The Efficacy of Live Attenuated Influenza Vaccine Against Influenza-associated Acute Otitis Media in Children

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Background: Acute otitis media (AOM) is a frequent complication of influenza in young children. Influenza vaccination is known to protect against AOM by preventing influenza illness. We sought to determine the efficacy of the live attenuated influenza vaccine (LAIV) against influenza-associated AOM compared with placebo and trivalent inactivated influenza vaccine (TIV). LAIV is approved for eligible children aged ≥2 years in the United States and in several other countries.

Methods: AOM incidence data from 6 randomized, double-blind, placebo-controlled trials and 2 randomized, double-blind, TIV-controlled trials in children 6 to 83 months of age were pooled and analyzed.

Results: A total of 290 cases of AOM were identified in 24,046 study subjects. LAIV efficacy against influenza-associated AOM was 85.0% (95% confidence interval [CI], 78.3%–89.8%) compared with placebo and 54.0% (95% CI, 27.0%–71.7%) compared with TIV. Efficacy trended higher in those ≥24 months of age compared with those aged 6 to 23 months. In placebo-controlled trials, among children who acquired influenza despite vaccination, AOM was diagnosed in 10.3% of LAIV recipients and 16.8% of placebo recipients, representing a 38.2% (95% CI, 11.0%–58.2%) relative reduction in the development of AOM. In TIV-controlled studies, among subjects with breakthrough influenza illness, the proportions of LAIV and TIV recipients who developed AOM were similar.

Conclusions: Children receiving LAIV had a high level of protection against influenza-associated AOM when compared with placebo or TIV. This was most evident in children older than 2 years, for whom LAIV is indicated. LAIV recipients who contracted breakthrough influenza illness despite vaccination developed AOM at a significantly lower rate than did unvaccinated children who developed influenza.

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

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Acute otitis media (AOM) is the most common bacterial infection diagnosed in children. It is also the most frequent reason for prescribing antibiotics to children, totaling 15 million prescriptions annually in the United States alone.[1–4] AOM has been estimated to account for 24.5 million healthcare visits per year in the United States and results in approximately 1 billion dollars in direct medical costs.[5,6] Most cases of AOM are preceded by a viral upper respiratory tract infection that causes inflammation of the mucosa of the upper respiratory tract, including the nasopharynx and the Eustachian tube, which facilitates subsequent secondary bacterial infection.[7,8] However, viruses can be solely responsible for AOM as well, and they have been recovered as the sole pathogen in the middle-ear fluid in approximately 5% of AOM cases.[9,10] Such cases are often treated as presumed bacterial infections and result in an unnecessary course of antibiotic treatment, leading to increased medical costs and bacterial antibiotic resistance.[11] The most common viruses known to be both a direct and indirect cause of AOM include RSV, adenovirus, parainfluenza, and influenza viruses.[8,11] For young children infected with culture-confirmed influenza, AOM has been shown to develop as a complication in 28% to 67% of influenza cases.[12–17]

Current American Academy of Pediatrics guidelines on the management of otitis media encourage its prevention by reducing known risk factors.[1] However, many risk factors cannot be mitigated, but the administration of influenza vaccines can decrease AOM morbidity as a sequela of influenza.[18] Trivalent inactivated influenza vaccines (TIV) are approved for children as young as 6 months of age in most countries; in Hong Kong, South Korea, Israel, Macau, Canada, and United States, a live attenuated influenza vaccine (LAIV) based on cold-adapted, temperature-sensitive vaccine viruses (Ann Arbor strains) is approved for eligible children aged 24 months and older.

Several large, randomized clinical studies in children have shown that LAIV is highly effective in preventing culture-confirmed influenza compared with both placebo and TIV.[19–25] In placebo-controlled trials that also collected data on AOM incidence, LAIV has been shown to reduce any episodes of AOM by 31.0%,[22] all-cause febrile AOM by 31.5% to 33.0%,[21,22] and AOM associated with a positive culture for influenza by 69.0% to 97.0%.[21,22,25] When compared with TIV, LAIV has been shown to reduce the numbers of influenza-associated AOM cases by 50.6%.[20] Other LAIV studies that collected data on AOM had too few cases to generate meaningful efficacy estimates.[19,24,26,27] The objective of this study was to analyze AOM data from all available LAIV studies to estimate the efficacy of LAIV in preventing AOM associated with culture-confirmed influenza illness compared with placebo or TIV.

