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Live attenuated influenza vaccine use and safety in children and adults with asthma

Jonathan Duffy, MD, MPH [*]; Melissa Lewis, MPH [*]; Theresa Harrington, MD, MPH&TM [*]; Roger Baxter, MD [†]; Edward A. Belongia, MD [‡]; Lisa A. Jackson, MD, MPH [§]; Steven J. Jacobsen, MD, PhD [||]; Grace M. Lee, MD, MPH [¶]; Allison L. Naleway, PhD [#]; James Nordin, MD, MPH [**]; Matthew F. Daley, MD [††]; on Behalf of the Vaccine Safety Datalink

[*] *Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, Georgia*
[†] *Kaiser Permanente Vaccine Study Center, Kaiser Permanente Northern California, Oakland, California*
[‡] *Marshfield Clinic Research Foundation, Marshfield, Wisconsin*
[§] *Group Health Research Institute, Seattle, Washington*
[||] *Kaiser Permanente Southern California, Pasadena, California*
[¶] *Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts*
[#] *Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon*
[**] *HealthPartners Institute, Minneapolis, Minnesota*
[††] *Institute for Health Research, Kaiser Permanente Colorado, Denver, Colorado*

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ABSTRACT

Background: Live attenuated influenza vaccine (LAIV) might increase the risk of wheezing in persons with asthma or children younger than 5 years with a history of recurrent wheezing.
Objective: To describe the use and assess the safety of LAIV in persons with asthma in the Vaccine Safety Datalink population.
Methods: We identified persons with asthma using diagnosis codes and medication records in 7 health care organizations over 3 influenza seasons (2008–2009 through 2010–2011) and determined their influenza vaccination rates. Using the self-controlled risk interval method, we calculated the incidence rate ratio of medically attended respiratory events in the 14 days after LAIV compared with 29 to 42 days after vaccination in persons 2 through 49 years old.
Results: In our population of 6.3 million, asthma prevalence was 5.9%. Of persons with asthma, approximately 50% received any influenza vaccine but less than 1% received LAIV. The safety study included 12,354 LAIV doses (75% in children; 93% in those with intermittent or mild persistent asthma). The incidence rate ratio for inpatient and emergency department visits for lower respiratory events (including asthma exacerbation and wheezing) was 0.98 (95% confidence interval 0.63–1.51) and the incidence rate ratio for upper respiratory events was 0.94 (95% confidence interval 0.48–1.86). The risk of lower respiratory events was similar for intermittent and mild persistent asthma, across age groups, and for seasonal trivalent LAIV and 2009 H1N1 pandemic monovalent LAIV.
Conclusion: LAIV use in asthma was mostly in persons with intermittent or mild persistent asthma. LAIV was not associated with an increased risk of medically attended respiratory adverse events.
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Introduction

Asthma is a risk factor for developing complications from influenza infection.[1] Influenza vaccine has been recommended for persons with asthma since 1964 in the United States.[1] Inactivated influenza vaccine (IIV) is considered safe for administration to persons with asthma.[2] Live attenuated influenza vaccine (LAIV) is approved in the United States for intranasal administration to individuals 2 to 49 years of age. The US prescribing information warns that persons of any age with asthma and children younger than 5

Reprints: Jonathan Duffy, MD, MPH, Centers for Disease Control and Prevention, 1600 Clifton Road NE, MS D-26, Atlanta, GA 30329; E-mail: jduffy@cdc.gov.
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years with recurrent wheezing could be at increased risk of wheezing after the administration of LAIV.[3] The precaution about LAIV use in asthma originated from inadequate study of LAIV in such persons.[3,4] The precaution in children younger than 5 years with recurrent wheezing originated from a pre-licensure clinical trial that observed an increased risk of asthma and wheezing in this age group, although the significance of these findings has been questioned.[5,6]

The US influenza vaccine recommendations are updated annually based on the most recent evidence. During the 2014 to 2015 season, LAIV was preferred over IIV for healthy children 2 to 8 years old because studies showed LAIV had superior efficacy in this age range.[1] This stimulated interest in expanding the use of LAIV in children with asthma. However, US influenza vaccine effectiveness studies in subsequent seasons found that LAIV was less effective than IIV, so the US recommendations were changed to state that LAIV should not be used in the 2016 to 2017 season.[7] LAIV is still recommended during 2016 to 2017 in other countries such as Canada and the United Kingdom.[8,9] In Canada and the European Union, the asthma-related precaution for LAIV is only for individuals with severe asthma or active wheezing.[8,10] If a preference for LAIV over IIV is recommended in a future influenza season, then interest in using LAIV in asthma in the United States might increase again. Even before LAIV was preferentially recommended, some people with asthma and children with recurrent wheezing received LAIV. Our objective was to describe the use of LAIV in persons with asthma and to assess the safety of this practice.

