A Post-licensure Evaluation of the Safety of Live Attenuated Influenza Vaccine in US Children 5–17 Years of Age

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Background

- The safety of live attenuated influenza vaccine (LAIV) has been evaluated in 26,031 children enrolled in placebo- and trivalent inactivated influenza vaccine (TIV)–controlled clinical trials and a community-based open-label study.[1,2]
- LAIV was initially approved in the United States in 2003 for eligible individuals 5–49 years of age; the age indication was lowered to include children as young as 2 years in 2007.
- As part of a postlicensure commitment to the US Food and Drug Administration, MedImmune conducted a postmarketing evaluation of the safety of LAIV in 60,000 LAIV recipients 5–49 years of age, including approximately 20,000 individuals in each of 3 age cohorts (5–8 y, 9–17 y, and 18–49 y).
- LAIV is also approved in other countries for use in eligible individuals aged 2–49 years (2–17 y in the European Union and 2–59 y in Canada).

Objective

- To evaluate the postlicensure safety of LAIV among US children aged 5–8 and 9–17 years

Methods

- Safety data were prospectively collected from a Kaiser Permanente Health Plan database of 4 million members in Northern California, Hawaii, and Colorado; members received LAIV and TIV as part of routine care.
- Rates of medically attended events (MAEs) and serious adverse events (SAEs) were assessed in eligible children 5–17 years of age receiving LAIV from October 2003–March 2008; comparators were multiple nonrandomized controls, including self-control, matched unvaccinated controls, and matched TIV recipients.
  - Subjects were matched based on age, sex, and previous healthcare use.
  - Children at high risk (eg, those with underlying medical conditions for whom LAIV was not recommended) were excluded from analysis.
  - MAEs were identified in the clinic, emergency department, and hospital.
- All MAEs and SAEs through 42 days postvaccination and all hospitalizations and deaths through 6 months postvaccination were analyzed **(Table 1)**.

Table 1. Summary of Safety Analyses

Event	Period, d	Setting
Anaphylaxis, urticaria	3	Clinic, ED, hospital
Individual MAEs	21* and 42	Clinic, ED, hospital
SAEs	21 and 42	All
Hospitalizations and deaths for all causes	21, 42 and 180	Hospital, any†
Hospitalizations and deaths for rare events potentially related to wild-type influenza	180 and entire study period‡	Hospital, any

ED=emergency department; MAE=medically attended event; SAE=serious adverse event.
*The analysis period for the within-cohort group was for 21-d outcomes only.
†Deaths were assessed in any setting.
‡The end of the entire study period was defined as 6 mo after completion of the primary dosing regimen by the last person vaccinated within the age cohort.

- Individual MAEs that were significantly increased or decreased after LAIV were organized by organ class in a 2-dimensional heat map **(Figures 1 and 2)**.
- Statistical significance was assigned without multiplicity adjustment.

Results

- In the analysis population, 43,702 subjects 5–17 years of age were vaccinated with 53,369 doses of LAIV; matched controls were TIV-vaccinated (n=44,656) and unvaccinated (n=50,854) subjects **(Table 2)**.

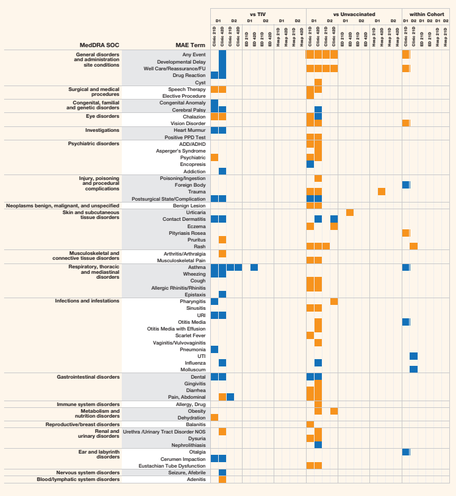
Table 2. Characteristics of Subjects Receiving Doses in All Analyses

	Type of Analysis				
	Within-Cohort Comparison	Comparison With Unvaccinated Controls		Comparison With TIV Controls	
Subject Characteristics, n (%)	LAIV Doses (n=53,369)	LAIV Doses (n=53,366)	Unvaccinated (n=53,175)	LAIV Doses (n=48,683)	TIV Doses (n=46,932)
Age category, y					
3–4*	0 (0.0)	0 (0.0)	172 (0.3)	0 (0.0)	1683 (3.5)
5–8	23,530 (44.1)	23,528 (44.1)	23,362 (43.8)	21,312 (43.8)	19,631 (40.3)
9–17	29,839 (55.9)	29,838 (55.9)	29,794 (55.8)	27,371 (56.2)	27,211 (55.9)
18–19*	0 (0.0)	0 (0.0)	38 (0.1)	0 (0.0)	158 (0.3)
Sex					
Female	28,123 (52.7)	28,121 (52.7)	28,121 (52.7)	25,487 (52.4)	25,487 (52.4)
Male	25,246 (47.3)	25,245 (47.3)	25,245 (47.3)	23,196 (47.6)	23,196 (47.6)
Healthcare use					
Low (0 or 1 visit)	37,940 (71.1)	37,939 (71.1)	37,939 (71.1)	37,731 (71.3)	34,731 (71.3)
High (≥2 visits)	15,429 (28.9)	15,427 (28.9)	15,427 (28.9)	13,952 (28.7)	13,952 (28.7)

LAIV=live attenuated influenza vaccine; TIV=trivalent inactivated influenza vaccine.
*One 3-year-old and one 19-year-old, both TIV controls, were included in the analysis.

