

Live Attenuated Influenza Vaccine and Reduction in Influenza-Associated Acute Otitis Media in Children Aged 24–83 Months

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Introduction

- Acute otitis media (AOM) has been found to complicate 28%–67% of culture-confirmed cases of influenza in young children.^{1,2}
- The influenza virus is known to be a direct cause of AOM³ and may indirectly result in AOM by causing respiratory infections which may allow the spread of bacteria from the nasopharynx into the middle ear.⁴
- Live attenuated influenza vaccine (LAIV) is approved for use in eligible children ≥24 months of age in the United States, South Korea, Israel, Hong Kong and Macau.
- Several large randomized clinical studies in children have shown that LAIV is highly effective in preventing culture confirmed influenza compared with both placebo and trivalent inactivated influenza vaccine (TIV).⁵⁻¹¹
- LAIV has been shown to reduce the severity of influenza illness, measured by reductions in fever, days of missed school/daycare, and total symptom score in breakthrough influenza cases compared with placebo and TIV; no previous analysis has sought to determine whether LAIV reduces the incidence of AOM in children with breakthrough influenza.^{5,12,13}

Objective

- To estimate the efficacy of LAIV in preventing AOM associated with culture-confirmed influenza illness in children ≥24 months of age versus placebo and TIV.

Methods

- We pooled data regarding influenza-associated AOM from 5 randomized, double-blind, placebo-controlled trials in children 24–83 months of age^{8,10,14-17} (LAIV, n=4278; placebo, n=2784), and 2 randomized, double-blind, TIV-controlled trials in children 24–71 months of age^{5,6} (LAIV, n=2872; TIV, n=2903) in which LAIV efficacy against AOM associated with culture-confirmed influenza was a prespecified endpoint (**Table 1**).
- Efficacy was calculated using the incidence of all influenza strains regardless of antigenic similarity to those strains in the vaccine in 9 influenza seasons for placebo-controlled trials and in 2 seasons for TIV-controlled trials.
- Subjects included healthy children, those with frequent respiratory tract infections, and those attending daycare.
- In 5 of the 7 studies, AOM was defined clinically by the presence of an abnormal tympanic membrane suggesting effusion in the middle ear cavity, with signs/symptoms consistent with acute infection.
- Study 5 defined otitis media as a clinical diagnosis made by a healthcare provider.
- Study 7 defined AOM as a diagnosis made by a healthcare provider (by parent report or chart review) concurrent with fever and the use of antibiotics.
- Influenza was detected by viral culture from the nasal passages.
- AOM associated with culture-confirmed influenza was evaluated in all LAIV and placebo recipients and in those with culture-confirmed influenza.

Table 1. LAIV Studies Measuring Efficacy Against AOM as a Prespecified Secondary Endpoint Among Children Aged ≥24 Months

Study Number	Age Range, mo	LAIV, n	Control, n	Location
<i>Placebo Controlled Studies</i>				
Study 1 ¹⁰ , Year 1	24–35	782	534	Asia*
Study 1 ¹⁰ , Year 2	24–47	362	238	Asia*
Study 2 ¹⁷ , Year 1	24–35	490	356	Europe†
Study 2 ¹⁷ , Year 2	24–47	340	250	Europe†
Study 3 ⁸ , Year 1	24–35	344	332	Multinational‡
Study 3 ⁸ , Year 2	24–47	121	116	Multinational‡
Study 4 ¹⁶	24–35	209	182	Asia [§]
Study 5 ¹⁵ , Year 1	24–71	713	335	United States
Study 5 ¹⁴ , Year 2	27–83	917	441	United States
<i>TIV Controlled Studies</i>				
Study 6 ⁵	24–71	790	819	Europe
Study 7 ⁶	24–59	2082	2084	Multinational¶

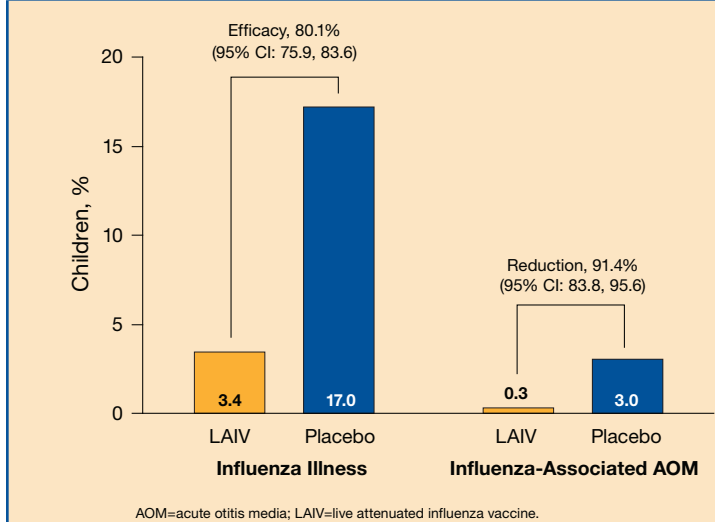
AOM=acute otitis media; LAIV=live attenuated influenza vaccine; TIV=trivalent inactivated influenza vaccine.
 *China, Hong Kong, India, Malaysia, Philippines, Singapore, Taiwan, Thailand
 †Belgium, Finland, Israel, Spain, United Kingdom
 ‡Argentina, Brazil, South Africa
 §Philippines, Thailand
 ||Belgium, Czech Republic, Finland, Germany, Israel, Italy, Poland, Spain, Switzerland, United Kingdom
 ¶Asia, Europe, Middle East, United States

