



A US postmarketing evaluation of the frequency and safety of live attenuated influenza vaccine use in nonrecommended children younger than 5 years: 2009–2010 season

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ARTICLE INFO

Article history:

Received 25 May 2012

Received in revised form 12 July 2012

Accepted 13 July 2012

Available online 25 July 2012

Keywords:

Asthma

Wheezing

Children

Immunocompromised

Live attenuated influenza vaccine

Trivalent inactivated influenza vaccine

ABSTRACT

The 2007 US approval for use of Ann Arbor strain live attenuated influenza vaccine (LAIV) in children aged 24 through 59 months included precautions against use in (1) children <24 months and children aged 24 through 59 months with (2) asthma, (3) recurrent wheezing, and (4) altered immunocompetence. Results from the third season (2009–2010) of a 3-year study postmarketing commitment to monitor LAIV vaccination rates and frequency of hospitalizations or emergency department visits within 42 days after LAIV are reported here. As in the first 2 seasons, LAIV usage in cohorts 1, 2, and 4 were low relative to those in LAIV-recommended populations. The only numerically increased risk observed was for respiratory events in children aged <24 months administered LAIV, compared to those administered trivalent inactivated influenza vaccine (TIV). The number of children vaccinated with LAIV was small and precluded precise quantification of rare event.

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1. Introduction

In September 2007, Ann Arbor strain LAIV was approved for use in children 2 through 4 years of age with precautions against use in children <24 months of age and children 24 through 59 months of age with asthma, recurrent wheezing, or altered immunocompetence. Because data from a large randomized study showed an increased risk of medically significant wheezing in LAIV-vaccinated children 6 through 23 months of age and an increased rate of hospitalization in LAIV-vaccinated children 6 through 11 months of age [1], LAIV was not approved for use in children younger than 24 months. MedImmune committed to the US Food and Drug Administration to conduct a 3-year study assessing the frequency of use and safety of LAIV in specific groups of children <5 years of age who are not recommended to receive LAIV.

The results from the first 2 study seasons have been reported by Tennis et al. in 2011 [2]. The current report describes the results from the third influenza vaccination season, 2009–2010. Among the 3 monitored seasons, 2009–2010 includes the largest number of children vaccinated with LAIV. This monitoring effort evaluated the

rate of LAIV vaccination and frequency of emergency department (ED) visits or hospitalizations within 42 days postvaccination with LAIV compared with that of trivalent inactivated influenza vaccine (TIV) among the nonrecommended pediatric populations. This activity was designed to monitor for previously unidentified safety concerns rather than test specific hypotheses about increased risks of specific conditions.

2. Methods

Detailed definitions are provided by Tennis et al. [2]. In brief, 4 cohorts of interest were ascertained among children younger than 60 months who received LAIV or TIV during the study period and enrolled in a health insurance plan with claims data captured by MarketScan® Research Data (Thomson Reuters, New York, NY, USA). Cohort 1 included all children <24 months of age. The cohorts aged 24 through 59 months of age were defined as follows: cohort 2, with asthma (i.e. with an asthma diagnosis and treatment in the previous 12 months), cohort 3, with recurrent wheezing (i.e. with a relevant treatment occurring ≥ 1 time in the previous 12 months but no asthma diagnosis), and cohort 4, with immunocompromise (i.e. with a relevant diagnosis, use of glucocorticosteroids, or use of immunosuppressive medication). To provide context for the frequency of use in the 24 through 59-month cohorts of interest, a

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general population cohort was created comprising children aged 24 through 59 months who met the enrollment criteria but did not meet the inclusion criteria for the other cohorts.

All cohort members had to meet the eligible ages between August 1, 2009, and February 17, 2010, and their cohort membership status was based on available claims from August 1, 2008, through February 17, 2010. Because children could move into a new age category and enter, leave, or change cohorts throughout the vaccination season, we used the number of relevant vaccinations/child-days of follow-up to derive a vaccination rate in each cohort. Vaccination rates were calculated by dividing the number of children vaccinated in a cohort by the total child-days of follow-up within a cohort. Confidence intervals were estimated using Episheet [3]. We evaluated the severity of disease classification by characterizing utilization of medical services for each cohort.

To assess the type and number of ED visits or hospitalizations occurring within 42 days postvaccination in each cohort, only vaccinated children were followed. The vaccinated asthma and recurrent wheezing cohorts were combined for the safety analysis because of the presumed similar pathophysiology in both cohorts. To avoid confounding from vaccination for the 2009 H1N1 pandemic influenza strain, we excluded children who had a vaccination for H1N1 on or within 42 days after seasonal influenza vaccination. Outcomes of interest were (1) in all cohorts, any unique ED visit or hospitalization, (2) among children ≤ 24 months of age and those with asthma and recurrent wheezing, any ED visit or hospitalization for specific lower respiratory conditions [4], and (3) among those in the immunocompromised cohort, any ED visit or hospitalization for an infectious disease.