Methods

The Vaccine Safety Datalink (VSD) is a collaboration between the Centers for Disease Control and Prevention and several integrated health care organizations (sites) in the United States that performs vaccine safety research and surveillance.[11] Seven sites contributed data to this study, which included health care visit diagnoses coded using the *International Classification of Diseases, Ninth Revision* (*ICD-9*), medication dispensing, and immunization records. We studied 3 influenza seasons: 2008 to 2009, 2009 to 2010 (which included the seasonal trivalent influenza vaccine and the pandemic influenza A [H1N1] 2009 monovalent vaccine), and 2010 to 2011. For each season, we retrospectively identified a cohort of VSD site members at least 2 years old who were enrolled for more than 91% of the days during the 12 months before July 1 (to identify pre-existing asthma) and were enrolled continuously from August 31 through April 1 (to have had a chance to receive an influenza vaccine). Age was calculated on July 1 of each year.

For persons at least 5 years of age, we defined a case of asthma as anyone who met at least 1 of the following criteria in the prior 12 months: (1) a diagnosis of asthma (*ICD-9* code 493.xx) for at least 2 clinic visits, or at least 1 emergency department (ED) visit, or at least 1 hospitalization; (2) at least 2 short-acting β-agonist (SABA) medications dispensed; (3) at least 1 SABA and at least 1 other asthma medication dispensed, which included inhaled corticosteroids, inhaled long-acting β-agonists, combination inhalers, methylxanthines, mast cell stabilizers, leukotriene modifiers, and omalizumab. For children younger than 5 years, we defined a case of asthma as anyone who had a diagnosis of asthma (*ICD-9* code 493.xx) in the prior 12 months for at least 2 clinic visits, or at least 1 ED visit, or at least 1 hospitalization. We defined a case of recurrent wheezing as a child younger than 5 years who had at least 1 of the following criteria in the prior 12 months: (1) at least 2 visits for any of the following *ICD-9* codes in any setting: acute bronchiolitis (466.1), bronchitis not specified as acute or chronic (490), chronic bronchitis (491), other disease of the trachea or bronchi (519.1), wheezing (786.07), or other respiratory distress or insufficiency (786.09); (2) at least 2 SABA medications dispensed; (3) at least 1 SABA and at least 1 other asthma medication dispensed. These definitions were adapted from previous studies.[12–14] Patients of any age who met only the medication-dispensing criteria were excluded if they had 1 of the following diagnoses listed: emphysema (492, 506.4, 518.1, 518.2), chronic obstructive pulmonary disease (491.2, 493.2, 496, 506.4), cystic fibrosis (277.0), or acute respiratory failure (518.81).[15] We assessed asthma severity using criteria developed by Leidy et al,[16] which classify asthma as intermittent or mild, moderate, or severe persistent based on the number of SABA and oral corticosteroid medications dispensed during the prior 12 months, whereby larger dispensing numbers indicate more severe asthma.

We calculated asthma prevalence as the number of persons with asthma divided by the number of persons enrolled in the cohort. For persons with asthma, we calculated IIV and LAIV vaccination rates. We assessed the safety of LAIV in persons with asthma 2 to 49 years of age using the self-controlled risk interval (SCRI) method, which compares the incidence of an adverse event in a risk interval after vaccination with the incidence of the event in a control interval.[17] The risk interval is chosen to represent a period during which LAIV might affect the outcome of interest, whereas the control interval represents a period during which LAIV should not have a biologically plausible effect on the outcome. Comparing 2 different intervals for the same individual inherently controls for factors that do not change over time. Choosing a control interval that is relatively short and close in time to the risk interval implicitly controls for factors that change over time, such as age and season. We used conditional Poisson regression to calculate the incidence rate ratio (IRR) of each outcome during the risk interval compared with the control interval using an offset term to account for different interval lengths. Each outcome was counted no more than once per interval.

The primary outcome of interest was lower respiratory tract events, including asthma exacerbation and wheezing. Other outcomes were selected based on findings from previous studies and postmarketing reports and included upper respiratory tract events (eg, nasopharyngitis and epistaxis), allergic reactions (eg, urticaria), and abdominal pain. Outcomes were defined as health care visits associated with selected *ICD-9* codes. ED visits and inpatient admissions were grouped together because they are more likely to represent acute or severe events, whereas clinic visits were analyzed separately. We also evaluated the risk of having a postvaccination health care visit for any reason and searched for any deaths within 90 days after vaccination. Subgroup analyses were performed to look for differences by age, asthma severity, or vaccine formulation (ie, seasonal trivalent or pandemic monovalent). Children younger than 5 years with recurrent wheezing were analyzed separately. Patients included in the safety study were continuously enrolled from the date of vaccination (defined as day 0) through postvaccination day 42. We excluded patients who received more than 1 LAIV dose during a season.

The power for the SCRI method is related to the number of events that occur in vaccinated individuals and therefore can be different for each outcome studied depending on how common the outcome is.[18] Our study had 80% power to detect an IRR of at least 1.3 for outcomes with at least 459 total events in the sum of the risk and control intervals when using intervals of 14 days each and an α value equal to 0.05 for a 2-sided test. This level of risk was detectable for the lower and upper respiratory outcomes in the clinic setting for the full cohort. For subgroup analyses and for inpatient and ED outcomes (which were less common), the level of detectable risk varied but was generally greater; we had 80% power to detect an IRR of at least 1.5 for outcomes with at least 194 total events, an IRR of at least 2.0 for outcomes with at least 69 total events, and an IRR of at least 3.0 for outcomes with at least 29 total events. Analysis was performed using SAS 9.4 (SAS Institute, Cary,