A Postmarketing Evaluation of the Frequency of Use and Safety of Live Attenuated Influenza Vaccine in Nonrecommended Children Less Than 60 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 6 months to 18 years of age receive influenza vaccine on a yearly basis.[1]
- Live attenuated influenza vaccine (LAIV) was initially approved for eligible individuals 5–49 years of age in 2003, and received an expanded indication to include eligible children 24–59 months of age in September, 2007.[2]
- Among other contraindications, warnings, and precautions, the package insert for LAIV contains warnings and precautions against use in children younger than 24 months, those 24 to 59 months of age with recurrent wheezing or asthma, or children with altered immunocompetence.[3]
  - LAIV was not approved for use in children younger than 24 months due to an increased risk of medically significant wheezing in children 6–23 months of age (LAIV, 5.9%; trivalent inactivated influenza vaccine [TIV], 3.8%) and an increased rate of hospitalization in children 6–11 months of age (LAIV, 6.1%; TIV, 2.6%).[3]
  - LAIV has not been sufficiently studied in children with asthma and those 24–59 months of age with recurrent wheezing.[4,5]
  - LAIV has not been sufficiently studied in immunocompromised children.[6,7]
- As part of a postmarketing commitment to the US Food and Drug Administration, a study was initiated to monitor LAIV use specifically in children younger than 24 months, those 24 to 59 months of age with asthma or recurrent wheezing, and in immunocompromised children.

Objective

- To monitor for vaccination with LAIV in nonrecommended children by comparing the rate of vaccination with LAIV with that for TIV in children <24 months of age, or those 24–59 months of age with asthma, recurrent wheezing, or immunocompromise and to monitor the safety of LAIV when used in those cohorts

Methods

Study Design

- This was a retrospective descriptive cohort study of children <60 months of age included in a large, employer-based, anonymized medical insurance claims database covering more than 17 million individuals per year.
- Claims from August 1, 2006, through March 31, 2010, were used to characterize patients and identify study outcomes.
  - Claims-based algorithms were used to identify 4 cohorts of children who were not recommended to receive LAIV
    - **Cohort 1:** Children younger than 24 months
    - **Cohort 2:** Children 24–59 months of age with asthma, defined as meeting *any one* of the following criteria
      - ≥2 outpatient claims for asthma during the previous 12 months, *or*
      - ≥1 hospital or emergency department (ED) claim of asthma within the previous 12 months, *or*
      - ≥1 outpatient asthma claim and >1 outpatient dispensing of a short-acting beta agonist (SABA) within the previous 12-month period
    - **Cohort 3:** Children 24–59 months of age with recurrent wheezing (as defined by the ACIP) who met the following criteria in the previous 12 months
      - No claims for asthma *and*
      - ≥1 SABA dispensation (used as a surrogate for wheezing)
    - **Cohort 4:** Children 24–59 months of age with immunocompromise 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 (SCST) in the previous 16 weeks; *or*
      - Received SCST: Cohort membership ended at end of the prescription period for oral SCST if supply was <14 days or ended 28 days after the prescription end date if SCST supply was >14 days.

Vaccination Rate

- Vaccination rates were calculated as the number of children vaccinated divided by the total number of child-days of follow-up for that cohort.
- Follow-up was based on insurance claims history and started at cohort entry and ended at the earliest of vaccination date or February 17 of the study year.
- LAIV vaccination incidence rates were compared with TIV vaccination incidence rates in each cohort and in the general population of children aged 24–59 months.
- Year 3 vaccination rate data are preliminary.

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 (children <24 mo): all lower respiratory tract infections (LRI)
    - In combined cohorts 2 (asthma) and 3 (wheezing): LRI known to complicate asthma admissions[8]
    - In cohort 4 (immunocompromised): any infectious disease
- Risk of adverse outcomes among children vaccinated with LAIV or TIV was calculated by dividing the number of vaccinated children with a claim for each outcome by the total number of children vaccinated.
- Safety data are not yet available for year 3.

