

A Postmarketing Commitment to Evaluate the Frequency of Use and Safety of Live Attenuated Influenza Vaccine Use in Non-Recommended Populations Less Than 59 Months of Age

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Introduction

- The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommends that all children aged 6 months through 18 years receive influenza vaccine on a yearly basis.¹
- Live attenuated influenza vaccine (LAIV; MedImmune, Gaithersburg, MD, USA) was initially approved in the United States for eligible individuals 5–49 years of age in 2003 and received an expanded indication to include eligible children aged 24–59 months in September 2007.²
 - Initial safety data in children aged 24–59 months from the Vaccine Adverse Event Reporting System included 222 adverse events (AE) in the 10.4 million doses distributed; AEs reported most frequently were fever (47%), vomiting (28%) and rhinitis (21%).³
- The LAIV label contains warnings and precautions against use in children younger than 24 months, asthmatics, those 24–59 months of age with recurrent wheezing, or children with altered immunocompetence.⁴
 - LAIV was not approved for use in children younger than 24 months because of an increased risk compared with trivalent inactivated influenza vaccine (TIV) of medically significant wheezing in children 6–23 months of age (5.9% vs 3.8%, respectively) and an increased rate of hospitalization in children 6–11 months of age (6.1% vs 2.6%, respectively).⁴
 - LAIV has not been sufficiently studied in children with asthma and those aged 24–59 months with recurrent wheezing.^{5,6}
 - LAIV has not been sufficiently studied in immunocompromised children.^{7,8}
- As part of a postmarketing commitment to the US Food and Drug Administration (FDA), a study was initiated to monitor LAIV use in children younger than 24 months, those aged 24–59 months with asthma or recurrent wheezing, and in immunocompromised children.

Objective

- To monitor children for whom vaccination with LAIV is not indicated by comparing the rate of vaccination of LAIV with that for TIV in children <24 months of age, or with asthma or recurrent wheezing or those who are immunocompromised and monitor the safety of LAIV when used in those cohorts.
- To meet the safety objective, we had no a priori hypotheses, but screened for changes in the frequency of selected emergency department (ED) visits and hospitalizations after LAIV vaccination compared with TIV vaccination.

Methods

Study Design

- This was a retrospective descriptive cohort study of children younger than 59 months who were included in a large employer based, anonymized, health insurance claims database covering >15 million individuals per year.
 - Included claims from August 1, 2006, through January 31, 2009 to characterize patients and identify study outcomes
 - Monitored safety outcomes in 2007–2008
- We used claims-based algorithms to identify children who were not recommended to receive LAIV and identified the following 4 cohorts:
 - Cohort 1:** Children younger than 24 months of age
 - Cohort 2:** Children 24–59 months of age with asthma, defined below:
 - ≥2 outpatient claims for asthma during the previous 12 months, or
 - ≥1 hospital or ED claim of asthma within the previous 12-months, or
 - ≥1 outpatient asthma claim and ≥1 outpatient use of a short-acting beta agonist (SABA) within the previous 12-month period.
 - Cohort 3:** Children 24–59 months of age with recurrent wheezing (based on the ACIP definition of recurrent wheezing) who met the following criteria in the previous 12 months:
 - No claims for asthma and
 - >1 use of a SABA (used as a surrogate for wheezing)

- Cohort 4:** Children 24–59 months of age who were immunocompromised meeting the following criteria:
 - ≥2 outpatient claims or ≥1 hospitalization or ED visit with diagnosis codes for transplantation, congenital immune deficiency, symptomatic HIV, or hematologic or lymphatic malignancy; or
 - ≥1 claim for immunosuppressive therapy other than systemic corticosteroids in the previous 16 weeks; or
 - Received systemic corticosteroid (SCST); cohort membership ended at the end of prescription period for oral SCST if supply was <14 days or ended 28 days after the prescription end date if SCST supply >14 days.

Vaccination Rate

- Vaccination rates were assessed for the 2007–2008 and 2008–2009 influenza seasons.
- Vaccination rates were calculated as the number of children vaccinated divided by the total number of child-days of follow up for the cohort.
- Follow-up was based on insurance claims history and started at cohort entry and ended at the earliest of the vaccination date or February 17 of 2008 or 2009.
- LAIV vaccination rates were compared with TIV vaccination rates in each cohort and in the general population (ie, all other children) of children aged 24–59 months.

Safety

- The primary safety outcome was any discharge diagnosis for a hospitalization or ED visit during the 42 days after vaccination with LAIV or TIV.
 - Special outcomes of interest were:
 - In cohort 1: all lower respiratory tract infections (LRI)
 - In combined cohorts 2 and 3: LRI known to complicate asthma admissions⁹
 - In cohort 4: infectious diseases
- The risk of adverse outcomes among children vaccinated with LAIV or TIV was calculated by dividing the number of vaccinated children with a claim for outcomes by the total number of children vaccinated.
- Safety data are not yet available for year 2.