3. Results

3.1. Vaccination incidence

During the 2009–2010 season, there were 666,599 total children in cohort 1 (<6 months of age, 12%; 6 through 11 months, 20%; 12 through 17 months, 28%; and 18 through 23 months, 40%), 79,325 children in cohort 2 (24 through 59 months of age with asthma), 86,849 children in cohort 3 (24 through 59 months of age with recurrent wheezing), and 54,809 children in cohort 4 (24 through 59 months of age with immunocompromise). Among cohorts 1, 2, 3 and 4, respectively, there were 775, 3457, 5821, and 361 children vaccinated with LAIV (Table 1). The incidence ratio for vaccination with LAIV in nonrecommended populations compared with LAIV vaccination in the general population ranged from 0.79 (95% CI, 0.77–0.81) for cohort 3 to 0.012 (95% CI, 0.011–0.013) for cohort 1.

3.2. Safety analysis

Among the 686 cohort 1 children vaccinated with LAIV and without vaccination for the 2009 H1N1 pandemic strain concurrently or during follow-up, there were few lower respiratory outcomes of interest (Table 2). Hospitalization or ED visits for asthma and pneumonia were more frequent among LAIV-vaccinated compared with TIV-vaccinated children (difference in frequency of asthma visits, 3.1 [95% CI, –1.9 to 8.0] per 1000; difference in frequency of pneumonia visits, 2.4 [95% CI, –2.6 to 7.3] per 1000). The frequency of any hospitalization or ED visit was similar among LAIV and TIV recipients.

Among the 8308 children aged 24 through 59 months with asthma or wheezing vaccinated with LAIV and without vaccination for H1N1 concurrently or during follow-up, there were few lower respiratory outcomes of interest (Table 3). Hospitalization or ED visits for each LRI evaluated were not more frequent among

LAIV-vaccinated compared with TIV-vaccinated children. The frequency of any hospitalization or ED visit among LAIV recipients did not show an excess relative to that among TIV recipients.

Of the 361 LAIV-vaccinated children in cohort 4, 229 (63%) qualified as immunocompromised because of a prescription for systemic corticosteroids, while 64 (18%) qualified due to a diagnosis code for chemotherapy, 55 (15%) qualified due to congenital immune deficiency, and 8 (2%) qualified due to a hematologic or lymphatic cancer. After excluding 37 (10%) children with a 2009 H1N1 pandemic vaccination, among the remaining 324 LAIV-vaccinated children with immunocompromise, 14 children experienced an ED visit for common childhood conditions and injuries; there were no hospitalizations. Six were associated with primary diagnosis codes that could be considered infectious diseases (3 for croup and 1 each for pharyngitis, acute respiratory infection, and otitis media), for a frequency of 18.5 (95% CI, 6.8–39.9) per 1000 vaccinations, compared with a frequency of 53.8 (95% CI, 43.5–65.8) per 1000 immunocompromised TIV-vaccinated children. The rate of ED visitation or hospitalization among LAIV recipients was 43.2 (95% CI, 23.6–72.5) per 1000 vaccinations, and among TIV-vaccinated children was 237 per 1765 vaccinations (134 [95% CI, 118–152] per 1000 vaccinations).

Over the 3 seasons of the entire study period, cumulative LAIV vaccinations included in the denominators for the annual safety analyses were 1361 children <24 months, 11,353 children with asthma or wheezing, and 425 immunocompromised children.

4. Discussion

As in previous years [2], the low rates of vaccination with LAIV in cohorts 1, 2, and 4 indicate that healthcare providers in general are complying with the product labeling. In addition, the rate of use in recommended and nonrecommended populations continued to rise at a similar rate to that observed between years 1 and 2, suggesting that clinicians are more often choosing to vaccinate young children with LAIV. This same increase in the use of LAIV in children was observed in another large database of US healthcare claims data [5].

Continuing the trend observed in the preceding 2 seasons, the somewhat similar rates of LAIV use in those with recurrent wheezing and in the general population suggest that our definition of recurrent wheezing may not match providers' definitions of recurrent wheezing and may have been overly inclusive. We based our study definition of recurrent wheezing, 1 or more dispensings of a short acting beta agonist in the previous 12 months and the absence of an asthma diagnosis, on the Advisory Committee on Immunization Practices (ACIP) recommended definition of 1 episode of asthma or wheezing in the previous 12 months. By definition, recurrent wheezing requires multiple episodes of wheezing and frequently in the medical literature a definition of 3 or more episodes is applied over a period of 6–12 months [6–12]. The disparity in these definitions and the subsequent vaccination decision-making by clinicians is likely at the root of the less restricted use of LAIV in this population.

Across the 3 evaluated seasons, the frequency of safety outcomes was numerically similar among the LAIV-vaccinated children compared with TIV-vaccinated children in all cohorts, except for among children younger than 24 months in the 2009–2010 season. Among the small number of children younger than 24 months who received LAIV compared with those who received TIV, the confidence interval around the difference in rates for asthma hospitalizations or ED visits was –1.9 to 8.0 per 1000 vaccinations and for pneumonia hospitalizations or ED visits was –2.6 to 7.3 per 1000. The numbers of events were too small to make definitive conclusions about the relative frequency of hospitalizations or ED visits for

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