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A postlicensure evaluation of the safety of Ann Arbor strain live attenuated influenza vaccine in children 24–59 months of age

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ABSTRACT

Background: In the United States, live attenuated influenza vaccine (LAIV) was initially approved for use in individuals aged 5–49 years in 2003, which was extended to individuals aged 2–49 years in 2007. At that time, a postlicensure commitment was made to describe the safety of LAIV within a cohort of eligible children aged 2–5 years.
Methods: A prospective observational postmarketing study was conducted to evaluate the safety of LAIV. Rates of medically attended events (MAEs) and serious adverse events (SAEs) in eligible children aged 24–59 months receiving LAIV as part of routine care from October 2007 to March 2010 were compared with rates in a within-cohort self-control, as well as matched unvaccinated and matched trivalent inactivated influenza vaccine (TIV)-vaccinated controls. Children with asthma and other high-risk medical conditions before vaccination were excluded. All MAEs and SAEs through 42 days postvaccination and all hospitalizations and deaths through 6 months postvaccination were analyzed. Statistical significance was declared without multiplicity adjustment.
Results: A total of 28,226 unique LAIV recipients were matched with similar numbers of TIV-vaccinated and unvaccinated children. Of 4696 MAE incidence rate comparisons, 83 (1.8%) were statistically significantly higher and 221 (4.7%) were statistically significantly lower in LAIV recipients versus controls. No pattern of MAE rate differences suggested a safety signal with LAIV. Asthma/wheezing MAEs were not statistically increased in LAIV recipients. No anaphylaxis events occurred within 3 days postvaccination. Rates of SAEs were similar between LAIV and control groups.
Conclusions: Results of this postlicensure evaluation of LAIV safety in US children are consistent with preapproval clinical studies and Vaccine Adverse Event Reporting System reports, both of which demonstrated no significant increase in asthma/wheezing events or other adverse outcomes among eligible children aged 24–59 months who received LAIV.

1. Introduction

The intranasal Ann Arbor strain live attenuated influenza vaccine (LAIV; MedImmune, LLC, Gaithersburg, MD) was initially licensed in 2003 for use in eligible individuals aged 5–49 years. Postlicensure studies revealed no safety concerns in this age range [1,2]. In 2003, LAIV was not approved for use in children younger than 5 years because 1 study noted an increase in wheezing events in young children [3]. A subsequent prospective study demonstrated an increase in medically attended wheezing in LAIV-vaccinated children aged <24 months, but no increase in LAIV-vaccinated children ≥24 months [4,5]. Based on this study, in 2007, the approval of LAIV was expanded to include children aged 24–59 months [6]. In the US, LAIV is recommended for use in children in this age group without underlying high-risk medical conditions (e.g. asthma, diabetes, immunocompromise, etc.) as well as those

Abbreviations: AGI, acute gastrointestinal tract; ART, acute respiratory tract; AW, asthma and wheezing; ED, emergency department; FU, follow-up; HR, hazard ratio; KP, Kaiser Permanente; LAIV, live attenuated influenza vaccine; MAE, medically attended event; PSDI, prespecified diagnoses of interest; RAD, reactive airway disease; RR, relative risk; RSV, respiratory syncytial virus; SAE, serious adverse event; SBI, systemic bacterial infections; SOB, shortness of breath; TIV, injectable trivalent inactivated influenza vaccine; URI, upper respiratory tract infection; WTI, wild-type influenza.

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Table 1
Summary of safety analyses.

Event	Postvaccination period, d	Clinical setting
Anaphylaxis, urticaria	3	Clinic, ED, hospital
Individual MAEs	21[a] and 42	Clinic, ED, hospital
SAEs	21 and 42	All
PSDIs	21, 42 and 180[b]	All
Hospitalizations and deaths for all causes	21, 42 and 180	Hospital, any[c]
Hospitalizations and deaths for rare events potentially related to wild-type influenza	180	Hospital, any

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

without an episode of wheezing in the 12 months prior to vaccination [7]. This study was designed to conduct a broad assessment of safety, evaluating all events and prespecified events in this younger age group.