Results

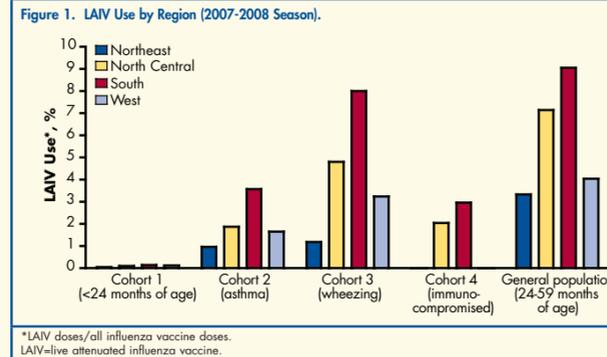
Vaccination Rate for Each Cohort

- In year 1 and year 2, rates of vaccination with LAIV in cohorts 1, 2, and 4 were lower than the rate in all other children aged 24–59 months (Table 1).
- For cohort 3 the rate of vaccination with LAIV was similar to that of all other children aged 24–59 months in year 1, but lower than the rate in all other children aged 24–59 months in year 2 (Table 1).
- The rate ratio (RR) of vaccination with LAIV in cohorts 1, 2, and 3 compared with the rate of vaccination with LAIV in children aged 24–59 months decreased from 0.47 in year 1 (0.02, 0.59, and 1.17 for cohorts 1, 2, and 3, respectively) to year 2 (0.01, 0.41, and 0.82 for cohorts 1, 2, and 3, respectively).
- The rate ratio of vaccination with LAIV in cohort 4 compared with the rate in all other children aged 24–59 months increased slightly from 0.47 in year 1 to 0.59 in year 2.
- In both years and in all cohorts the rate of vaccination with TIV was higher than that of LAIV.
- The rate of vaccination with TIV was unchanged from year 1 to year 2 while the rate of vaccination with LAIV increased 2- to 5-fold.
- The prevalence of vaccination with LAIV among all influenza vaccinations was the least common in the Northeast for all of the cohorts of interest (Figure 1).
- For cohort 3, the prevalence of vaccination with LAIV compared with the prevalence in the general population was relatively high in the South (prevalence ratio=0.88) and the West (prevalence ratio=0.80; Figure 1).

Table 1. Vaccination Rates Using LAIV or TIV in Years 1 and 2

| Cohort | LAIV | | | | TIV | | | |
|------------------------------------|------------|----------------------------|-------------------------|----------------------------|------------|----------------------------|-------------------------|----------------------------|
| | 2007–2008 | | 2008–2009 (preliminary) | | 2007–2008 | | 2008–2009 (preliminary) | |
| | Vaccinated | Vaccination Rate* (95% CI) | Vaccinated | Vaccination Rate* (95% CI) | Vaccinated | Vaccination Rate* (95% CI) | Vaccinated | Vaccination Rate* (95% CI) |
| Cohort 1 (Aged <24 months) | 138 | 0.029 (0.024–0.034) | 219 | 0.061 (0.053–0.069) | 120,901 | 25.16 (25.02–25.30) | 93,206 | 26.03 (25.87–26.20) |
| Cohort 2 (Asthma) | 325 | 0.78 (0.70–0.87) | 675 | 2.35 (2.18–2.53) | 12,843 | 30.72 (30.19–31.25) | 8463 | 29.52 (28.90–30.15) |
| Cohort 3 (Recurrent wheezing) | 308 | 1.55 (1.38–1.73) | 616 | 4.66 (4.29–5.03) | 4880 | 24.55 (23.86–26.25) | 2836 | 21.45 (20.66–22.24) |
| Cohort 4 (Immunocompromised) | 12 | 0.62 (0.32–1.08) | 46 | 3.33 (2.37–4.29) | 634 | 32.71 (30.22–35.36) | 382 | 27.64 (24.87–30.41) |
| General population (Aged 24–59 mo) | 11,696 | 1.32 (1.30–1.34) | 37,300 | 5.68 (5.62–5.73) | 158,215 | 17.85 (17.76–17.93) | 109,254 | 16.63 (16.53–16.73) |

*Rate per 10,000 child-days.
 LAIV=live attenuated influenza vaccine; TIV=trivalent inactivated influenza vaccine.



Characterization of Children with Asthma or Recurrent Wheezing

- Children in cohorts 2 and 3 who were vaccinated with LAIV used less SABA and inhaled corticosteroids within the previous 12 months than children who were vaccinated with TIV (Table 2).

| Prescription Frequency by Time Period | Cohort 2, Asthma, % | | Cohort 3, Recurrent Wheezing, % | |
|--|---------------------|----------------|---------------------------------|--------------|
| | LAIV (n=325) | TIV (n=12,843) | LAIV (n=308) | TIV (n=4880) |
| SABA prescriptions in 0 to <6 mo before vaccination, n | | | | |
| 0 | 75.1 | 75.8 | 66.6 | 63.9 |
| 1 | 20.6 | 18.5 | 30.2 | 32.1 |
| ≥2 | 4.3 | 5.7 | 3.3 | 4.1 |
| SABA prescriptions 6–12 mo before vaccination, n | | | | |
| 0 | 60.6 | 64.6 | 23.1 | 24.8 |
| 1 | 31.1 | 23.8 | 69.5 | 61.8 |
| ≥2 | 8.3 | 11.6 | 7.9 | 13.4 |
| Used ICS during 12 mo before vaccination | 52.0 | 60.6 | 28.6 | 30.7 |

ICS=inhaled corticosteroid; LAIV=live attenuated influenza vaccine; SABA=short-acting beta agonist; TIV=trivalent inactivated influenza vaccine.

