SAFETY, EFFICACY, AND USE OF INACTIVATED INFLUENZA VACCINE IN CHILDREN*

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ABSTRACT

A review of selected clinical trials of influenza vaccine shows that the vaccines are safe and effective in children. Both healthy children as well as high-risk children, such as those with asthma and other conditions associated with increased risk for infection, derive similar benefits from vaccination. Depending on the clinical trial, influenza vaccination may afford protection against acute otitis media. Vaccination rates among healthy and high-risk children are low. Physicians should encourage immunization, and inform parents about the risks, benefits, and eligibility for childhood influenza immunization.

RANDOMIZED TRIALS COMPARING INACTIVATED AND COLD-ADAPTED VACCINES

RESULTS OF THE FIRST STUDY

The first study in this review enrolled 189 children who were 3 to 18 years of age at the time of immunization. The children were randomized by family into 1 of 3 vaccine groups: either to inactivated or cold-adapted vaccine or placebo. The vaccine strains included in the trivalent inactivated vaccine were influenza A Chile (H1N1), influenza A Philippines (H3N2), and influenza B Russia. The cold-adapted vaccine contained only the identical H1N1 and the H3N2 strains. Unfortunately, the predominant circulating strain that season was influenza B Ann Arbor (drift strain), reflecting the imprecision involved in determining the vaccine makeup for a given influenza season. Because the cold-adapted vaccine did not contain influenza B, the efficacy of the 2 active vaccines could not be compared.

Both vaccines demonstrated a safety profile that was comparable to that of placebo. The trivalent vaccine was associated with a 20% incidence of tenderness at the injection site, compared to 19% in the placebo group. Upper respiratory symptoms occurred...
in 19% of placebo patients and 15% of patients who received the intranasally administered cold-adapted bivalent vaccine. Because upper respiratory symptoms are a common problem in children, determining the proportion attributable to the vaccine is problematic. At the very least, however, the vaccine did not increase respiratory symptoms.

With respect to immunogenicity, both vaccines produced good responses. The inactivated trivalent vaccine stimulated a 4-fold rise in hemagglutination inhibition antibody (HIA) to both influenza A antigens in 80% to 90% of older children (6 years and older). Children younger than 6 years of age developed a 4-fold rise in HIA (response rate) to both influenza A antigens in 50% to 60% of subjects. The investigational cold-adapted vaccine achieved a 50% to 60% overall response rate to H3N2 (40% versus about 20% for older children), leading to better overall immunogenicity in younger children. Across all age groups, the children had good immunologic responses to both cold-adapted vaccines.

With respect to protection against influenza B, patients who received the trivalent vaccine fared well when compared to the placebo group. Overall efficacy was 62% for prevention of infection, 58% for clinical illness, and 76% for febrile illness. For prevention of clinical illness and infection, the inactivated vaccine did not perform as well in younger children, achieving efficacy about half the time. The results are consistent with the immunogenicity data showing that younger children receiving inactivated trivalent vaccine do not generate as great an immune response as older children.

In summary, this study showed that both the trivalent inactivated vaccine and the cold-adapted bivalent vaccine were safe across all age groups. With the trivalent vaccine, higher antibody responses were noted in the older children. In contrast, the cold-adapted vaccine demonstrated better overall immunogenicity in younger children. The efficacy of the trivalent vaccine was 40% to 60% in children younger than 6 years of age and 80% or greater in older children.

**Results of the Second Study**

The second study in this review involves a trial that continued the evaluation of influenza vaccines in the same population involved in the previous study. The number of patients increased only slightly to 192. The trial design was the same, a comparison of the trivalent inactivated vaccine and the cold-adapted bivalent vaccine to placebo. The inactivated vaccine contained influenza A Chile (H1N1), influenza A Bethesda A (H3N2), and influenza B Ann Arbor B. The cold-adapted vaccine contained the same influenza A H1N1 and H3N2 strains. The circulating strain for the year of the study (1986-1987) was Taiwan A (H1N1), slightly drifted.

