed for treatment only in individuals 13 years or older. It is not known whether treatment with amantadine or rimantadine decreases the risk of serious complications of influenza in high-risk patients. Both drugs are excreted in the urine, and dosage adjustments are necessary for children with renal disease. Rimantadine is metabolized in the liver before renal excretion, so adjustment of dosage also is suggested for patients with severe liver disease. Disadvantages of amantadine and rimantadine include: 1) lack of activity against influenza B; 2) emergence of resistant influenza isolates during treatment; and 3) occurrence of reversible adverse effects on the central nervous system, including nervousness, lightheadedness, difficulty with concentration, and rarely, tremors or seizures. However, these drugs are substantially less expensive than are the newly licensed neuraminidase inhibitors; thus, they have a role, particularly in control of outbreaks attributable to influenza A.

Neuraminidase Inhibitors

Zanamivir and oseltamivir phosphate are 2 members of a class of antiviral drugs called neuraminidase inhibitors that were first licensed by the FDA in 1999 for treatment of uncomplicated disease caused by influenza A or B when symptoms have been present for fewer than 48 hours.⁵¹ Zanamivir (Relenza [GlaxoSmithKline, Middlesex, United Kingdom]) is an inhaled topical powder that is licensed for treatment of influenza in children as young as 7 years. A dose of 10 mg is administered twice daily for 5 days. Zanamivir should not be given to patients with a history of reactive airway disease, because it may induce bronchospasm. Oseltamivir (Tamiflu [Roche Laboratories, Nutley, NJ]) is an oral formulation (tablet and suspension) licensed for treatment of children older than 1 year and for prophylaxis in those 13 years and older. The dose is 2 mg/kg, administered twice daily (maximum dose is 75 mg twice a day) for 5 days.

Zanamivir treatment was studied in a random-

TABLE 2. Antiviral Drugs for Influenza

| | Amantadine | Rimantadine | Zanamivir | Oseltamivir |
|--------------------------|---------------------------------|---------------------------------|--------------|------------------|
| Virus | A | A | A and B | A and B |
| Administration | Oral | Oral | Inhalation | Oral |
| Treatment indications* | ≥1 y of age | ≥13 y | ≥7 y | ≥1 y |
| Prophylaxis indications* | ≥1 y | ≥1 y | Not licensed | ≥13 y |
| Adverse effects | Central nervous system, anxiety | Central nervous system, anxiety | Bronchospasm | Nausea, vomiting |

* Licensed ages.

ized, controlled trial in 346 children between 5 and 12 years of age who were infected with influenza A or B.⁵² Treatment decreased symptoms by a median of 1.25 days, compared with placebo recipients, representing a 24% decrease in duration of symptoms and a 15% more rapid return to normal activity. There was no difference in occurrence of adverse events between zanamivir and placebo recipients.

Oseltamivir treatment of influenza has been evaluated in children between 1 and 12 years of age in a randomized, double-blind, placebo-controlled study.⁵³ Among 457 children with documented influenza infection who were treated within 48 hours of onset of symptoms, the median duration of illness was decreased by 36 hours in the oseltamivir group. Incidence of AOM was decreased by 44% in oseltamivir recipients (12%, vs 21% in the control group). There also was a significant decrease in the number of antimicrobial prescriptions for children receiving oseltamivir (31%, vs 41% in the control group). Gastrointestinal disturbances occurred in 14.3% of oseltamivir and 8.5% of placebo recipients, although fewer than 2% discontinued medication because of adverse effects.

The efficacy of postexposure oseltamivir prophylaxis among household contacts of an individual with an index case of influenza⁵⁴ was 89%, compared with placebo, when prophylaxis was initiated within 48 hours of exposure. A similar level of protection among persons 5 years and older using zanamivir has been demonstrated in a family study,⁵⁵ but zanamivir currently is not licensed for this indication. Studies comparing neuraminidase inhibitors with amantadine or rimantadine for treatment or prophylaxis in children are not available.

CONCLUSIONS

Young children are hospitalized for influenza at rates similar to those experienced by the elderly. Among the young, hospitalization rates are inversely related to the age of the child, being highest in those younger than 6 months. However, no influenza vaccine is licensed for use in infants younger than 6 months. Immunization is recommended for women who will be in their second or third trimester of pregnancy during influenza season, because they are at increased risk of cardiopulmonary complications from influenza infection. Studies are needed to determine whether maternal immunization affords subsequent protection to the infant.

It appears that more widespread influenza immunization of young children and their close contacts is justified. An immediate recommendation for universal immunization appears to be premature, however, until logistic and economic issues have been evaluated further.

RECOMMENDATIONS

1. Practitioners should increase their efforts through tracking and recall systems to ensure that children traditionally considered at high risk of severe disease and complications from influenza infection receive annual immunization. High-risk children and adolescents who should receive priority for

influenza immunization are those with the following (evidence grade II-3 [see Appendix A]):

- 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 syndrome
- 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)
 - Persons who are in close contact with high-risk children, including (evidence grade II-3):
 - All health care personnel in contact with pediatric patients in hospital and outpatient settings
 - Household contacts, including siblings and primary caregivers, of high-risk children
 - Children who are members of households with high-risk adults, including those with symptomatic HIV infection
 - Home caregivers for children and adolescents in high-risk groups
2. Young, healthy children also are at high risk of hospitalization for influenza infection; therefore, the American Academy of Pediatrics encourages influenza immunization of healthy children between 6 and 24 months of age to the extent logistically and economically feasible (evidence grade II-3). This applies to any child who will be 6 through 23 months of age at any time during 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 also is encouraged when feasible (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. Antiviral drugs are an adjunct to, not a substitute for, the prevention of influenza with immunization. Amantadine and rimantadine are licensed for chemoprophylaxis of influenza A in children 1 year or older. Oseltamivir may be used for prevention of influenza A and B in persons 13 years and older (evidence grade I). Chemoprophylaxis may be considered in the following situations (evidence grade III):
 - Protection of high-risk children during the 2 weeks after immunizations while an immune response is developing, if the children are im-

- munized after circulation of influenza virus has been documented
- Protection of high-risk children for whom the vaccine is contraindicated (ie, those with a history of anaphylactic reaction to eggs)
 - Protection of nonimmunized close contacts of high-risk children
 - Protection of immunocompromised children who may not respond to vaccine
 - Control of influenza outbreaks in a closed setting, such as an institution with high-risk children
 - Protection of immunized high-risk individuals if the vaccine strain poorly matches the circulating influenza strain(s)

Appendix A. US Preventive Services Task Force Rating System of Quality of Scientific Evidence⁵⁶

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 more than 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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