METHODS

Eight randomized studies were identified in which LAIV efficacy against influenza-associated AOM was a prespecified secondary end point. These studies, performed by Wyeth Vaccines Research (Pearl River, NY) and MedImmune (Gaithersburg, MD), have been described previously as individual studies.[19,20,22,24–28]

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Six trials compared LAIV with placebo and 2 trials compared LAIV with TIV (Table, Supplemental Digital Content 1, http://links.lww.com/INF/A609, LAIV studies which measured efficacy against AOM as a prespecified secondary endpoint).

In all studies, the efficacy of LAIV was analyzed in the according-to-protocol population. The analyses included only those children who were fully vaccinated (2 doses if previously unvaccinated, 1 dose if previously vaccinated). In the study by Forrest et al,[26] which evaluated multiple dosage levels of LAIV, only data from subjects who received LAIV at the standard postlicensure dosage ($10^{6.5–7.5}$ FFU/mL) were included in the analysis. Surveillance for influenza illness and AOM was performed in all studies throughout the entire influenza season.

Statistical analyses adhered to the methodologies that were used in the original studies. Data were pooled separately for placebo-controlled studies and TIV-controlled studies. The efficacy of LAIV was calculated as $1 - I_L/I_C$, where I_L refers to the incidence rate in children vaccinated with LAIV and I_C refers to the incidence rate in children who received the control vaccine (placebo or TIV). Exact methods were used to calculate 95% confidence intervals (CIs) of efficacy in the pooled analysis where the total number of influenza cases and the total number of subjects from the integrated pool were used. The CI for vaccine efficacy is an exact CI conditional on the total number of cases. No other adjustments were made. Efficacy was measured against all influenza strains regardless of antigenic similarity to the vaccine. Data from all studies were analyzed separately in subjects 6 to 23 months of age and those ≥24 months of age.

Influenza was detected by viral culture in nasal swab specimens, and AOM was diagnosed clinically by the study investigators in all studies. An episode of influenza-associated AOM was defined as an episode of AOM in a child with a positive culture for influenza virus. The rate of AOM in subjects with breakthrough influenza was defined as the number of cases of AOM in those with a positive culture for influenza virus divided by the total number of vaccine recipients with a positive culture for influenza virus. In 6 of the 8 studies, AOM was defined using identical criteria: by the demonstration of a visually abnormal tympanic membrane (with regard to color, position, and/or mobility) suggesting effusion in the middle ear cavity, 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 otorrhea not caused by external otitis, or other symptoms of respiratory infection. The placebo-controlled study by Belshe et al[28] defined otitis media as a clinical diagnosis made by a healthcare provider without further criteria. The TIV-controlled study by Belshe et al[20] defined AOM as a healthcare provider diagnosis of AOM concurrent with fever (≥100°F oral or ≥100.6°F rectal/tympanic or ≥99.6°F axillary) and associated with the use of antibiotics; for this study only, investigators relied on parent report or chart review for cases not diagnosed at the study site.

As LAIV elicits an immune response by replicating in the nasopharynx and may cause increased rates of rhinorrhea or nasal congestion, the incidence of AOM as an unsolicited adverse event (AE) was also assessed. Reported rates of AOM as an unsolicited AE were evaluated in the entire study population. Consistent with the design of the original studies, rates were calculated through 10 days postvaccination in placebo-controlled studies and through 28 days postvaccination in TIV-controlled studies. AE rates for each study were calculated for each study season, after the first and second dose, and for all studies combined.

In all studies, written informed consent was obtained from the parents or legal guardians of all children before entry into the studies. Trials were conducted in accordance with the Declaration of Helsinki and principles of Good Clinical Practice and human study guidelines of the US Department of Health and Human Services.