Results

Vaccination Rate for Each Cohort

- In seasons 1, 2, and 3, there were 12,479, 67,657, and 70,502 LAIV vaccinations noted, respectively, among children <60 months of age.
- In years 1–3, the incidence rates of vaccination with LAIV in cohort 1 (<24 mo of age), cohort 2 (asthma), and cohort 4 (immunocompromise) were lower than the rates in the general population (aged 24–59 mo; **Figure 1A**).
- Among cohort 3 (wheezing) the LAIV vaccination rates were similar to the rates in the general population (aged 24–59 mo) in years 1–3 **(Figure 1A)**.
- In each consecutive study year, the LAIV vaccination rate in the nonrecommended cohorts increased at a rate similar to or less than the rates in the general population **(Figure 1A)**.
- In all years and in all cohorts the incidence rates of vaccination with TIV were higher than those of LAIV **(Figure 1B).**

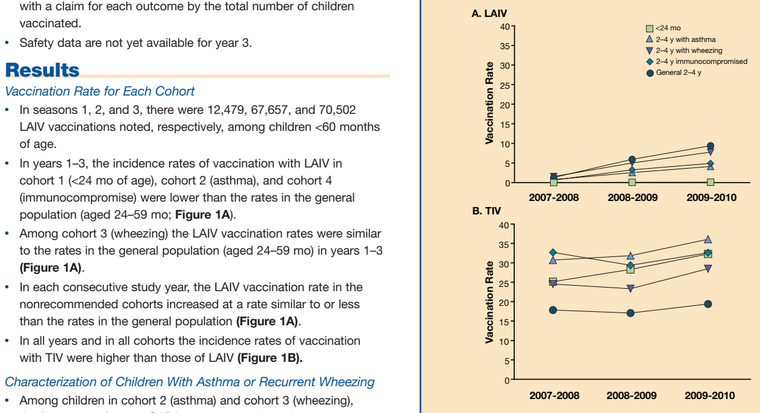
Characterization of Children With Asthma or Recurrent Wheezing

- Among children in cohort 2 (asthma) and cohort 3 (wheezing), the frequency of recent SABA use averaged over 2 seasons was generally similar among LAIV and TIV recipients.
  - The frequency of inhaled corticosteroids (ICS) dispensed in the past 12 months was lower among cohort 3 (wheezing) compared with cohort 2 (asthma) and in both cohorts there was a trend toward fewer LAIV recipients compared with TIV recipients having ICS dispensed in the past 12 months **(Figure 2)**.

Safety Assessment Within Each Cohort

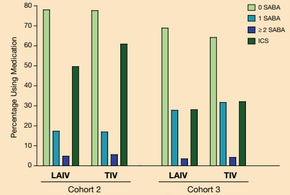
- Among the 4 cohorts, the risk of ED visits or hospitalizations for any cause within 42 days postvaccination was lower in those who received LAIV compared with those who received TIV **(Table 1)**.
- In a combined cohort 2/3 (asthma/wheezing) the frequencies of ED visits or hospitalizations for specific LRIs known to complicate asthma were similar among children vaccinated with LAIV or TIV, except for asthma-related events, which were more common among TIV recipients **(Table 2)**.
- In cohort 1 (<24 mo of age) there were no claims for LRIs and in cohort 4 (immunocompromised) there were 2 ED visits associated with primary diagnosis codes that were considered infectious diseases (unspecified otitis media and croup) after vaccination with LAIV.

Figure 1. Vaccination Rates* in Each Nonrecommended Cohort and in the General Population†



LAIV=live attenuated influenza vaccine; TIV=trivalent inactivated influenza vaccine.
*Rate per 10,000 child-days.
†General population=those 24–59 months of age who did not meet the criteria for entry into any nonrecommended cohort.

