Does Live Attenuated Influenza Vaccine Reduce All-Cause Acute Otitis Media in Children?

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Background

- Acute otitis media (AOM) is a frequent complication of viral infections, including influenza, in young children and occurs in 28%–67% of culture-confirmed cases of influenza.[1,2]
- Live attenuated influenza vaccine (LAIV) has been shown to help protect against influenza-associated AOM compared with placebo or trivalent inactivated influenza vaccine (TIV) by preventing influenza illness.[3]
  - LAIV efficacy against influenza-associated AOM was 85% compared with placebo and 54% compared with TIV.[3]
- In randomized clinical trials, the pneumococcal conjugate vaccine has been shown to reduce the annual incidence of all-cause AOM by 7.8% (95% CI: 5.4, 10.2) in children 3–42 months of age[4] and by 6% (95% CI: –4, 16) in children 6–24 months of age.[5]
  - Reductions in all-cause AOM shown by Fireman et al were similar during the influenza season (7.5% reduction) compared with the noninfluenza season (8.0% reduction).[4]
- The impact of LAIV from pooled randomized clinical trials on all-cause AOM has not been previously assessed.
- LAIV is approved for eligible children 2 years of age and older and is not approved for use in children younger than 24 months of age.

Objective

- To estimate the efficacy of LAIV against all-cause AOM in young children during the influenza season compared with placebo and TIV

Methods

- All-cause AOM incidence for the entire influenza season was calculated for 6 randomized, double-blind, placebo-controlled trials in children 6–83 months of age (LAIV, n=8037; placebo, n=5602)[6-13] and 2 randomized, double-blind, TIV-controlled trials in children 6–71 months of age (LAIV, n=4949; TIV, n=4955).[14,15]
  - 4 placebo-controlled studies were 2-year studies; others were conducted over a single influenza season (**Table 1**).

Table 1. LAIV Studies Measuring Efficacy Against AOM as a Prespecified Secondary Endpoint

Study Number	Age Range, mo	LAIV, n	Control, n	Location
Placebo-controlled studies				
Study 1, Year 1	12–35	1649	1105	Asia*
Study 1, Year 2	24–47	770	494	Asia*
Study 2, Year 1	6–35	951	664	Europe†
Study 2, Year 2	18–47	639	450	Europe†
Study 3, Year 1	6–35	944	941	Multinational‡
Study 3, Year 2	18–47	338	342	Multinational‡
Study 4	6–35	521	515	Asia§
Study 5	11–23	624	312	Multinational‖
Study 6, Year 1	15–71	854	417	US
Study 6, Year 2	27–83	747	362	US
TIV-controlled studies				
Study 7	6–71	1048	1034	Europe¶
Study 8	6–59	3900	3919	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.
‖Bangladesh, Belgium, Finland, Germany, Hong Kong, Lithuania, Malaysia, Mexico, Philippines, Poland, Singapore, South Korea, Thailand.
¶Belgium, Czech Republic, Finland, Germany, Israel, Italy, Poland, Spain, Switzerland, United Kingdom.
#Asia, Europe, Middle East, United States.

- In 5 of the 6 placebo-controlled studies (studies 1-5), AOM was defined clinically by the presence of an abnormal tympanic membrane (regarding color, position, and/or mobility) suggesting effusion in the middle ear cavity, with signs/symptoms consistent with acute infection (fever [≥38°C rectal or oral, or ≥37.5°C axillary], ear ache, irritability, diarrhea, vomiting, acute otorrhea not caused by external otitis, or other symptoms of respiratory infection).
  - Study 6 defined otitis media as a clinical diagnosis made by a healthcare provider without further criteria.
- For TIV controlled studies (studies 7 and 8), AOM was defined as a healthcare provider diagnosis of AOM concurrent with fever.
- A new episode of AOM was considered to occur when ≥30 days had elapsed since the previous AOM episode, regardless of etiology.
- Only AOM episodes occurring during the influenza season specific to the study country were assessed.
  - The influenza season was assigned based on the weekly number of episodes of culture-confirmed influenza.
- AOM rates were calculated using the number of AOM cases as defined above divided by total surveillance time within influenza seasons for each treatment group. Efficacy was calculated as 1 minus the hazard ratio (HR), where the HR and 95% CI were obtained from the Anderson-Gill model, with treatment as the only effect.
- Data were pooled for efficacy analyses; efficacy for year 1 and year 2 were analyzed separately.

Results

- Compared with placebo, the pooled efficacy of LAIV in children 6–71 months of age against all-cause AOM was 12.4% (95% CI; 2.0, 21.6) in year 1 (**Table 2**).

