Effectiveness of Intranasal Live Attenuated Influenza Vaccine Against All-cause Acute Otitis Media in Children

Terho Heikkinen, MD, PhD,* Stan L. Block, MD,† Seth L. Toback, MD,‡ Xionghua Wu, PhD,‡ and Christopher S. Ambrose, MD‡

Background: Acute otitis media (AOM) is a frequent complication of influenza in children, and influenza vaccination helps protect against influenza-associated AOM. A live attenuated influenza vaccine (LAIV) approved for eligible children aged ≥2 years for the prevention of influenza also effectively reduces influenza-associated AOM. However, the annual effectiveness of LAIV against all-cause AOM is unknown.

Methods: AOM rates in children aged 6–83 months from 6 randomized, placebo-controlled trials and 2 randomized, inactivated influenza vaccine-controlled trials were pooled and analyzed. To enable comparison with studies of AOM prevention by pneumococcal conjugate vaccines, 12-month effectiveness was calculated assuming that LAIV had no effect outside of influenza seasons.

Results: During influenza seasons, LAIV efficacy compared with placebo against all-cause AOM in children aged 6–71 months (N = 9497) was 12.4% (95% confidence interval [CI]: 2.0%, 21.6%) in year 1. In year 2, the efficacy in children aged 18–83 months (N = 4142) was 6.2% (95% CI: −12.4%, 21.7%). Compared with inactivated influenza vaccine, the efficacy of LAIV in children aged 6–71 months (N = 9901) against febrile all-cause AOM was 9.7% (95% CI: −2.1%, 20.1%). The estimated 12-month effectiveness of LAIV compared with placebo against all-cause AOM was 7.5% (95% CI: −2.4%, 16.2%).

Conclusions: LAIV reduced the incidence of all-cause AOM compared with placebo in children. The estimated 12-month effectiveness of LAIV was comparable with 7-valent pneumococcal conjugate vaccine. The effects of the vaccines will overlap somewhat; however, because pneumococcal conjugate vaccines only prevent a fraction of all pneumococcal AOM and influenza-associated AOM can be caused by other pathogens, LAIV could further reduce the incidence of AOM in children.

Key Words: acute otitis media, live attenuated influenza vaccine, trivalent inactivated influenza vaccine

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Aacute otitis media (AOM) remains the most common bacterial infection and the most frequent reason for antibiotic treatment in infants and young children. Although the incidence of AOM peaks around the age of 1 year, the rates of AOM are substantial in older children. The high prevalence of antimicrobial resistance among common bacteria causing AOM has substantially complicated the management of AOM, and efforts to reduce the use of antibiotics for this disease are being assessed. As a consequence, prevention of AOM through vaccination is an important area of research.

Pneumococcal conjugate vaccines (PCVs) are currently used in most developed countries to prevent severe invasive pneumococcal illnesses in children. Although these 7- to 13-valent vaccines are very effective against invasive pneumococcal infections, they have also shown some efficacy against pneumococcal AOM. In a large clinical trial in Finland, the efficacy of the 7-valent PCV (PCV7) was 34% against AOM caused by any pneumococci in children followed up to 24 months of age. However, because other bacteria and viruses account for the majority of all AOM cases, PCV7 was able to reduce the annual incidence of all-cause AOM by 6%. Similar results were obtained in the United States, where PCV7 was shown to reduce the rates of all-cause AOM episodes by 6.6% and office visits by 7.8% in children aged 3–42 months. Higher reductions in all-cause AOM due to PCV7 have been reported in non-randomized studies that are influenced by herd protection, potential temporal confounding from more stringent criteria for diagnosing AOM and increasing use of influenza vaccines in US children.

The key role of respiratory viruses in the etiology and pathogenesis of AOM is well established. Influenza viruses are known to predispose a child to AOM. In a large prospective study of respiratory infections in children, AOM developed as a complication of influenza in 40% of children aged <3 years and in 20% of children aged 3–6 years. Several clinical studies have demonstrated that influenza-associated AOM can be effectively prevented by influenza vaccination. However, because influenza vaccine cannot exert its effect outside of the influenza season, the public health impact of influenza vaccination in reducing the overall annual incidence of AOM remains unknown.

