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Current Recommendations for Influenza Vaccination in Children

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In May, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics issued new recommendations on the administration of influenza virus vaccine to children.[1,2] Included in these policy statements is a recommendation for immunization of healthy children between the ages of 6 and 23 months. This recommendation, first announced by the ACIP in October 2003, was based on epidemiologic studies showing that children in this age group were at higher risk for hospitalization after influenza infection and suffered from more complications than older children. Yearly immunization for influenza is also recommended for household contacts and other caregivers of young children.[1,2] These new recommendations are an addition to the previous recommendation for immunization of all health care providers and high-risk patients, including children over 6 months of age who have chronic medical conditions. This issue of *Pediatric Pharmacotherapy* will review the new guidelines and the influenza vaccines currently available.

Influenza in Children

Hospitalization rates for otherwise healthy children infected with influenza have been estimated at 100 per 100,000 children. In infants and children with chronic medical conditions, the rate of hospitalization is increased to 500 per 100,000 children.[1-3] In a study of children admitted to the Montreal Children's Hospital for influenza, the mean age of the patients was 26.1 months, and 34% were less than 6 months of age.[3]

Mortality resulting from influenza infection in children is rare. The fatality rate in children is estimated at 3.8 cases per 100,000. During the 2003-2004 influenza season, there were 143 reported deaths in children. Nearly half of the children who died were less than 2 years of age.[1]

In addition to morbidity and mortality, influenza creates an economic burden. In 2003, Principi and colleagues compared the clinical course of 352 otherwise healthy children with documented influenza to 3,419 influenza-negative children with symptoms of an upper respiratory tract infection seen in the same emergency departments and clinics.[4] The authors found a significantly longer duration of fever and more missed school days in the influenza-positive group, as well as more medical visits and more missed days of school or work for their household contacts.

Impact of the New Recommendations

In 2002, the ACIP began to encourage influenza vaccination in children 6 to 23 months of age, based on the higher rates of hospitalization and serious complications in this age group.[5] The addition of the influenza vaccine to the routine childhood immunization schedule, however, was delayed until more information became available on the safety and efficacy of the available vaccines in this population. In addition, the impact of widespread immunization on vaccine supplies and physician/clinic resources had to be evaluated.[6-8]

The availability of an adequate vaccine supply remains a concern. Previous recommendations for the immunization of high-risk patients and health care providers resulted in a need for coverage of approximately 180 million people per year in the United States. With routine immunization of healthy 6 to 23 month olds, that number is increased by another 7 million patients each year.[6]

Available Vaccines

There are currently three influenza virus vaccines available in the United States.[9-12] All are trivalent vaccines, standardized to contain the hemagglutinins of 2 type A and one type B influenza strains. Two of the influenza vaccines, Fluzone® (Aventis Pasteur) and Fluvirin® (Evans Vaccine Ltd/Chiron), are trivalent inactivated split-virus vaccines (TIV) for intramuscular administration. The term "split-virus" is used interchangeably with "subviron" or "purified antigen preparation." Fluzone® is approved by the Food and Drug Administration (FDA) for use in patients 6 months of age or older. Fluvirin® is approved in children 4 years of age and older. Both TIV products are available in 0.5 ml pre-filled syringes and 5 ml multidose vials. Both products contain thimerosal. Fluzone® is also available in preservative-free 0.25 ml pre-filled syringes with trace amounts of thimerosal for use in patients less than 3 years of age. All TIV products must be refrigerated until use.

In patients 6 to 35 months of age, a 0.25 ml dose of TIV should be administered intramuscularly. In patients 3 to 8 years of age, the standard 0.5 ml dose should be used. In patients less than 9 years of age who have not been previously immunized with TIV, a second dose should be administered at least one month after the initial dose. It is recommended that children being immunized for the first time be given their initial dose in September or October with the second dose given before December, in order to maximize protection during the peak of the influenza season. Patients 9 years of age or older should receive a single TIV dose of 0.5 ml given intramuscularly.[9-11]