RESULTS

Across all 8 studies, data from 24,046 subjects 6 to 83 months of age were collected throughout Asia, Europe, the Middle East, South America, and the United States (Table, Supplemental Digital Content 1, http://links.lww.com/INF/A609, provides the pertinent data regarding these studies). In all studies, LAIV recipients were similar with regard to gender, race, and mean age compared with placebo or TIV recipients. Of all 24,046 study subjects, 20,199 (84%) were healthy children without additional qualifications; 2706 (11%) subjects attended ≥12 hours of daycare per week,[25] 2085 (9%) reported a history of 2 or more respiratory tract infections (eg, common colds, AOM, bronchitis, pneumonia, and bronchiolitis) in the previous 12 months.[19] In addition, 2718 (11%) subjects had a history of any wheezing in the past, and 11,209 (47%) were younger than 24 months.

In the individual studies, the rates of influenza-associated AOM in the placebo recipients throughout the entire influenza season ranged from 0.2% to 5.4%. Among placebo recipients with culture-confirmed influenza illness, 1.7% to 30.4% had AOM reported.

Efficacy of LAIV Against Influenza-associated AOM Compared With Placebo and TIV

For the pooled analysis of the 6 placebo-controlled studies, which encompassed 10 study years, a total of 36 cases of AOM associated with culture-confirmed influenza because of any strains were found in 8353 (0.4%) LAIV recipients and 165 cases were found in 5756 (2.9%) placebo recipients (Table 1). Therefore, the overall efficacy of LAIV against influenza-associated AOM was

TABLE 1. Rate of AOM Associated With Culture-confirmed Influenza* in 6 Placebo-controlled Trials

Age Group	LAIV, n/N (%)	Placebo, n/N (%)	Efficacy, %	95% CI
AOM attack rate in all subjects				
6–23 mo	25/4075 (0.61)	82/2972 (2.76)	77.8	64.8, 86.4
24–83 mo	11/4278 (0.26)	83/2784 (2.98)	91.4	83.8, 95.6
All ages	36/8353 (0.43)	165/5756 (2.87)	85.0	78.3, 89.8
Proportion of AOM in influenza positive subjects				
6–23 mo	25/203 (12.32)	82/512 (16.02)	23.1	−21.6, 52.9
24–83 mo	11/145 (7.59)	83/473 (17.55)	56.7	18.6, 79.2
All ages	36/348 (10.34)	165/985 (16.75)	38.2	11.0, 58.2

*Due to all strains regardless of antigenic match to the vaccine.

AOM indicates acute otitis media; LAIV, live attenuated influenza vaccine; CI, confidence interval.

TABLE 2. Rate of AOM Associated With Culture-confirmed Influenza* in 2 TIV-controlled Trials

Age Group	LAIV, n/N (%)	TIV, n/N (%)	Efficacy, %	95% CI
AOM attack rate in all subjects				
6–23 mo	17/2094 (0.81)	32/2068 (1.55)	47.5	2.7, 72.7
24–83 mo	11/2872 (0.38)	29/2903 (1.00)	61.7	20.9, 82.7
All ages	28/4966 (0.56)	61/4971 (1.23)	54.0	27.0, 71.7
Proportion of AOM in influenza positive subjects				
6–23 mo	17/65 (26.15)	32/147 (21.77)	−20.1	−122.9, 37.4
24–83 mo	11/117 (9.40)	29/251 (11.55)	18.6	−67.8, 63.3
All ages	28/182 (15.38)	61/398 (15.33)	−0.4	−59.5, 38.2

*Due to all strains regardless of antigenic match to the vaccine.
AOM indicates acute otitis media; LAIV, live attenuated influenza vaccine; TIV, trivalent inactivated influenza vaccine; CI, confidence interval.

