# A Postlicensure Evaluation of the Safety of Live Attenuated Influenza Vaccine in Children 2 to 4 Years of Age

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## Background

- In the United States, intranasal live attenuated influenza vaccine (LAIV) and injectable trivalent inactivated influenza vaccine (TIV) are approved for use in eligible children and adolescents.
  - Some TIV formulations are approved for use in eligible children 6 months and older, while LAIV is approved for use in eligible children ≥24 months of age.[1]
- LAIV (MedImmune, LLC, Gaithersburg, MD) was licensed in 2003 for use in eligible individuals 5–49 years of age and, in 2007, the US Food and Drug Administration expanded its approval of LAIV to include children 24–59 months of age.[2]
- In 2007, MedImmune committed to conduct a postlicensure evaluation of the safety of LAIV in children 24–59 months of age.

## Objective

- To describe the incidence of medically attended events (MAEs) following LAIV administration among eligible children 24–59 months of age

## Methods

- Eligible individuals received LAIV in Kaiser Permanente Northern California as part of routine care from October 2007 through March 2010 and were monitored afterward using their healthcare database.
- MAEs in LAIV recipients were compared with rates in 3 different nonrandomized controls; a self-control, unvaccinated controls, and TIV recipients.
  - Subjects were matched for age and sex.
- For each control group, rate comparisons were made for each postvaccination period (3, 21, 42, or 180 days) and setting (clinic, hospital, emergency department, all settings; **Table 1**).
- All MAEs through 42 days postvaccination and all hospitalizations/deaths through 6 months postvaccination were analyzed.
  - Individual chart reviews were performed for specific diagnoses of interest.
- MAEs were also grouped together in 5 event categories and analyzed cumulatively across all settings as prespecified diagnoses of interest (PSDI).
  - These included (1) acute respiratory tract events, (2) acute gastrointestinal tract events, (3) asthma and wheezing events, (4) systemic bacterial infections, and (5) rare diagnoses potentially related to wild-type influenza.
- Individual MAEs and PSDIs that were significantly increased or decreased after vaccination with LAIV were organized by organ class in a 2-dimensional heat map **(Figures 1 and 2)**.
- Statistical significance was assigned without multiplicity adjustment.

## Results

- 33,443 LAIV recipients were matched to 30,815 TIV recipients and 28,766 unvaccinated subjects **(Table 2)**.
- Of the 4396 rate comparisons, 83 and 221 occurred at a significantly higher and lower rate, respectively, after vaccination with LAIV; 177 significant comparisons were from individual MAEs **(Figure 1)** and 127 were from PSDIs **(Figure 2)**.
  - For the within-cohort comparisons, 60 were statistically significant, of which 7 (12%) comparisons occurred at a higher rate during the risk period relative to the reference period.
  - For the unvaccinated controls, 104 comparisons were statistically significant, of which 64 (62%) comparisons occurred at a higher rate in LAIV recipients relative to unvaccinated controls.
  - For the TIV controls, 140 comparisons were statistically significant, of which 12 (9%) comparisons occurred at a higher rate in LAIV recipients relative to TIV controls.
- Only urticaria within 21 days of vaccination occurred at a significantly higher rate after LAIV in comparison with all 3 control groups.
- Among 82 asthma/wheezing comparisons, only 4 occurred at a significantly higher rate after vaccination with LAIV and were in comparison with unvaccinated children **(Figures 1 and 2)**.
- No anaphylaxis events occurred within 3 days postvaccination.
- A total of 30 serious adverse events (SAEs) within 42 days of vaccination occurred in 29 LAIV recipients; only 2 events were considered possibly related to LAIV.
  - A 4-year-old male subject developed right middle lobe pneumonia 5 days after vaccination with LAIV and a 31-month-old male subject was diagnosed with intussusception and a viral infection 2 days after vaccination with LAIV.
- No SAE occurred at a significantly higher rate among LAIV recipients.
- No deaths occurred among LAIV recipients throughout the study.

**Table 1. Summary of Safety Analyses**

| Event | Postvaccination Period | Clinical Setting |
|---|---|---|
| Anaphylaxis, urticaria | 3 days | Clinic, ED, Hospital |
| Individual MAEs | 21* and 42 days | Clinic, ED, Hospital |
| SAEs | 21 and 42 days | All |
| PSDIs | 21, 42, and 180† days | All |
| Hospitalizations and deaths for all causes | 21, 42, and 180 days | Hospital, Any‡ |
| Hospitalizations and deaths for rare events potentially related to wild-type influenza | 180 days | Hospital, Any |

ED=emergency department; MAE=medically attended event; PSDI=prespecified diagnoses of interest; SAE=serious adverse event.
*The analysis period for the within-cohort group was for 21-day outcomes only.
†Asthma and wheezing events only.
‡Deaths were assessed in any setting.

