A Postlicensure Evaluation of the Safety of Live Attenuated Influenza Vaccine in Individuals 5 to 49 Years of Age

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Background

- Live attenuated influenza vaccine (LAIV) was approved for eligible children and adults 5 to 49 years of age in June 2003.
  - Subsequent approval for eligible children 2 to 4 years of age occurred in 2007.
- A postlicensure commitment was made to describe LAIV safety among 60,000 unique recipients.

Methods

- Eligible children and adults 5 to 49 years of age received LAIV as part of routine care from October, 2003, through March, 2008.
- Using the Kaiser Permanente database, rates of medically attended events (MAEs) in LAIV recipients were compared with rates in the following nonrandomized controls
  - Self-control
  - Matched unvaccinated (with any influenza vaccine) controls
  - Matched trivalent inactivated influenza vaccine (TIV) recipients
- Controls were matched by age, gender, and previous healthcare use.
- All MAEs and serious adverse events (SAEs) through 42 days postvaccination and all hospitalizations and deaths through 6 months postvaccination were analyzed **(Table 1)**.
- Three prespecified groups of MAEs were analyzed separately across all settings as prespecified grouped diagnoses (PSGD) and included acute respiratory tract events, acute gastrointestinal tract events, and systemic bacterial infections.
  - Rare events potentially related to wild-type influenza infection (PRWI) were analyzed separately in a similar manner.
- Individual MAEs that were significantly increased or decreased after vaccination with LAIV were organized by organ class in a 2-dimensional "heatmap".
- Statistical significance was assigned without multiplicity adjustment.

Table 1. Summary of Safety Analysis

Event	Period	Setting
Anaphylaxis	3 days	Clinic, ED, Hosp
Urticaria	3 days	Clinic, ED, Hosp
Individual MAEs	21* and 42 days	Clinic, ED, Hosp
Prespecified group diagnoses	21 and 42 days	All
Serious adverse events	21 and 42 days	All
Asthma and wheezing	21, 42, and 180 days	All
Hospitalizations and deaths for all causes	21, 42, and 180 days	Hosp, Any†
Hospitalizations and deaths due to rare events potentially related to wild-type influenza	180 days Entire study period‡	Hosp, Any Hosp, Any

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

Results

- 63,061 subjects received LAIV **(Table 2)**.
  - 62,492 control patients were vaccinated with TIV.
  - 71,949 control patients did not receive any influenza vaccine.

Table 2. Summary of Unique Subjects Vaccinated With Live Attenuated Influenza Vaccine

Influenza Season	5–8 years	9–17 years	18–49 years	Totals
2003–2004	2974	3904	1268	8146
2004–2005	2601	3467	9120	15,188
2005–2006	3013	4345	5780	13,138
2006–2007	3175	4037	3191	10,403
2007–2008	7598	8588	0*	16,186
Totals	19,361	24,341	19,359	63,061

*Enrollment was closed for subjects 18–49 years of age after the 2006–2007 season.

- Of approximately 23,000 incidence rate comparisons performed, 1058 (4.6%) were statistically significant **(Table 3)**.
- For individual MAEs, significant events are presented in **Figure 1**.
  - Increased events were clustered in the unvaccinated control columns.
  - Decreased events were clustered in the TIV control column.
- No anaphylaxis events occurred within the 3-day risk period after vaccination with LAIV.
- Few MAEs were significantly increased or decreased after vaccination with LAIV across all 3 comparison groups; all were deemed biologically implausible.
- Within the PSGDs, acute respiratory tract events are presented in **Tables 4 and 5**.
  - After vaccination with LAIV, acute gastrointestinal events were generally decreased compared with TIV-vaccinated controls and increased compared with unvaccinated controls.
  - No PSGDs of systemic bacterial infections were seen.
- No asthma/wheezing MAEs were statistically increased among LAIV recipients.
  - 31 asthma/wheezing rate comparisons were decreased after vaccination with LAIV.
- 114 SAEs (5 in the clinic setting, 1 in the ED setting, and 108 in the hospital setting) occurred in 107 individuals within 42 days postvaccination, including 1 death.
  - 5 SAEs were considered possibly or probably related to vaccination with LAIV: Bell palsy (n=3), nonspecific paroxysmal spell (n=1), and migraine/sinusitis (n=1).
- 9 deaths occurred within 180 days postvaccination; all were considered unrelated to LAIV.
  - No deaths occurred in subjects 5–8 years of age, 3 deaths occurred in subjects 9–17 years of age, and 6 deaths occurred in subjects 18–49 years of age.