TABLE 3. Rates of Unsolicited Adverse Events of AOM in Placebo-controlled Studies Through 10 Days and TIV-controlled Studies Through 28 Days Postvaccination

	Season 1 Dose 1			Season 1 Dose 2			Season 2 Dose 1		
	LAIV, %	Comparator, %	*P*	LAIV, %	Comparator, %	*P*	LAIV, %	Comparator, %	*P*
Placebo-controlled studies									
Belshe et al[28,39]	1.9	0.9	0.200	3.2	1.9	0.273	1.3	1.4	>0.99
Bracco et al[22]	1.4	1.6	0.367	1.8	2.2	0.113	1.1	1.9	0.172
Forrest et al[26]	0.4	1.5	0.116	0.0	1.0	0.234	NA	NA	NA
Lum et al[27]	2.3	1.7	0.535	1.6	1.6	>0.99	NA	NA	NA
Tam et al[24]	0.1	0.1	>0.99	0.1	0.3	0.309	0.0	0.1	0.498
Vesikari et al[25]	5.8	4.0	0.100	4.7	4.7	>0.99	2.6	2.8	>0.99
Total	1.8	1.5	0.196	1.8	1.9	0.668	1.0	1.1	0.674
TIV-controlled studies									
Ashkenazi et al[19]	4.6	4.2	0.677	6.8	5.6	0.281	NA	NA	NA
Belshe et al[20]	14.8	14.4	0.772	7.1*	8.6*	0.028*	NA	NA	NA
Total	10.8	10.4	0.687	7.0	7.9	0.148	NA	NA	NA

*Statistical significance.
AOM indicates acute otitis media; LAIV, live attenuated influenza vaccine; NA, not applicable; TIV, trivalent inactivated influenza vaccine.

85.0% (95% CI, 78.3%–89.8%). Analyzed by age at the time of vaccination, the rate of influenza-associated AOM in placebo recipients was similar in children 6 to 23 months of age compared with those ≥24 months of age. However, the efficacy of LAIV against influenza-associated AOM trended higher in children ≥24 months of age (91% vs. 78%; Table 1).

In the 2 TIV-controlled studies, 28 cases of influenza-associated AOM due to any influenza strains were found in 4966 (0.6%) LAIV recipients and 61 cases were found in 4971 (1.2%) TIV recipients. The relative efficacy of LAIV compared with TIV for influenza-associated AOM was 54.0% (95% CI, 27.0%–71.7%; Table 2). Similar to the placebo-controlled studies, the relative efficacy of LAIV compared with TIV against influenza-associated AOM trended higher in children ≥24 months compared with those 6 to 23 months of age (Table 2).

Rates of AOM Among Children With Culture-confirmed Influenza Illness

To examine whether LAIV had any effect on the incidence of AOM beyond simply preventing influenza illness, the rates of AOM were analyzed among only those LAIV, TIV, and placebo recipients who developed culture-confirmed influenza illness. Among these children in the placebo-controlled studies, 10.3% of LAIV recipients and 16.8% of placebo recipients with influenza illness developed AOM, which represented a relative reduction of 38.2% (95% CI, 11.0%–58.2%) among the LAIV recipients (Table 1). The relative reduction was statistically significant among children ≥24 months of age (56.7% [95% CI, 18.6%–79.2%]), but not significant among those 6 to 23 months of age (23.1% [95% CI, −21.6% to 52.9%]). In TIV-controlled studies, among subjects with breakthrough influenza illness, the proportions of LAIV and TIV recipients who developed AOM were similar (Table 2).

Rates of AOM as an AE Postvaccination

The incidence of AOM as an unsolicited AE in days 0 to 10 postvaccination was not significantly different between LAIV and placebo recipients in any of the individual studies or when the studies were pooled (Table 3). In TIV-controlled studies, the individual and pooled study rates of AOM as an unsolicited AE were similar between LAIV and TIV recipients in days 0 to 28 postvaccination with the exception of the incidence of AOM following the second dose in the study by Belshe et al[20] In that study, the rate of AOM as an AE was significantly lower in LAIV recipients than in TIV recipients (7.1% vs. 8.6%; $P = 0.028$; Table 3).

DISCUSSION

In this pooled analysis of multiple vaccine efficacy studies conducted in children 6 to 83 months of age, LAIV demonstrated high efficacy against influenza-associated AOM compared with placebo and TIV. A trend toward greater efficacy was seen in those ≥24 months of age, the population for whom LAIV is approved for use.