Table 2. LAIV Efficacy Against All-Cause AOM in Placebo-Controlled and TIV-Controlled Studies

Study Number	LAIV, n/N (%)	Control, n/N (%)	Vaccine Efficacy (95% CI)	Mean Surveillance Period, wk
Placebo-controlled studies				
Study 1, Year 1	61/1649 (3.7)	41/1105 (3.7)	1.6 (–58.7, 39.0)	33
Study 1, Year 2	16/770 (2.1)	12/494 (2.4)	13.4 (–91.1, 60.8)	26
Study 2, Year 1	274/951 (28.8)	199/664 (30.0)	4.5 (–14.5, 20.3)	15
Study 2, Year 2	90/639 (14.1)	60/450 (13.3)	–6.1 (–49.7, 24.7)	13
Study 3, Year 1	190/944 (20.1)	233/941 (24.8)	19.3 (–0.4, 35.1)	18
Study 3, Year 2	80/338 (23.7)	81/342 (23.7)	–0.1 (–41.9, 29.4)	20
Study 4	23/521 (4.4)	33/515 (6.4)	31.5 (–26.7, 62.9)	23
Study 5	45/624 (7.2)	35/312 (11.2)	37.0 (–1.0, 60.7)	9
Study 6, Year 1	265/854 (31.0)	160/417 (38.4)	20.0 (0.6, 35.6)	17
Study 6, Year 2	143/747 (19.1)	84/362 (23.2)	18.3 (–8.6, 38.6)	14
Year 1 pooled data	858/5543 (15.5)	701/3954 (17.7)	12.4 (2.0, 21.6)	21
Year 2 pooled data	329/2494 (13.2)	237/1648 (14.4)	6.2 (–12.4, 21.7)	18
TIV-controlled studies				
Study 7	50/1048 (4.8)	50/1034 (4.8)	1.8 (-47.7, 34.7)	8
Study 8	503/3900 (12.9)	558/3919 (14.2)	10.3 (-2.0, 21.2)	16
Pooled data	553/4948 (11.2)	608/4953 (12.3)	9.7 (-2.1, 20.1)	14

AOM=acute otitis media; LAIV=live attenuated influenza vaccine; TIV=trivalent inactivated influenza vaccine.

- In year 2 of placebo-controlled studies, the available sample size was significantly reduced. The pooled efficacy of LAIV in children 18–83 months of age in year 2 was 6.2% (95% CI: –12.4, 21.7; **Table 2**).
- Compared with TIV, the pooled efficacy of LAIV in children 6–71 months of age against all-cause AOM was 9.7% (955 CI: -2.1, 20.1); **Table 2**).
- Similar trends of efficacy were observed in the subgroups of children 6–23 and ≥24 months of age, although none were statistically significant owing to the smaller sample size.
- By region, efficacy in all ages vs placebo was 20.0% (95% CI: 0.6, 35.6) and 32.6% (95% CI: 6.1, 51.7) in year 1 in the United States and South America, respectively; no statistically significant efficacy was seen in other regions in years 1 or 2.
  - For TIV-controlled studies, the efficacy against all-cause AOM in all ages was 15.5% (95% CI: 0.3, 28.4) in the United States; no statistically significant efficacy was seen in other regions.

Conclusions

- **Among children 6–71 months of age, LAIV reduced the incidence of all-cause AOM during the influenza season compared with placebo.**

References

1. Heikkinen T, et al. *Am J Dis Child.* 1991;145:445-448.
2. Poehling KA, et al. *N Engl J Med.* 2006;355:31-40.
3. Block SL, et al. *Pediatr Infect Dis J.* 2011;30:203-207.
4. Fireman B, et al. *Pediatr Infect Dis J.* 2003;22:10-16.
5. Eskola J, et al. *N Engl J Med.* 2001;344:403-409.
6. Ashkenazi S, et al. *Pediatr Infect Dis J.* 2006;25:870-879.
7. Belshe RB, et al. *J Pediatr.* 2000;136:168-175.
8. Belshe RB, et al. *N Engl J Med.* 1998;338:1405-1412.
9. Bracco Neto H, et al. *Pediatr Infect Dis J.* 2009;28:365-371.
10. Forrest BD, et al. *Clin Vaccine Immunol.* 2008;15:1042-1053.
11. Lum LC, et al. *Vaccine.* 2010;28:1566-1574.
12. Tam JS, et al. *Pediatr Infect Dis J.* 2007;26:619-628.
13. Vesikari T, et al. *Pediatrics.* 2006;118:2298-2312.
14. Belshe RB, et al. *N Engl J Med.* 2007;356:685-696.
15. Fleming DM, et al. *Pediatr Infect Dis J.* 2006;25:860-869.

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