Table 3. Summary of Significant Rate Comparisons by Analysis Categories

		Increased After LAIV				Decreased After LAIV			
Analysis category	Comparisons (n)	Total n, (%)	TIV n (%)	Unvax n (%)	Within n (%)	Total n (%)	TIV n (%)	Unvax n (%)	Within n (%)
Individual MAEs	922	421 (46)	71 (17)	308 (73)	42 (10)	501 (54)	359 (72)	108 (22)	34 (7)
PSGD*	90	31 (33)	1 (3)	26 (84)	4 (13)	59 (67)	51 (86)	1 (2)	7 (12)
Asthma/wheezing	31	0 (0)	0 (0)	0 (0)	0 (0)	31 (100)	23 (74)	6 (19)	2 (6)
SAE	8	0 (0)	0 (0)	0 (0)	0 (0)	8 (100)	4 (50)	4 (50)	0 (0)
Hospitalization/death	4	0 (0)	0 (0)	0 (0)	0 (0)	4 (100)	2 (50)	2 (50)	0 (0)
Urticaria	2	2 (100)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)
PRWI	1	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)
Total	1058	454				604			

LAIV=live attenuated influenza vaccine; MAE=medically attended event; PRWI=rare event potentially related to infection with wild-type influenza; PSGD=prespecified group diagnoses; SAE=serious adverse event; TIV=trivalent inactivated influenza vaccine; Unvax=not vaccinated with any influenza vaccine.
*Prespecified group diagnoses (acute respiratory tract and acute gastrointestinal events).

Table 4. Acute Respiratory Tract Events Associated With a Statistically Significantly Increased Risk in LAIV Recipients

Diagnosis	Comparison	Risk Period, d	Dose	Age, y	Hazard Ratio	P*
Asthma/reactive airway disease	Within cohort	21	1	18–49	2.08	0.05
Cough	Unvaccinated	21	1	9–17	2.25	0.02
Cough	Unvaccinated	42	1	All	1.24	0.04
Cough	Unvaccinated	42	1	5–8	1.57	<0.01
Cough	Unvaccinated	42	1	9–17	1.66	0.03
Influenza	Within cohort	21	1	9–17	8.98	0.04
Otitis media	Unvaccinated	42	1	All	1.14	0.02
Otitis media	Unvaccinated	42	1	5–8	1.23	<0.01
Pharyngitis	Unvaccinated	42	1	5–8	1.18	0.05
Pharyngitis	Unvaccinated	42	2	5–8	2.09	0.03
Sinusitis	Unvaccinated	21	1	All	1.33	0.01
Sinusitis	Unvaccinated	21	1	5–8	1.56	0.04
Sinusitis	Unvaccinated	42	1	All	1.29	<0.01
Sinusitis	Unvaccinated	42	1	5–8	1.38	0.03
Sinusitis	Unvaccinated	42	1	9–17	1.51	<0.01
Any acute respiratory tract event	Unvaccinated	21	1	All	1.09	0.02
Any acute respiratory tract event	Unvaccinated	21	1	5–8	1.12	0.05
Any acute respiratory tract event	Unvaccinated	42	1	All	1.08	<0.01
Any acute respiratory tract event	Unvaccinated	42	1	5–8	1.15	<0.01
Any acute respiratory tract event	Unvaccinated	42	2	5–8	1.39	<0.01

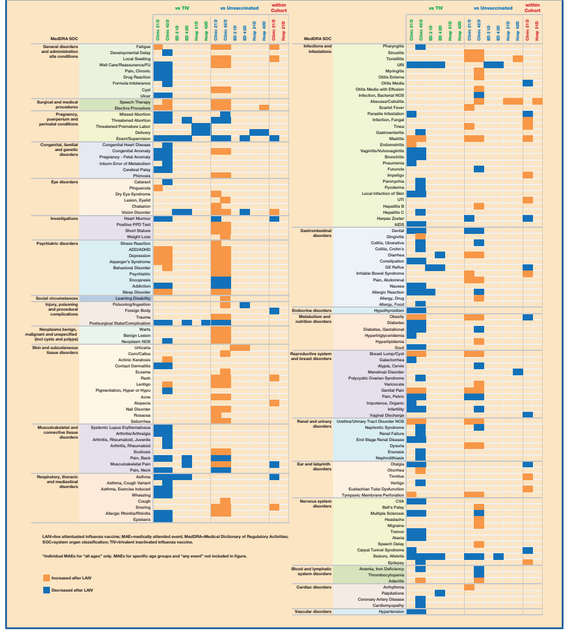
LAIV=live attenuated influenza vaccine.
*P-value for chi-square comparison.