2. Material and methods

2.1. Study design

The prospective observational study collected data from Kaiser Permanente (KP) health plan databases of participants in northern California from October 2007 to March 2010; study design and analysis were similar to previous safety studies of LAIV using KP data in older children and adults 5–49 years of age [1,2]. Subjects were given LAIV in their usual medical clinics, under routine conditions. Screening for underlying medical conditions and vaccination decisions were made by the patient and medical provider. The safety of LAIV was assessed by comparing the rates of medically attended events (MAEs) in LAIV recipients to 3 nonrandomized control groups. MAEs included all medical diagnoses associated with a medical encounter. In addition, the study analyzed serious adverse events (SAEs), anaphylaxis, urticaria, asthma, wheezing, prespecified diagnoses of interest (PSDI), and rare events potentially related to wild-type influenza (WTI). The protocol was approved by the northern California KP institutional review board.

2.2. Study populations

Approximately 25,000 children aged 24–59 months immunized with LAIV as part of routine clinical practice were identified through KP immunization registries. Study subjects with high-risk underlying medical conditions such as cancer, organ transplantation, diabetes, blood disorders, kidney disorders, and cardiopulmonary disorders (for whom LAIV was not recommended) were identified via health care databases and excluded from all analysis cohorts [1,2]. Vaccination with the 2009 monovalent H1N1 vaccine was determined, but no exclusions or adjustments were made.

Three nonrandomized control groups were identified for comparison: a within-cohort (ie, self-control) control, matched concurrent unvaccinated controls, and matched concurrent trivalent inactivated influenza vaccine (TIV)-vaccinated controls. The within-cohort analysis was a self-controlled risk-interval analysis based on event rates in different time periods after vaccination [1,2,8]. Risk intervals of 0–3 and 0–21 days postvaccination were compared with reference intervals from 4 to 42 days postvaccination and 22–42 days postvaccination, respectively. In the prespecified analysis, the 3 control groups were considered of equal importance. Frequency matching was used to identify cohorts with similar age (by each month of age) and geographic distributions. Unvaccinated controls were selected from KP membership; the index date for calculating risk intervals was the date the matched LAIV recipient was vaccinated. TIV-vaccinated controls were vaccinated during the same month as the reference LAIV recipient

2.3. Outcome measures

Medically attended adverse events were collected from clinic visits, emergency department (ED) visits, and hospital admissions, as described [1,2]. Consistent with a prior study of LAIV safety conducted by KP [3], MAEs hypothesized to be potentially causally related to vaccination were grouped as PSDI, and included acute respiratory tract (ART) events, acute gastrointestinal tract (AGI) events, asthma and wheezing (AW) events, systemic bacterial infections (SBIs), and rare diagnoses potentially related to WTI. AW was a subset of ART and was followed up for 180 days versus 42 days for other PSDIs. SAEs were identified 0–42 days postvaccination and reported regardless of potential association with LAIV, which was determined by KP staff based on time postvaccination and biological plausibility. Individual chart reviews were performed post hoc for selected outcomes of interest to confirm specific diagnoses.

Event rates were calculated per 1000 person-months using a Cox proportional hazard model. Counting process style of data input was implemented to control for seasonal effects. The counting process style of data input used start date and stop date or event date as the input to proportional hazard Cox model so that the seasonal difference in background rates were adjusted by using calendar time intervals. Sex and healthcare utilization (0–1 vs. $\geq$2 visits in prior 12 months) were included as covariates in the model. For each incidence rate comparison, a rate ratio was calculated. Rate comparisons were made for each period (3, 21, 42, or 180 days), age group (24–35 months, 36–59 months, all ages), setting (clinic, hospital, ED), and dose number. For MAEs occurring in the hospital, any duration of inpatient hospitalization was counted (Table 1). Statistical significance was based on the exact 95% CI or the CI constructed from the Cox proportional model. When the control group had zero events, the relative risk or the hazard ratio was not estimable due to a zero value in the denominator.

For the analysis of AW events, the term "asthma/reactive airway disease (RAD)" encompassed the individual diagnoses of asthma, cough variant asthma, and exercise-induced asthma; the term "wheezing/shortness of breath (SOB)" included the diagnoses of wheezing and dyspnea/SOB. Detailed methods pertaining to event rates and the determination of statistical significance have been previously described [1,2]. Post hoc analyses to adjust for multiplicity were conducted using the Bonferroni method.

3. Results

A total of 28,226 unique subjects 24–59 months of age, including 8126 subjects 24–35 months, were vaccinated with 33,443 doses of LAIV during 3 study seasons; 27,937 unique TIV recipients, and 25,981 unique unvaccinated subjects were used as matched controls. Subject characteristics are summarized in Table 2.