Figure 2. Medication Use* in Children 2–4 Years of Age With Asthma or Wheezing



ICS=inhaled corticosteroids; LAIV=live attenuated influenza vaccine; SABA=short-acting beta agonist; TIV=trivalent inactivated influenza vaccine.
*Medication use=the number of prescriptions for SABA and ICS dispensed within 6 mo and 12 mo of vaccination, respectively.

Table 1. ED Visits or Hospitalizations Within 42 Days of Vaccination

	Season 1						Season 2					
	LAIV			TIV			LAIV			TIV		
Cohort	n	Visits*	Rate†	n	Visits*	Rate†	n	Visits*	Rate†	n	Visits*	Rate†
1 (<24 mo of age)	138	2	14.5	120,901	7279	60.2	537	19	35.4	182,365	9416	51.6
2/3 (Asthma/recurrent wheezing)	633	30	47.4	17,723	1191	67.2	2412	102	42.3	21,656	1431	66.1
4 (Immunocompromised)	12	1	83.3	634	107	168.8	89	7	78.7	801	111	138.6

ED=emergency department; LAIV=live attenuated influenza vaccine; TIV=trivalent inactivated influenza vaccine.
*Includes ED visits and hospitalizations.
†Rate per 1000 vaccinations.

Table 2. Number of ED Visits or Hospitalizations for Lower Respiratory Conditions Among Children With Asthma or Recurrent Wheezing Within 42 Days of Vaccination

	Season 1				Season 2			
	LAIV (n=633)		TIV (n=17,723)		LAIV (n=2412)		TIV (n=21,656)	
LRI*	Visits†	Rate‡	Visits†	Rate‡	Visits†	Rate‡	Visits†	Rate‡
Croup	3	4.7	81	4.5	5	2.1	73	3.4
Pneumonia§	3	4.7	81	4.5	3	1.2	73	3.4
Bronchiolitis	0	0.0	15	0.8	1	0.4	18	0.8
Asthma	1	1.6	177	10.0	14	6.2	243	11.2
Influenza	0	0.0	7	0.4	1	0.4	3	0.1
Total	7	11.1	361	20.4	24	10.0	410	18.9

ED=emergency department; LAIV=live attenuated influenza vaccine; LRI=lower respiratory tract infection; TIV=trivalent inactivated influenza vaccine.
*Cohorts with each LRI may not be mutually exclusive if a child experienced 2 separate diagnoses on separate occasions.
†Includes ED visits and hospitalizations.
‡Rate per 1000 vaccinations.
§One event was coded as influenza with pneumonia (ICD-9-CM code 487.0) but categorized as the potentially more severe pneumonia to avoid double counting.

Strengths of Using Claims Data to Monitor Real-World Experience

- The results are not influenced by clinician knowledge of study participation.
- The study population includes diverse regions, clinics, and patients and is likely to be more nationally representative than studies that require clinician or patient participation.
- This method is an accepted approach to screening for previously undiscovered safety issues.

Limitations of Using Claims Data to Monitor Real-World Experience

- Use of the claims algorithms to identify children with specific conditions may not align with practitioners' clinical assessment.
- Use of ED visits and hospitalizations from claims without validation using medical records can result in overestimation of the rates of the events of interest.
- Subsequent hypothesis testing would require more rigorous definition and validation of outcomes.

Conclusions

- **In children 24–59 months of age, use of LAIV in the United States increased substantially from 2007–2008 to 2009–2010, while TIV use remained relatively constant.**
- **The low rate of use of LAIV in 3 of the 4 nonrecommended cohorts indicates that healthcare providers in general are complying with the product indication.**
- **The similar rates of use of LAIV in those with wheezing and the general population of the same age suggest that the definition of recurrent wheezing based on the ACIP recommended screening criteria is not consistent with provider definitions of recurrent wheezing.**
- **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 hospitalizations among patients vaccinated with TIV compared with LAIV likely is the result of more frequent use of TIV among children who are less healthy and, therefore, more likely to be hospitalized.**

References

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