Safety Assessment within Each Cohort

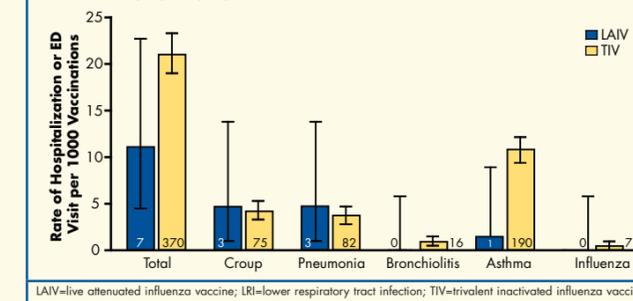
- For all cohorts, the risk of hospitalization or ED visit for any cause within 42 days after vaccination was lower in those who received LAIV compared with those who received TIV (Table 3).

| Cohort | All-Cause Hospitalizations or ED Visits Within 42 Days Postvaccination | |
|------------|--|---------------------|
| | LAIV*, rate (95% CI) | TIV*, rate (95% CI) |
| Cohort 1 | 14.5 (1.8–51.4) | 74.8 (73.3–76.3) |
| Cohort 2/3 | 49.0 (33.5–68.8) | 84.0 (80.0–88.2) |
| Cohort 4 | 83.3 (2.1–384.8) | 200.3 (169.8–233.6) |

ED=emergency department; LAIV=live attenuated influenza vaccine; TIV=trivalent inactivated influenza vaccine.
 *Rate per 1000 vaccinations.

- In combined cohorts 2 and 3 (asthma and recurrent wheezing) the frequencies of ED visits or hospitalizations for specific LRIs known to complicate asthma were similar in those vaccinated with LAIV or TIV, except for asthma-related events, which were more common in TIV recipients (Figure 2).

Figure 2. Risk (per 1000 Children Vaccinated) of Hospitalization or ED Visit for LRIs Within 42 Days of Vaccination Among Children With Asthma or Recurrent Wheezing, Aged 24–59 Months (LAIV, n=633; TIV, n=17,723).



- The difference in risk of all LRI events among the combined cohort 2/3 (asthma/recurrent wheezing) between children vaccinated with LAIV or TIV appeared to be attributable to the excess risk of asthma events among children vaccinated with TIV.
- In cohorts 1 and 4 there were no claims for events of special interest (LRI in children younger than 24 months and infectious diseases in immunocompromised children) in LAIV recipients.

Discussion

Strengths of Using Claims Data to Monitor Real World Experience

- Results are not influenced by clinician knowledge of study participation.
- Study population includes diverse regions, clinics, and patients and is likely to be more nationally representative than studies that require clinician or patient participation.

Limitations

- The claims algorithm, because it included many children with no SABA use during the 6 months before vaccination, may have included children not perceived by clinicians as having recurrent wheezing at the time of vaccination.
- Use of hospitalizations and ED visits from claims without validation using medical records can result in overestimation of the rates of the events of interest.
 - This is an accepted approach to screening for previously undiscovered safety issues.
 - Subsequent hypothesis testing would require more rigorous definition and validation of outcomes.

Conclusions

- Use of LAIV in children aged 24–59 months in the United States increased significantly from 2007–2008 to 2008–2009; use of TIV was relatively constant.
- The low rates of use of LAIV in nonindicated groups in both study years demonstrate that health care providers in general comply with the product labeling.
- The similar rates of LAIV use in those with recurrent wheezing compared with those in the general population of the same age suggest that an overly sensitive definition of recurrent wheezing (based on the ACIP recommended definition) was used, one that is not consistent with provider definitions of recurrent wheezing.
- No undue safety concerns were noted in the low number of children who were inappropriately vaccinated with LAIV in year 1 of this 3-year study.
- No excess risk of all-cause or respiratory hospitalizations/ED visits was seen in those vaccinated with LAIV compared with TIV.
 - The etiology of the higher rates of hospitalization among patients vaccinated with TIV compared with LAIV is unknown.
 - One hypothesis is that clinicians use TIV more often in children who are less healthy and, therefore, more likely to be hospitalized.

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P. Tennis and E. Andrews work collaboratively with MedImmune to jointly publish findings relating to safety but maintain the right to publish independently following appropriate communication and review from MedImmune.

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