A reduction in AOM after vaccination with LAIV has been demonstrated in previous studies; however, the current analysis provides a consensus estimate across multiple studies.[20–22,25] The efficacy of TIV against influenza-associated AOM has also been demonstrated in some studies, but the results have varied across studies with different designs and different age popula-

tions.[12,29–31] The study by Hoberman et al[31] failed to demonstrate that TIV reduced the incidence of all-cause AOM in young children 6 to 24 months of age (N = 786; mean age = 14 months), but in a post hoc analysis of study year 1 the efficacy of TIV against influenza-associated AOM was 62%.[30] Clements et al[29] were able to show a 30% reduction in all-cause AOM in subjects 6 to 30 months of age (N = 186; mean age = 20 months). Heikkinen et al[12] were able to demonstrate an 83% efficacy of TIV against influenza-associated AOM and a 36% efficacy against all-cause AOM in subjects 7 to 50 months of age (N = 374; mean age = 26 months). It is worth noting that, although the incidence of all-cause AOM is highest in children <24 months of age,[32–34] the current analysis demonstrates that the incidence of influenza-associated AOM among unvaccinated children is similar among children 6 to 23 months and 24 to 83 months of age.

The fact that LAIV provides a high level of protection against influenza-associated AOM is expected given the efficacy of the vaccine against influenza illness. In a meta-analysis of 6 placebo-controlled studies,[35] the efficacy of 2 doses of LAIV against antigenically similar strains in previously unvaccinated young children was 77%, and the mean efficacy of 1 dose in previously vaccinated children was 87%. The efficacy of LAIV against any strain regardless of antigenic match was 72% and 76%, respectively. The lower efficacy against any strain regardless of antigenic match is largely due to inclusion of influenza cases caused by opposite-lineage influenza B viruses (B viruses of a lineage not matching the vaccine strain), against which LAIV efficacy is lower, estimated at approximately 30%.[36]

In the current analysis, the efficacy of LAIV to prevent influenza-associated AOM was greater than what one would expect from the vaccine's efficacy against influenza illness alone. LAIV recipients who contracted breakthrough influenza illness despite vaccination developed AOM at a significantly lower rate than did unvaccinated children who developed influenza. To the best of our knowledge, such a reduction in AOM by modulation of breakthrough illness severity has not been previously demonstrated with an influenza vaccine. However, the ability of LAIV to reduce the severity of breakthrough illness has been seen in other aspects, including less febrile illnesses compared with TIV in 2 studies in children aged <6 years,[19,20] fewer days of missed daycare/school compared with TIV in 1 study of children <6 years of age,[19] and reduced symptoms compared with TIV and placebo in a wild-type challenge study of adults 18 to 45 years of age.[37]

In addition, the present study has also demonstrated that, despite the fact that LAIV replicates in the nasopharyngeal mucosa and can cause rhinorrhea and nasal congestion, the incidence of AOM is not increased within the period immediately following vaccination when compared with placebo and TIV. In the study by Belshe et al,[20] the incidence of AOM during days 0 to 28 after receipt of dose 2 was significantly lower among LAIV recipients compared with TIV recipients. This finding is likely due to chance, because a similar reduction was not observed after receipt of dose 1 in the same study or after either dose in the study by Ashkenazi et al.[19]

The strengths of this study include the large sample size derived from all randomized trials conducted in a diverse population. In addition, 6 of the 8 studies used similar diagnostic criteria for defining AOM. Subjects included in these studies had few exclusion criteria, which further increases the generalizability of the results. Similarities between study designs also decreased statistical heterogeneity. Despite the similarities in the definition of AOM used in many of these studies, the placebo-controlled study by Belshe et al[28] 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 is the lack of validation in the making of a clinical diagnosis of AOM. The diagnosis of AOM was not validated by additional researchers or confirmed by tympanocentesis in any of the studies, and therefore variations in the diagnostic skills of clinicians in multiple countries across all studies may have influenced the reported incidences of AOM.[38] In fact, the overall low incidence of AOM among placebo recipients in many of the studies suggests that AOM may have been underdiagnosed.[12,31] However, this should not have affected the reported efficacy estimates, given the blinded nature of all of the placebo-controlled studies and the larger of the 2 TIV-controlled studies.

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