Results

- The pooled efficacy of LAIV against influenza-associated AOM due to all strains was 91.4% (0.3% vs 3.0%; 95% CI: 83.8, 95.6) vs placebo and 62.7% (0.4% vs 1.0%; 95% CI: 20.9, 82.7) vs TIV.
- Compared with placebo, when analyzing only those children with culture-confirmed influenza illness, 7.6% of LAIV recipients with breakthrough influenza had AOM vs 17.6% of placebo recipients with influenza illness, resulting in a 56.7% reduction (95% CI: 18.6, 79.2; **Figure 1**).
- Compared with TIV, among only those children with culture-confirmed influenza illness, AOM was diagnosed in 9.4% of LAIV recipients and 11.6% of TIV recipients, for a nonsignificant relative reduction of 18.6% (95% CI: –67.8, 63.3; **Figure 2**).

Figure 1.

A. Reduction in Influenza Illness and Influenza-Associated AOM Among Children Receiving LAIV and Placebo



B. Proportion of Influenza-Positive LAIV and Placebo Recipients With and Without AOM

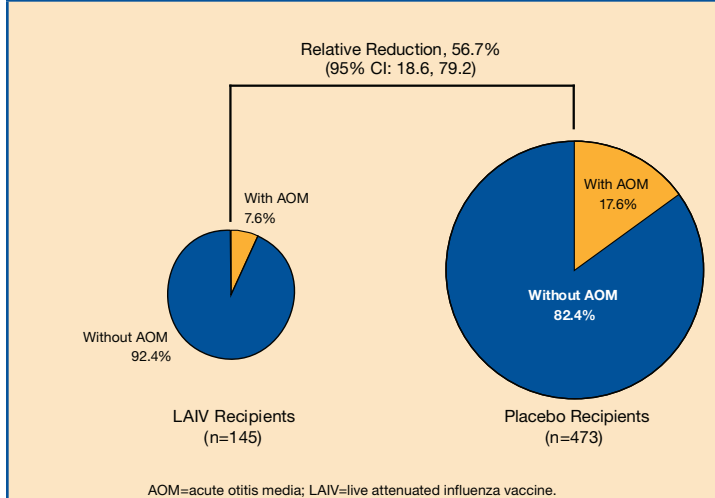
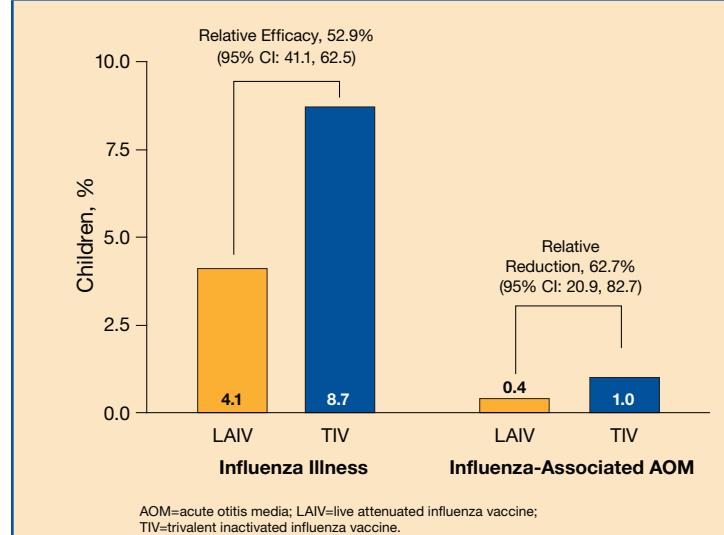
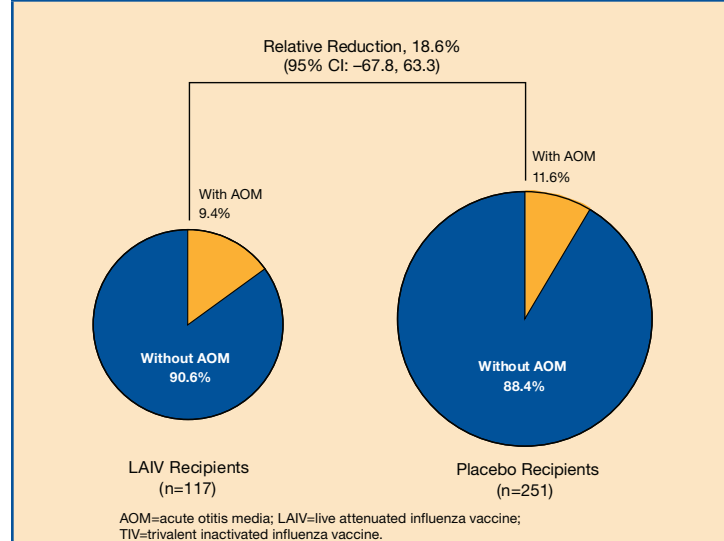


Figure 2.

A. Reduction in Influenza Illness and Influenza-Associated AOM Among Children Receiving LAIV and TIV



B. Proportion of Influenza-Positive LAIV and TIV Recipients With and Without AOM



Conclusions

- Among children 24–83 months of age, LAIV substantially reduced influenza-associated AOM compared with placebo and TIV.
- Compared with placebo recipients with confirmed influenza, LAIV recipients who developed breakthrough influenza had less severe disease as evidenced by 57% fewer children developing AOM.
- LAIV recipients had substantially fewer cases of influenza-associated AOM than TIV recipients.
- Rates of AOM among LAIV and TIV recipients who developed influenza illness were statistically similar.

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