An intranasally administered, Ann Arbor strain live attenuated influenza vaccine (LAIV) is approved for eligible children aged ≥2 years. We have previously shown that the efficacy of LAIV against influenza-associated AOM was 85% compared with placebo and 54% compared with inactivated influenza vaccine (IIV). The aim of this study was to determine the effectiveness of LAIV against all-cause AOM in children during influenza seasons, total study surveillance periods and throughout an entire year.

MATERIALS AND METHODS

Eight randomized studies were identified in which LAIV efficacy against AOM was a prespecified secondary endpoint. These studies were conducted in the United States, Europe and Asia (Table 1). These studies have been described previously as individual studies and in an integrated analysis of influenza-associated AOM incidence. Six trials compared LAIV with
placebo, and 2 trials compared LAIV with IIV. Data on episodes of AOM due to any cause were extracted by treatment group from all studies for the per-protocol population. The analyses included only those children who were fully vaccinated (2 doses if previously unvaccinated, 1 dose if previously vaccinated). If multiple potencies of LAIV were studied, only data from the approved dose potency (10^5.5-7.5 fluorescent focus units/mL) were included in the analysis.

All-cause AOM was defined as AOM due to any cause in study subjects, regardless of viral culture results. As in the study of PCV7 by Eskola et al, an AOM episode was considered as a new episode if it occurred at least 30 days after the previous AOM episode. In 5 of the 6 placebo-controlled studies and in the IIV-controlled study by Ashkenazi et al, AOM was defined using the criteria used by Eskola et al: by the demonstration of a visually abnormal tympanic membrane (with regard to color, position and/or mobility) suggesting effusion in the middle ear, concomitantly with ≥1 of the following signs and/or symptoms of acute infection: fever (≥38°C rectal or oral or ≥37.5°C axillary), earache, irritability, diarrhea, vomiting, acute otitis media not caused by external otitis or other symptoms of respiratory infection. In the placebo-controlled study by Belshe et al, otitis media was defined as a clinical diagnosis made by a healthcare provider without further criteria. The IIV-controlled study by Belshe et al also defined otitis media as a clinical diagnosis made by a healthcare provider, but required fever as part of the diagnosis. Thus, in the current analysis, for both IIV-controlled studies and placebo studies, fever (≥100°F rectal or ≥100.6°F rectal/tympanic or ≥99.6°F axillary) was a requirement for the diagnosis of AOM.

### Efficacy Estimates During Influenza Seasons and Study Surveillance Periods

AOM rates were calculated by dividing the number of AOM episodes by the total population in each treatment group. Surveillance for AOM was conducted throughout each study using regular, weekly telephone contacts, clinic visits or home visits with the subject and their parent(s)/legal guardian(s). Efficacy estimates were calculated for the study-specific influenza seasons (as defined for each study country based on the weekly numbers of episodes of culture-confirmed influenza) as well as for the entire study surveillance periods. To examine the potential impact of PCV7 use on AOM rates and LAIV efficacy, a separate analysis was conducted that excluded seasons and areas in which there was published evidence of significant PCV7 use.

Because all subjects in year 2 of the placebo-controlled studies had also been subjects in year 1, the data from these 2 years were not independent from each other and thus not suitable for a pooled analysis. Therefore, pooled analyses were performed separately for years 1 and 2. An estimate of efficacy against all-cause AOM episodes was calculated using the Andersen-Gill method with robust sandwich covariance estimate of Cox proportional hazards model with treatment as the only effect. The efficacy was calculated as (1 – hazard ratio) × 100.

### Projected 12-Month Effectiveness Estimate

To estimate the annual impact of LAIV on all-cause AOM, AOM rates were projected for months outside of the study surveillance periods. To make comparisons with the randomized, placebo-controlled studies of PCV7 that were conducted in the United States and Europe, only data from subjects in the United States and Europe in placebo-controlled studies were used. Actual study data were used for AOM rates for months during the study surveillance periods. For other months, AOM rates were extrapolated by multiplying the average AOM rate in placebo recipients during the study surveillance periods by the published ratio of AOM rates in the United States for May to October versus November to April. To assume no effect of LAIV outside of the influenza season, the same extrapolated AOM rate was applied to LAIV and placebo recipients for the months of June to October. The effectiveness of LAIV against all-cause AOM during the 12-month period was calculated using Poisson regression.