Consistent with results from the previous year, the trivalent vaccine achieved better immunogenicity in older children (10 to 19 years), who had about a 70% response rate. In younger children, the immune

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<tr>
<td>Population/Number</td>
<td>189 children age 3-18 years</td>
<td>192 children age 3-18 years</td>
<td>791 healthy children age 1-16 years</td>
</tr>
<tr>
<td>Type of Study</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Randomized, double-blind, placebo-controlled</td>
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<tr>
<td>Vaccines</td>
<td>CA bivalent, TIV, placebo</td>
<td>CA bivalent, TIV, placebo</td>
<td>CA bivalent, TIV, placebo</td>
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<tr>
<td>Vaccine Strain</td>
<td>B/USSR/83, A/Chile/83/H1N1, A/Philip/82/H3N2</td>
<td>B/Ann Arbor/86, A/Chile/83/H1N1, A/Bethesda/85/H3N2</td>
<td>Year 1, Influenza B 2 Years, H3N2 circulation (1 drift) 2 Years, H1N1 circulation (1 drift)</td>
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**Table 1. Summary of 3 Clinical Trials Comparing Licensed Trivalent Inactivated Influenza Vaccine and Experimental Cold-Adapted Influenza Vaccine**

TIV = trivalent inactivated vaccine; CA = cold adapted; A/Chile/83/H1N1 = influenza A Chile; A/Philip/82/H3N2 = influenza Philippines; B/USSR/83 = influenza Russia; B/Ann Arbor/86 = influenza B Ann Arbor (drift strain); A/Bethesda/85/H3N2 = influenza A Bethesda.
response rate was slightly greater than 50%. The opposite response pattern was observed in children who received the cold-adapted bivalent vaccine. About 70% of younger children achieved adequate immune responses (defined as a 4-fold rise in HIA), compared to about 40% of older children.

The inactivated trivalent vaccine achieved a 62% overall efficacy rate for H1N1 infection, while the cold-adapted vaccine efficacy was 51%. Collectively, the results of both of these trials demonstrated that both vaccines were safe and efficacious in a population of children 3 to 18 years of age.

Results of the Third Study

The National Institutes of Health supported a large 5-year randomized clinical trial comparing the inactivated influenza vaccine and the cold-adapted vaccine. The study involved 5210 patients who spanned a broad age range. The trial included 791 healthy children 1 to 16 years of age, and this review focuses on that pediatric subgroup.

During 2 years of the evaluation, the primary circulating strain was H3N2, in 2 other years the strain was H1N1, and in 1 year the strain was Influenza B. Since the cold-adapted vaccine did not contain influenza B, the efficacy of the 2 vaccines could not be compared in the year with influenza B. Prior to the first immunization, between 35% and 85% of children across all age groups were seropositive for H1N1, and 50% to 90% were seropositive H3N2. About 40% of seronegative patients 1 to 5 years of age had a 4-fold rise in HIA titer to H1N1 and H3N2 after initial vaccination with the trivalent vaccine. About 80% of seronegative patients 6 to 10 years of age responded to the vaccine, and between 80% and 90% of older patients responded.

The cold-adapted vaccine elicited a response similar to that of the trivalent vaccine for H1N1. Response rates were slightly lower for H3N2, ranging from less than 40% for children 1 to 5 years of age to about 60% in older patients.

Patients who were seropositive prior to initial immunization with the trivalent vaccine had response rates ranging from 50% to about 80% for H1N1, with younger children having the lower response rate. The response to H3N2 was about 80% across all age groups.

Seropositive patients did not have vigorous responses to the cold-adapted vaccine, in contrast to their response to the trivalent vaccine. Responses to H1N1 occurred in 30% to 40% of patients, and the response to H3N2 ranged from a high of about 20% in younger patients to 10% or less in older patients who received the cold-adapted vaccine.

Self-reported local reactions in older children occurred in 4% to 7% of cases within 5 days of vaccination. Induration occurred in more patients who received the trivalent vaccine, 14.2% compared to approximately 5% in the placebo group and the cold-adapted vaccine group. Those rates were slightly higher than the rates reported for younger children.

Table 2. Summary of Results from 3 Clinical Trials

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<th>Gruber et al</th>
<th>Clover et al</th>
<th>Neuzil et al</th>
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<tbody>
<tr>
<td>Safety</td>
<td>Both vaccines appear to be safe</td>
<td>TIV improved immunogenicity in older children</td>
<td>TIV was safe; frequency of local reaction increased with age</td>
</tr>
<tr>
<td>Antibody Response, CA</td>
<td>Antibody titers improved with age</td>
<td>CA improved immunogenicity in younger children</td>
<td>Immunogenicity: 50%-60% &lt; 6 years and 75%-100% &gt; 6 years had 4-fold HIA response after 1 dose TIV</td>
</tr>
<tr>
<td>Antibody Response, TIV</td>
<td>40%-60% &lt; 6 years and 80%-100% &gt; 6 years had 4-fold HIA response after 1 dose TIV</td>
<td>TIV efficacy for H1N1 infection: 62%</td>
<td>TIV was efficacious for preventing seroconversion and culture-positive illness</td>
</tr>
<tr>
<td>Efficacy</td>
<td>TIV efficacy for influenza B was 62% for all infections and 72% for febrile illness</td>
<td>CA efficacy for H1N1 infection: 51%</td>
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CA = cold adapted; HIA = hemagglutination inhibition antibody; H1N1 = antigen used in study; TIV = trivalent inactivated vaccine.
For all age groups, the incidence of culture-positive influenza illness was significantly lower in the 2 immunized groups compared to the placebo group. Overall protection against H1N1 was 91.4% with the trivalent vaccine and 95.5% with the cold-adapted vaccine. For H3N2, the trivalent vaccine was effective in 77.3% of patients versus 67.7% of patients immunized with the cold-adapted vaccine. Statistical analysis revealed overlapping confidence intervals, suggesting that both vaccines were highly efficacious for prevention of influenza illness and that they did not differ significantly from one another.