**Table 2. Subject and Dose Characteristics**

| Subject or Dose Characteristic | Doses of LAIV, n (%) (n=33,443) | Unvaccinated Controls, n (%) (n=28,766) | Doses of TIV, n (%) (n=30,815) |
|---|---|---|---|
| Age, mo | | | |
| 24–35 | 8655 (26) | 7350 (26) | 8184 (27) |
| 36–59 | 24,788 (74) | 21,416 (75) | 22,631 (73) |
| Sex | | | |
| Boy | 16,121 (48) | 14,574 (51) | 15,634 (51) |
| Girl | 17,322 (52) | 14,192 (49) | 15,181 (49) |
| Vaccine season | | | |
| 2007–2008 | 5328 (16) | 4726 (16) | 5295 (17) |
| 2008–2009 | 13,927 (42) | 10,794 (38) | 12,193 (40) |
| 2009–2010 | 14,188 (42) | 13,246 (46) | 13,327 (43) |
| Vaccine dose | | | |
| 1 | 32,261 (97) | 28,766 (100) | 30,815 (100) |
| 2 | 1182 (4) | NA | NA |
| Utilization | | | |
| High (≥2 visits) | 11,813 (35) | 9416 (33) | 12,069 (39) |
| Low (≤1 visit) | 21,630 (65) | 19,350 (67) | 18,746 (61) |

LAIV=live attenuated influenza vaccine; TIV=trivalent inactivated influenza vaccine.

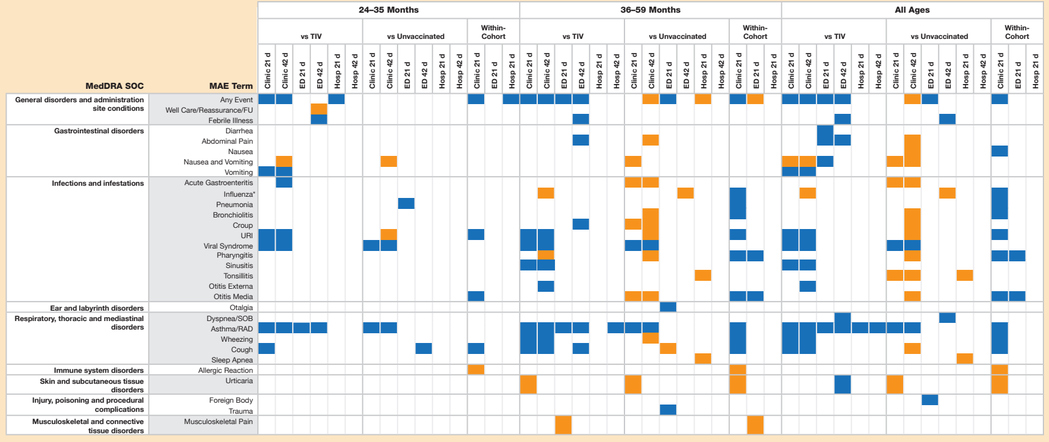
## Conclusion

- **The results of this postlicensure evaluation of LAIV safety in US children 24–59 months of age are consistent with preapproval clinical studies and Vaccine Adverse Event Reporting System reports, both of which demonstrated no significant increase in asthma and wheezing events or other adverse outcomes among eligible children who received LAIV.**

## References

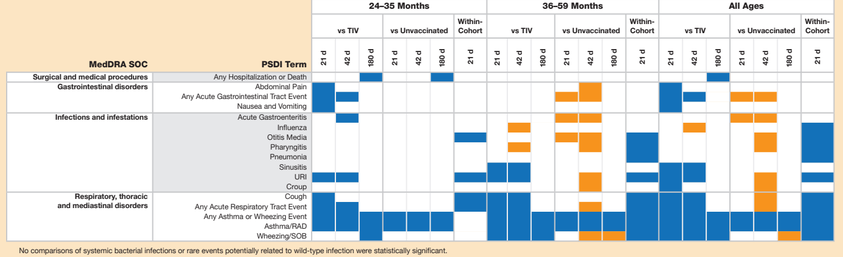
1. Grohskopf L, et al. *MMWR Morb Mortal Wkly Rep*. 2011;60:1128-1132.
2. US Food and Drug Administration. FDA Approves Nasal Influenza Vaccine for Use in Younger Children. US Food and Drug Administration. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108988.htm. Accessed February 15, 2012.

**Figure 1. Statistically Significant Differences in Individual MAEs in LAIV Recipients Relative to Controls in Subjects 24–35, 36–59, and 24–59 Months of Age**




*99% of influenza cases were due to pandemic H1N1 and results are likely due to differential pandemic vaccination rates within control groups.

**Figure 2. Statistically Significant Differences in Prespecified Diagnoses of Interest in LAIV Recipients Relative to Controls in Subjects 24–35, 36–59, and 24–59 Months of Age**




No comparisons of systemic bacterial infections or rare events potentially related to wild-type infection were statistically significant.

**Figures 1 and 2.** Individual events are grouped by organ class and medical term according to the Medical Dictionary for Regulatory Activities (MedDRA) along figure rows. Columns represent individual analyses which are organized by comparison group (versus trivalent inactivated influenza vaccine [TIV], unvaccinated, within-cohort), location (clinic, emergency department [ED], hospital [Hosp], all locations), and time interval (21, 42, and 180 days). Events occurring at a significantly higher rate after live attenuated influenza vaccine (LAIV) are coded orange and those occurring at a significantly lower rate after LAIV are coded in blue. The within-cohort analysis (self-control) columns are fewer in number because this analysis was performed within the 21-day postvaccination interval only. Most events occurring at a higher rate after LAIV (orange) are found within the unvaccinated comparison group columns, whereas most events that occurred at a lower rate after LAIV (blue) are found within the TIV-vaccinated comparison group columns. Comparisons of events occurring within 3 days of vaccination are not included in the figure. FU=follow-up; MAE=medically attended event; PSDI=prespecified diagnoses of interest; RAD=reactive airway disease; SOB=shortness of breath; SOC=system organ class; URI=upper respiratory tract infection.



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