### RESULTS

In the placebo-controlled trials, data for pooled analyses were available for 9497 children aged 6–71 months for year 1 and for 4142 children aged 18–83 months for year 2 (Tables 2 and 3). In IIV-controlled trials, data were available for 9301 children aged 6–71 months. Of all 23,540 study subjects, 84% were healthy children without additional qualifications; 11% were enrolled in a placebo-controlled study that required all participants to attend ≥12 hours of daycare per week; 9% were enrolled in an IIV-controlled study that required a history of ≥2 or more respiratory tract infections (eg, common cold, AOM, bronchitis, pneumonia and bronchiolitis) in the previous 12 months; and 47% were younger than 24 months.

### Efficacy of LAIV Against All-cause AOM During Influenza Seasons

The mean durations of the study influenza seasons were 21.3 weeks in year 1 and 18.2 weeks in year 2 of the placebo-controlled studies (Table 2) and 14.3 weeks in the IIV-controlled studies (Table 3). AOM rates varied considerably by study, with especially low rates reported in Asian studies (studies 1 and 4); placebo recipients...
in these studies had AOM rates of 2.4–6.4 per 100, whereas the mean rates in other studies were 27.0 and 19.5 per 100 in years 1 and 2, respectively.

In the placebo-controlled studies, the pooled rates of AOM in year 1 were 17.7 per 100 among placebo recipients and 15.5 per 100 among LAIV recipients, for an efficacy of 12.4% (95% confidence interval [CI]: 2.0%, 21.6%) against all-cause AOM (Table 2). A similar trend was observed in year 2, but the difference did not reach statistical significance. In year 1, AOM rates were similar in subjects <24 months versus those aged ≥24 months: among placebo recipients, the rates in these age groups were 17.9 and 17.5 per 100, respectively, and among LAIV recipients, the corresponding rates were 15.1 and 15.9 per 100. The small numbers of children aged <24 months in year 2 prevented a meaningful comparison between the age groups. In year 1, LAIV efficacy against all-cause AOM was 13.4% (95% CI: −0.8%, 25.6%) in subjects aged <24 months (N = 5217) and 10.5% (95% CI: −5.5%, 24.0%) in subjects aged ≥24 months (N = 4280).

In the IIV-controlled studies, the pooled febrile all-cause AOM rates were 12.3 per 100 among IIV recipients and 11.2 per 100 among LAIV recipients, yielding a 9.7% (95% CI: −2.1%, 20.1%) efficacy of LAIV relative with IIV (Table 3). In these studies, among IIV recipients, the rates of febrile all-cause AOM were 18.8 and 7.6 per 100 for subjects aged <24 and ≥24 months, respectively, whereas among LAIV recipients, the corresponding rates were 16.2 and 7.5 per 100. The relative efficacy of LAIV was 15.2% (95% CI: 0.8%, 27.4%) in children aged <24 months (N = 4151) and 1.2% (95% CI: −20.4%, 18.8%) in those aged ≥24 months (N = 5750).

All placebo-controlled studies and all IIV-controlled studies outside the United States were conducted before the widespread utilization of PCV7 or in countries with no PCV7 availability. However, in the IIV-controlled study conducted in 2004 to 2005, PCV7 use was already widespread in the United States; by 2003, 70% of eligible US children had received at least 3 doses of PCV7. In that particular study, LAIV efficacy compared with IIV in US subjects

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(N = 3819) was 15.5% (95% CI: 0.3%, 28.4%), whereas the corresponding efficacy in subjects in European countries (N = 3494) was 4.2% (95% CI: −17.9%, 22.2%).

**Efficacy of LAIV Against All-cause AOM During Total Study Surveillance Periods**

Overall, the mean total study surveillance periods were 31.7 weeks in year 1 and 31.5 weeks in year 2 of the placebo-controlled studies (Table 2) and 25.3 weeks in the IIV-controlled studies (Table 3). As expected, LAIV efficacy estimates for the longer total surveillance periods were generally lower than the estimates for the study-specific influenza seasons. However, despite the total surveillance periods substantially exceeding the influenza seasons, the efficacy of LAIV against all-cause AOM in year 1 of the placebo-controlled studies was 10.9% (95% CI: 1.3%, 19.7%).