FluMist® (MedImmune Vaccines/Wyeth) is currently the only trivalent live-attenuated intranasal influenza vaccine (LAIV). It is packaged in 0.5 ml preservative-free pre-filled single-use sprayers. FluMist® must be stored in a non-frost-free freezer or with a special freezer box supplied by the manufacturer for frost-free freezers. It should be thawed just prior to use. However, it can be thawed in a refrigerator and stored for up to 60 hours if not used immediately. FluMist® is approved by the FDA for healthy individuals between 5 and 49 years of age. Children between the ages of 5 and 8 years who have not previously received FluMist® should be given two 0.5 ml doses at least 6 weeks apart. Children who have previously received FluMist® or are 9 years of age or older should receive a single 0.5 ml dose. FluMist® is administered by giving half the dose (0.25 ml) into each nostril with the patient in an upright position.[1,9,12]

Clinical Efficacy in Children

The efficacy of the inactivated influenza vaccines and the live virus intranasal product has been demonstrated in numerous clinical trials.[13-15] Overall efficacy of TIV has been estimated to range between 31 to 91% in children. In a recent review by Zangwill and Belshe published in *The Pediatric Infectious Disease Journal*, the authors identified seven randomized, controlled trials of TIV which included children less than 9 years of age.[13] Using the five studies that enrolled only children, the authors estimated a pooled vaccine efficacy of 63%.

Only one study has been published which evaluated the efficacy of TIV specifically in the new target population. During their first study year, Hoberman and colleagues reported an efficacy of 66% in 411 children 6 to 23 months of age. Efficacy declined to –7% the second year of the study with a new group of 375 children, likely as a result of a low attack rate that year. In both study years, the rate of seroconversion to each of the three strains included in the vaccine was greater than 90%.[15]

The efficacy of the intranasal live virus influenza vaccine has also been established in several trials.[16-18] In 1998, Belshe and colleagues published the first study of LAIV in children. A total of 1,602 children between 15 and 71 months of age were randomized to receive either LAIV (in one or two doses given 2 months apart) or placebo.[16] The rate of seroconversion was 61 to 96%, depending on the influenza strain. The incidence of culture-proven influenza was significantly lower in the treatment groups (14 cases in 1,070 children) than in those given placebo (95 cases in 532 children). Vaccine efficacy was estimated at 89% for the children given a single dose and 94% in those given two doses. Subsequent studies have provided similar results, with efficacy rates of approximately 72 to 90%.[12,13,19]

Contraindications and Precautions

All influenza vaccines are contraindicated in individuals allergic to egg or egg products. The trivalent inactivated vaccines are also contraindicated in patients with a history of hypersensitivity to thimerosal. It is recommended that patients with a history of Guillain-Barre syndrome not be given the influenza virus vaccine unless they are at high risk for severe complications from influenza infection. Although Guillain-Barre syndrome was associated with the use of influenza vaccine in the past (the 1976 swine flu vaccine), it has not been reported with the current vaccine products. Influenza virus vaccine should not be

administered to patients with active neurological disorders until their condition has stabilized.[9-11]

FluMist® should not be administered during an acute febrile illness. Patients with a respiratory illness should not receive FluMist® until their symptoms have cleared. Mild upper respiratory tract infection is not a contraindication to its use. It is not recommended for children with chronic cardiovascular or pulmonary disorders, including asthma, diabetes, renal dysfunction, or hemoglobinopathies.[9,12]

FluMist® should not be administered to patients receiving aspirin therapy because of the association with Reye syndrome. In addition, it should not be used in patients with known or suspected immunodeficiency or who are immunosuppressed as a consequence of treatment with corticosteroids, chemotherapeutic agents, radiation, or other immunosuppressive therapies. Vaccine recipients should avoid close contact with other severely immunocompromised individuals for at least 7 days. FluMist® should not be administered at the same time as other vaccines. The manufacturer recommends that their product not be administered within one month of another live virus vaccine or within two weeks of an inactivated vaccine.[9,12]

Adverse Effects

The most frequent adverse effect after administration of TIV is soreness at the injection site, reported in 10 to 64% of patients in clinical trials. Fever, malaise, and myalgia have also been reported after vaccine administration, more frequently in children receiving their first dose. These reactions may persist for up to 1 to 2 days.