- 9496 MAE incidence rate comparisons were performed, 372 (4%) of which yielded statistically significant differences: 204 incidence rates were higher and 168 incidence rates were lower in LAIV recipients compared with controls.
- No anaphylaxis events occurred within 3 days postvaccination.
- No MAE rate differences suggested a safety signal for LAIV among children aged 5–8 years **(Figure 1)** or 9–17 years **(Figure 2)** relative to controls.
- Events occurring at a higher rate after LAIV were clustered in the unvaccinated control columns; events occurring at a lower rate after LAIV were clustered in the TIV control column.
  - Asthma/wheezing MAEs were not statistically increased in LAIV recipients; in 40 comparisons, asthma/wheezing MAEs decreased among LAIV recipients.
  - Only 1 MAE was significantly increased among LAIV recipients relative to all 3 control groups; breast lump/cyst in subjects 9–17 years of age (n=7).
- The incidence rates of SAEs were low and not significantly higher or lower in LAIV recipients relative to control groups in any comparison.
- 2 SAEs (Bell palsy [n=2] and nonspecific paroxysmal spell [n=1]) were considered possibly related to LAIV.
  - In children 9–17 years of age, Bell palsy occurred in 2 children vaccinated with LAIV, 7 vaccinated with TIV, and no unvaccinated children.
- The rate of hospitalization was low and not significantly higher or lower in LAIV recipients relative to control groups in any comparison.
- 3 deaths occurred within 180 days postvaccination; all were considered unrelated to LAIV.

Figure 1. Statistically Significant Differences in Events in LAIV Recipients 5–8 Years of Age Relative to Controls

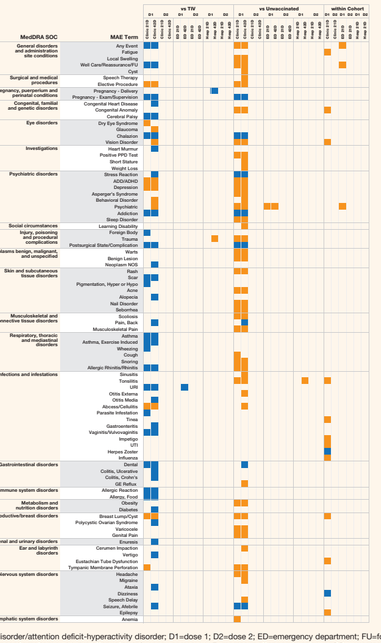


ADD/ADHD=attention deficit disorder/attention deficit-hyperactivity disorder; D1=dose 1; D2=dose 2; ED=emergency department; FU=follow-up; Hosp=hospitalization; LAIV=live attenuated influenza vaccine; MAE=medically attended event; MedDRA=Medical Dictionary for Regulatory Activities; NOS=not otherwise specified; SOC=system organ class; TIV=trivalent inactivated influenza vaccine; URI=upper respiratory tract infection; UTI=urinary tract infection.

References

1. Ambrose CS, et al. *Influenza Other Respir Viruses*. 2011;5:67-75.
2. Piedra PA, et al. *Pediatrics*. 2005;116:e397-407.
3. Izurieta HS, et al. *JAMA*. 2005;294:2720-2725.

Figure 2. Statistically Significant Differences in Events in LAIV Recipients 9–17 Years of Age Relative to Controls



ADD/ADHD=attention deficit disorder/attention deficit-hyperactivity disorder; D1=dose 1; D2=dose 2; ED=emergency department; FU=follow-up; GE=gastroesophageal; Hosp=hospitalization; LAIV=live attenuated influenza vaccine; MAE=medically attended event; MedDRA=Medical Dictionary for Regulatory Activities; NOS=not otherwise specified; SOC=system organ class; TIV=trivalent inactivated influenza vaccine; URI=upper respiratory tract infection; UTI=urinary tract infection.

Conclusions

- **Similar to preclinical studies and an analysis from the Vaccine Adverse Events Reporting System (VAERS) from the first 2 postlicensure years of LAIV,[3] this study did not identify any unexpected significant adverse outcomes when the vaccine was used in the approved population.**
- **The incidence of MAEs was comparable between LAIV recipients and multiple nonrandomized controls, and no pattern of MAEs was found to occur at higher rates than in control groups.**
  - **Specifically, no increase in asthma or wheezing events were seen after vaccination with LAIV.**
- **Because of the lack of adjustment for multiple comparisons, a large number of significant outcomes would be expected owing to chance alone.**
- **Likely because of bias in health-seeking behavior and underlying health status, most events that were increased after vaccination with LAIV were in comparison with unvaccinated controls, and most events that were decreased after vaccination with LAIV were in comparison with TIV-vaccinated controls.**

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