**Projected 12-Month Effectiveness of LAIV Against All-cause AOM**

The rates of all-cause AOM in US and European subjects in the placebo-controlled studies were available for November through May (Table 4). The efficacy of LAIV against all-cause AOM in these subjects during the actual influenza seasons was 14.9% (95% CI: 1.6%, 26.5%). During the total study surveillance periods that exceeded the influenza seasons (November through May), the corresponding efficacy was 11.6% (95% CI: −1.4%, 23.0%). The mean rate of AOM among placebo recipients during the study surveillance periods was 9.05 per 100 person-months. According to the report by Fireman et al., otitis media in US children occurred at a rate 1.5-fold higher in November through April relative to May through October. Using this ratio, the rate of AOM in LAIV and placebo subjects for the months outside of the study surveillance periods was estimated at 6.03 events per 100 person-months. With this assumption, the cumulative 12-month AOM rates for LAIV and placebo recipients were estimated to be 7.21 and 7.80 per 100 person-months, respectively, yielding a projected 12-month effectiveness of LAIV against all-cause AOM of 7.5% (95% CI: −2.4%, 16.2%) (Fig. 1).

**DISCUSSION**

This is the first multistudy analysis to assess the impact of LAIV on all-cause AOM. For AOM associated with culture-confirmed influenza, LAIV has demonstrated an 85% reduction compared with placebo and a 54% reduction compared with IIV.17

**TABLE 4. Monthly All-cause AOM Incidence Rate for LAIV and Placebo Recipients in US and European Placebo-controlled Studies**

<table>
<thead>
<tr>
<th>Month*</th>
<th>LAIV</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>November</td>
<td>9.50</td>
<td>13.80</td>
</tr>
<tr>
<td>December</td>
<td>8.62</td>
<td>10.50</td>
</tr>
<tr>
<td>January</td>
<td>8.57</td>
<td>7.90</td>
</tr>
<tr>
<td>February</td>
<td>9.16</td>
<td>11.40</td>
</tr>
<tr>
<td>March</td>
<td>8.86</td>
<td>10.20</td>
</tr>
<tr>
<td>April</td>
<td>5.62</td>
<td>6.27</td>
</tr>
<tr>
<td>May</td>
<td>5.47</td>
<td>6.27</td>
</tr>
<tr>
<td>June through October</td>
<td>6.03</td>
<td>6.03</td>
</tr>
<tr>
<td>Total</td>
<td>7.21</td>
<td>7.80</td>
</tr>
</tbody>
</table>

*Study data used for November through May; projected data used for June through October.

However, to understand the full public health impact of this reduction in influenza-associated AOM, an evaluation of the vaccine’s effect on annual all-cause AOM was necessary. The estimated 7.5% reduction in the annual burden of AOM by LAIV is comparable with the 6–7% reduction demonstrated in randomized clinical trials of PCV7.15 The present evidence for an effect against all-cause AOM also demonstrates that reductions in influenza-associated AOM are not offset by increased rates of AOM due to other pathogens.

Although 2 previous placebo-controlled studies of LAIV demonstrated a 21% reduction in all-cause AOM incidence and 30–32% reductions in all-cause febrile otitis media,20,22 the current analysis provides a more robust estimate across multiple studies. Statistically significant efficacy was observed in year 1 of placebo-controlled studies. Although there was a trend for an effect also in year 2 of the placebo-controlled studies, no statistically significant difference was observed; this might be due to the smaller sample size and thus reduced statistical power to observe an effect.

The efficacy of IIV against all-cause AOM has also been demonstrated in some previous studies that have shown 30–36% reductions in all-cause AOM during the peak influenza activity in young children attending day care.5,16 By contrast, the study by Hoberman et al.15 failed to demonstrate an effect during 2 mild influenza seasons in a general population of young children, although there was a trend for an effect among children aged 19–24 months. As demonstrated also in the current analysis, the level of influenza vaccine effectiveness against all-cause AOM is significantly influenced by the incidence of influenza and the proportion of AOM caused by other pathogens during the surveillance period. Because influenza vaccines should not be able to prevent AOM cases associated with other viral infections in the months after vaccination, the estimates of influenza vaccine effectiveness against all-cause AOM are always lower with longer surveillance periods that exceed the period of major influenza activity in any area.