In summary, this study showed that the trivalent vaccine was safe and resulted in immunogenicity rates of 50% to 60% in children younger than 6 years of age compared to rates as high as 100% in older children. The trivalent vaccine effectively prevented culture-positive illness.

SUMMARY OF RESULTS OF THESE STUDIES

Collectively, the 3 studies reviewed above show that trivalent vaccines are well tolerated in all age groups (Table 2). The data also suggest that younger children should receive 2 doses of vaccine because a single dose of the inactivated vaccine has less immunogenicity in younger children. Most important, the 3 studies—collectively and individually—demonstrate the protective efficacy of the trivalent vaccine against all 3 strains of influenza virus and demonstrate protection in drift years. Cold-adapted vaccines were found to be safe and effective for all age groups. However, cold-adapted vaccines had better overall immunogenicity in younger children.

HIGH-RISK POPULATIONS

Relatively little published data exist to permit thorough assessment of the efficacy of inactivated vaccine in high-risk groups, such as patients with asthma. In general, the immunogenicity and safety of the vaccine appear comparable in high-risk and healthy children (Table 3).

The largest study to date involved 137 asthmatic Japanese children with moderate to severe asthma. Of the study participants, 134 patients could be evaluated for vaccination status and response. The study was controlled but not randomized, and 82 of the 134 children were immunized with a trivalent vaccine manufactured in Japan. At the time of the study, Japan was experiencing an influenza epidemic caused by the H3N2 virus with marked antigenic drift and by influenza B with a good vaccine match.

The primary endpoint of the study was clinical efficacy based on the incidence of febrile illnesses accompanied by a rise in antibody titers or isolation of the virus. Sera for HIA response were obtained 3 to 4 weeks after administration of the second dose of vaccine, and HIA assessment was repeated the following spring. Patients were evaluated at 2-week intervals, or more frequently if clinically indicated. Patients with
respiratory symptoms or fever were evaluated for the presence of influenza viruses.

Unfortunately, little immunogenicity data and no safety data are available from the study. Available efficacy data showed that H3N2 virus was isolated from 62% of nonimmunized patients and 20% of vaccinated patients, representing an efficacy rate of 68%. The vaccination achieved a 54% efficacy rate in children younger than 7 years of age and 78% efficacy in children ≥ 8 years of age. Influenza B virus was isolated from 48% of the control group and 27% of the vaccinated patients, resulting in an overall efficacy rate of 44%. Similar to the H3N2 experience, efficacy against influenza B was lower in children younger than 7 years of age (22%) than in children older than age 7 years. Although the data are limited in scope, they indicate that administration of influenza vaccine effectively protected pediatric patients against influenza A (H3N2) despite antigenic drift and was most effective in children older than age 7 years. Protection against influenza B was also reduced in younger children. The lower rate of protection against influenza B occurred despite a good match between the vaccine strain and the circulating viral strain.

In general, the results of the Japanese study reflect findings from smaller studies of influenza immunization in high-risk pediatric patient populations. Safety profiles have been favorable in high-risk patients and comparable to profiles reported in healthy children. Limited immunogenicity data suggest immunization has comparable effects in high-risk and healthy populations.

**RATES OF VACCINE ADMINISTRATION**

In studies recently conducted, influenza vaccination rates for hospitalized children with and without high-risk medical conditions were 31% and 14%, respectively. For both groups of children, the vaccination status was strongly influenced by recommendations from physicians. More than 70% of children were vaccinated if a physician had recommended the influenza vaccine, whereas only 3% were vaccinated if a physician had not. Lack of awareness that children can receive the influenza vaccine was a commonly cited reason for nonvaccination.

**CONCLUSION**

Influenza vaccines have proven to be safe and effective for prevention of influenza in children. High-risk children, such as those with asthma and other chronic respiratory conditions, derive at least as much benefit from vaccination as healthy children. Only a small percent of children eligible for vaccination actually receive the vaccine. Physicians and parents must work together to extend the benefits of influenza vaccination to more children.

**REFERENCES**