Table 5. Acute Respiratory Tract Events Associated With a Statistically Significantly Decreased Risk in LAIV Recipients

Diagnosis	Comparison	Risk Period, d	Dose	Age, y	Hazard Ratio	P*
Asthma/reactive airway disease	Within cohort	21	1	All	1.13	0.44
Asthma/reactive airway disease	Within cohort	21	1	5–8	0.69	0.17
Asthma/reactive airway disease	TIV	21	1	All	0.24	<0.01
Asthma/reactive airway disease	TIV	21	1	5–8	0.15	<0.01
Asthma/reactive airway disease	TIV	21	1	9–17	0.28	<0.01
Asthma/reactive airway disease	TIV	21	1	18–49	0.37	<0.01
Asthma/reactive airway disease	TIV	21	2	5–8	0.27	0.09
Asthma/reactive airway disease	TIV	42	1	All	0.29	<0.01
Asthma/reactive airway disease	TIV	42	1	5–8	0.28	<0.01
Asthma/reactive airway disease	TIV	42	1	9–17	0.28	<0.01
Asthma/reactive airway disease	TIV	42	1	18–49	0.35	<0.01
Asthma/reactive airway disease	TIV	42	2	5–8	0.29	0.03
Bronchitis	TIV	21	1	All	0.57	<0.01
Bronchitis	TIV	21	1	5–8	0.44	0.03
Bronchitis	TIV	21	1	18–49	0.58	0.02
Bronchitis	TIV	42	1	All	0.67	<0.01
Bronchitis	TIV	42	1	5–8	0.56	0.02
Bronchitis	TIV	42	1	18–49	0.69	0.02
Influenza	Unvaccinated	42	1	5–8	0.13	0.05
Influenza	TIV	42	1	5–8	NE	NE
Otitis media	Within cohort	21	1	All	0.98	0.79
Otitis media	Within cohort	21	1	5–8	1.01	0.94
Otitis media	TIV	42	1	9–17	0.80	0.04
Pharyngitis	TIV	21	1	5–8	0.77	0.02
Pharyngitis	TIV	42	1	All	0.88	0.02
Pneumonia	TIV	21	1	All	0.62	0.01
Pneumonia	TIV	21	1	5–8	0.53	<0.01
Upper respiratory infection	TIV	21	1	All	0.76	<0.01
Upper respiratory infection	TIV	21	1	5–8	0.78	<0.01
Upper respiratory infection	TIV	21	1	9–17	0.76	0.01
Upper respiratory Infection	TIV	21	1	18–49	0.72	0.01
Upper respiratory infection	TIV	42	1	All	0.77	<0.01
Upper respiratory infection	TIV	42	1	5–8	0.79	<0.01
Upper respiratory infection	TIV	42	1	9–17	0.77	<0.01
Upper respiratory infection	TIV	42	1	18–49	0.74	<0.01
Wheezing/shortness of breath	TIV	21	1	All	0.53	<0.01
Wheezing/shortness of breath	TIV	21	1	5–8	0.60	0.03
Wheezing/shortness of breath	TIV	21	1	9–17	0.54	0.05
Wheezing/shortness of breath	TIV	21	1	18–49	0.29	0.03
Wheezing/shortness of breath	TIV	42	1	All	0.63	<0.01
Wheezing/shortness of breath	TIV	42	1	5–8	0.60	<0.01
Any acute respiratory tract event	Within cohort	21	1	All	0.96	0.33
Any acute respiratory tract event	Within cohort	21	1	5–8	0.96	0.45
Any acute respiratory tract event	TIV	21	1	All	0.77	<0.01
Any acute respiratory tract event	TIV	21	1	5–8	0.77	<0.01
Any acute respiratory tract event	TIV	21	1	9–17	0.80	<0.01
Any acute respiratory tract event	TIV	21	1	18–49	0.73	<0.01
Any acute respiratory tract event	TIV	42	1	All	0.79	<0.01
Any acute respiratory tract event	TIV	42	1	5–8	0.82	<0.01
Any acute respiratory tract event	TIV	42	1	9–17	0.77	<0.01
Any acute respiratory tract event	TIV	42	1	18–49	0.77	<0.01

LAIV=live attenuated influenza virus; NE=not estimable; TIV=trivalent inactivated influenza vaccine.
*P-value for chi-square comparison.

Figure 1. MAEs Grouped by MedDRA Dictionary According to Organ Class, Higher Level Term, and Lower Level Term*



Conclusions

- **The study did not identify any unexpected significant adverse outcomes associated with LAIV use among eligible individuals 5–49 years of age.**
- **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 LAIV were in comparison with unvaccinated controls and most events that were decreased after LAIV were in comparison with TIV-vaccinated controls.**
- **The results of the current postlicensure evaluation of LAIV safety in individuals 5–49 years of age are consistent with preapproval clinical studies and reports to the US Vaccine Adverse Events Reporting System in the years after LAIV approval.**

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