The projected annual rate of AOM in unvaccinated US and European children in the current analysis was 0.94 episodes per person-year, which is comparable to but slightly lower than the 1.24 episodes per person-year observed by Eskola et al.12 who used a similar definition for AOM. The most likely explanation for the
difference is that the participants in the study by Eskola et al were substantially younger than those in the present studies and therefore more susceptible to the development of AOM. The difference could also be partially due to seasonal variation, but it is also possible that not all AOM cases were detected in the LAIV studies, especially in the 2 Asian studies in which the observed rates of AOM were lower than elsewhere. However, even if some AOM cases were missed in the LAIV studies, both treatment groups should have been similarly affected due to randomization and blinding, and thus the relative efficacy estimates would remain unaffected.

AOM is frequently associated with a concomitant or immediately preceding upper respiratory viral illness. Virus-induced inflammation leads to Eustachian tube dysfunction, which facilitates pathogen entry into the middle ear. Even in the era of widespread PCV7 vaccination, influenza-associated AOM is commonly caused by Streptococcus pneumoniae, but in most cases of AOM other bacterial pathogens can be found in the middle ear fluid, most frequently together with viruses. Because influenza virus and S. pneumoniae often act as copathogens in AOM, one would expect some degree of overlap between the all-cause AOM efficacies of PCV7 and LAIV. In the study by Eskola et al., the observed 6% overall reduction associated with PCV7 was driven by a 34% reduction in pneumococcal AOM. The efficacy against AOM caused by vaccine and cross-reactive serotypes was partially offset by an increased number of AOM cases due to other pneumococcal serotypes and other bacterial species. In the current analysis, US subjects in the IIV-controlled study by Belshe et al. were widely vaccinated with the PCV7 vaccine before enrollment. The statistically significant 15.5% reduction in all-cause AOM in these subjects demonstrates that LAIV can significantly reduce all-cause AOM even in the setting of PCV7 vaccination.

An important limitation of the ability of LAIV to impact the burden of AOM in young children is that LAIV is only approved for children aged ≥2 years. The incidence of AOM is highest in younger children, but the burden of AOM is significant also in children aged ≥2 years. For example, in a prospective cohort study among outpatient children, 20% of children aged 3–6 years developed AOM as a complication of influenza. Fireman et al. reported approximately 10 medical visits for otitis per 100 children per month among children aged 24–42 months. Moreover, they estimated that PCV7 efficacy against all-cause otitis visits in children aged 24–42 months was 3.7%, lower than the efficacy observed in younger children.

The strengths of this study include the large sample size derived from all randomized trials conducted in a diverse population. Additionally, 5 of the 6 placebo-controlled studies used similar diagnostic criteria for defining AOM. However, the placebo-controlled study by Belshe et al. used a different definition and used the term otitis media rather than AOM, which may have allowed inclusion of children with both AOM and otitis media with effusion. Another limitation was the requirement for fever as part of the diagnosis of AOM in the IIV-controlled studies, as AOM can frequently occur in the absence of fever. Validation of the investigators in the clinical diagnosis of AOM was also not performed in these studies; however, on the contrary, this reflects the true situation in everyday clinical practice for the diagnosis and management of AOM. Finally, the annualized efficacy of LAIV against all-cause AOM required the use of extrapolated data, as no data were collected in the trials for June through October. However, it is reassuring that the modeled rates for these months were similar to the actual trial data for months with generally low influenza activity (eg, April and May). Additionally, the projected annual effectiveness represents a conservative estimate as no LAIV effect was assumed in these months. The annual effectiveness estimate is essentially a scaled dilution of the statistically significant effectiveness observed during the study influenza seasons.

Conclusions

LAIV reduced the rate of all-cause AOM compared with placebo in young children. The estimated 12-month efficacy of LAIV against all-cause AOM in young children was comparable with that of PCV7. As PCV7 has been shown to only prevent approximately one-third of all pneumococcal AOM cases, and influenza-associated AOM can be caused by S. pneumoniae and other bacterial pathogens as well as influenza virus alone, the use of LAIV in addition to PCVs would help further reduce the incidence of AOM in young children.

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