The most frequent adverse effects after administration of LAIV include nasal congestion (46-48% of pediatric patients in clinical trials), cough (26-38%), sore throat (9-12%), irritability (9-19%), headache (6-17%), chills (2-6%), vomiting (4-5%), muscle aches (5-6%), fever (0-10%), and tiredness or decreased activity (10-14%). Other adverse effects reported in pediatric clinical trials include abdominal pain, otitis media, accidental injury, and diarrhea. These reactions occurred in similar numbers in patients given placebo.[9,12,20]

Rare serious reactions reported with influenza vaccines include hypersensitivity reactions, including anaphylaxis, and neurologic disorders, including encephalitis, paresthesia, brachial neuritis, demyelinating disease, labyrinthitis, meningitis, encephalopathy, optic neuritis, and facial paralysis. Causality for these neurologic adverse effects has not been established.[9-12]

Cost

The average wholesale price (AWP) for Fluvirin® is $10.80 per 0.5 ml pre-filled syringe and $8.70 per 0.5 ml dose using the 5 ml multidose vial. Fluzone® is comparable at $14.21 for a pre-filled 0.5 ml syringe, $15.00 for the 0.25 ml preservative-free pediatric syringe, and $10.63 per 0.5 ml dose using the multidose vial. The AWP for FluMist® is $23.50 per dose.[21,22]

Summary

Recent recommendations from the ACIP and American Academy of Pediatrics call for routine influenza immunization in healthy children between 6 and 23 months of age, as well as close contacts of infants and young children. These guidelines are in addition to the previous recommendations for immunization of health care providers and patients at high-risk for severe infection, such as those with chronic medical conditions. During this first year of routine childhood influenza vaccination, much will be learned about the safety and efficacy of the available products, as well as the impact of wide-spread influenza vaccine administration on health care resources.

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Pharmacology Literature Review

Budesonide Compatibility

Nebulized medications are frequently mixed together to reduce administration times for patients with asthma. The authors of this study evaluated the compatibility and stability of budesonide with levalbuterol, albuterol, cromolyn, and ipratropium. The budesonide-ipratropium combination retained 93% of the initial concentration of each medication. The other combinations retained at least 97% of the initial concentrations. There were no pH changes or precipitation in the solutions prepared. The authors concluded that these combinations were compatible for at least 30 minutes after mixing. McKenzie JE, Crus-Rivera M. Compatibility of budesonide inhalation suspension with four nebulizing solutions. **Ann Pharmacother 2004;38:967-72.**

Medication Errors in Children

This review describes the incidence and type of medication errors encountered in the treatment of children, using an analysis of 16 previous studies. Dosing errors were the most common in 11 of the papers reviewed. There was considerable variation among the rates of errors reported, likely the result of differences in reporting mechanisms and error definitions. The authors suggest that methods to reduce errors in calculations be a priority for educational programs. Wong JCK, Ghaleb MA, Franklin BD, et al. Incidence and nature of dosing errors in paediatric medications: a systematic review. **Drug Safety 2004;27:661-70.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 7/23/04:

1. Tiotropium bromide inhalation powder (Spiriva® HandiHaler®) was added to both the Inpatient and Outpatient Formularies for use in patients with chronic obstructive pulmonary disease.

2. Two antihelmintics, albendazole (Albenza®) and praziquantil (Biltricide®), were added to the Inpatient Formulary. These agents, along with mebendazole (Vermox®), were also added to the Outpatient Formulary.

3. Intravenous N-acetylcysteine (Acetadote®) was added to the Inpatient Formulary with restriction to the management of acetaminophen overdoses or fulminant hepatic failure.

4. The restriction on polyethylene glycol 3350, NF (Miralax®) was amended to include prescribing by adult Gastroenterology and use in patients who are maintained on this therapy at home.

5. As a result of the yearly review, the following agents were deleted from the Inpatient Formulary: spectinomycin, methenamine, parenteral cefuroxime, clarithromycin 250 mg, amprenavir, and delavirdine. Minocycline, pyrantel pamoate, and thiabendazole were also removed, but can be ordered if needed for an individual patient. Clarithromycin 250 mg and amprenavir were also removed from the Outpatient Formulary.

6. The use of oral naloxone for chronic opioid-induced constipation was approved.

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