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

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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.

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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.

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 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 in-terval.[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 post-vaccination 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, North Carolina). Institutional review boards at the Centers for Disease Control and Prevention and each site approved this study.

Results

Asthma Prevalence

Our study population had more than 6.3 million persons meeting the enrollment criteria in each of the 3 influenza seasons studied and overall 5.9% had asthma (Table 1). Of persons at least 5 years old for whom our asthma case definition could be met by either diagnosis or medication-dispensing criteria, 23% met the diagnosis criteria only, 47% the medication-

dispensing criteria only, and 30% met both criteria. Asthma severity was classified as persistent in 52% of cases (mild in 39%, moderate in 9%, and severe in 4%).

Influenza Vaccination Rates

Approximately 50% of persons with asthma received a seasonal influenza vaccine in each of the 3 seasons studied and 28% received a 2009 H1N1 pandemic vaccine (Table 2). Of persons with asthma who received an influenza vaccine, 98% received IIV and 2% received LAIV. LAIV use was greatest in children 2 to 8 years old and decreased with age. Influenza vaccine coverage varied by asthma severity; persons with greater severity were more likely to receive an influenza vaccine but were less likely to receive LAIV (Table 3).

LAIV Safety

Of persons with asthma 2 to 49 years old, there were 11,761 unique individuals contributing 12,354 doses of LAIV to the safety study. These included 8,413 seasonal doses (2,383 in 2008—2009; 2,414 in 2009–2010; 3,616 in 2010–2011) and 3,941 pandemic doses; 9,294 doses (75%) were received by children 2 to 17 years old. For all ages, 855 doses (7%) were received by persons with moderate or severe persistent asthma.

The risk of having a health care visit for any reason during postvaccination days 1 to 14 was not significantly different from the risk during postvaccination days 29 to 42. The number of inpatient visits was 25 compared with 41 (IRR 0.61; 95% confidence interval [CI] 0.37–1.00), the number of ED visits was 118 compared with 92 (IRR 1.28; 95% CI 0.98–1.68), and the number of clinic visits was 2,096 compared with 2,072 (IRR 1.01; 95% CI 0.95–1.07).

Three percent of LAIV recipients had clinic visits for lower respiratory outcomes during the 14 days after vaccination and 0.3% had an inpatient or ED visit. The risk of medically attended lower respiratory events was not increased in either setting; findings were similar for seasonal and pandemic LAIV formulations and across age groups (Table 4). Asthma severity subgroup analyses were well powered for the clinic setting for all severity levels but were underpowered for the inpatient and ED setting for the moderate and severe persistent asthma subgroups.

Medically attended upper respiratory events, which occurred less frequently than lower respiratory events, were not significantly increased after LAIV (Table 5). Upper respiratory event subgroup analyses had lower power for the inpatient and ED setting and for the moderate and severe persistent severity subgroups in the clinic setting because of the small number of events.

Clinic visits with urticaria (*ICD-9* code 708.xx) were increased during postvaccination days 1 to 14 compared with days 29 to 42 (16 vs 4 events; IRR4.0; 95% CI 1.34–12), with cases occurring in all age groups. Most patients (81%) with a clinic visit for urticaria during the risk interval had only 1 visit (range 1–4), which was similar to patients in the control interval (P = .79). There were 1.3 urticaria clinic visits per 1,000 doses. There was no increased risk of urticaria in the inpatient and ED setting (IRR 0.50; 95% CI 0.05–5.51). There were no visits for abdominal pain during post-vaccination days 1 to 14. There were no deaths from any cause within 90 days after vaccination.

Children Younger Than 5 Years With Recurrent Wheezing

Of children 2 to 4 years old, 5.3% had asthma and an additional 4.5% had a history of recurrent wheezing. Children with recurrent wheezing were less likely to receive an influenza vaccine (48.3%) than children with asthma (53.5%) but were more likely to receive LAIV (5.6% vs 2.9%). The LAIV safety study of those with recurrent wheezing included 1,709 seasonal doses and 430 pandemic doses. There were no significantly increased risks of lower or upper respiratory adverse events (Table 6). There was no increased risk of health care visits for any reason during postvaccination days 1 to 14 compared with days 29 to 42 (data not shown).

Discussion

In our safety study of persons with asthma who received LAIV, we observed no increased risk of medically attended lower respiratory tract adverse events, including asthma exacerbation or wheezing, during the 14 days after vaccination. Our safety study population consisted mostly of children 2 to 17 years old (n = 9,294 doses) and persons with intermittent or mild persistent asthma. Of LAIV recipients with moderate or severe asthma, we did not observe an increased risk of lower respiratory adverse events attended in the clinic setting; inpatient and ED setting events were not increased either, but the relatively small number of LAIV doses and associated events in those 2 severity subgroups made those analyses less informative. We also studied children 2 to 4 years old who did not have an asthma diagnosis but did have a history of recurrent wheezing (n = 2,139 doses) and found no risk of lower respiratory adverse events after LAIV.

Most clinical trials of LAIV have excluded persons with asthma or children with a history of wheezing. Our findings are consistent with the few previous studies of LAIV in persons with asthma or wheezing, which have focused on children. A randomized placebo-controlled trial conducted in 1997 studied 48 children 9 to 17 years old who had stable moderate to severe asthma (defined as forced expiratory volume in 1 second < 80% predicted) and did not find any difference in spirometric or clinical outcomes between LAIV and placebo.[19] An open-label field trial of LAIV (n = 2,196 doses) conducted from 1998 through 2002 studied children 1.5 to 18 years old with a history of intermittent asthma or wheezing and used a risk interval design to compare exposed with unexposed person time for the cohort; it found no increased risk for medically attended acute respiratory illnesses, including asthma exacerbation.[20] A randomized study compared LAIV (n = 1,114 children) with IIV during the 2002 to 2003 influenza season in children 6 to 17 years of age with a clinical diagnosis of asthma; it found no difference in adverse pulmonary outcomes, including asthma exacerbations.[21] Two randomized trials comparing LAIV with IIV in children 24 to 71 months old during 2002 to 2003 and 2004 to 2005 did not exclude persons with mild or moderate asthma or history of wheezing; post hoc analysis of children with a diagnosis of asthma (n = 333 LAIV recipients) found no difference in rates of wheezing.[22] A manufacturer-funded postmarketing study using the MarketScan claims database that compared children 24 to 59 months old with asthma or recurrent wheezing who received LAIV (n = 12,323 doses) with those who received IIV over 3 influenza seasons (2007–2008 through 2009–2010) found that the children who received LAIV appeared to have less

severe forms of asthma and did not detect any safety signals.[23,24] A cohort study with 4 weeks of follow-up performed during 2014 through 2015 focused on administration of LAIV to persons 2 to 18 years old with egg allergy, which included 445 children with physician- diagnosed asthma or recurrent wheeze; these children had no worsening of their asthma control test score after vaccination compared with baseline, and the investigators concluded that LAIV seemed to be well tolerated in those with well-controlled asthma or recurrent wheeze.[25] We also studied LAIV in adults with asthma 18 to 49 years old (n = 3,060 doses), a group with little previous post-licensure information, and found no increased risk of lower respiratory adverse events.

We also evaluated several other outcomes. Rhinorrhea and nasal congestion were the most commonly reported adverse events after LAIV in clinical trials.[3] We found no increased risk of medically attended upper respiratory tract adverse events, although risk estimates for inpatient and ED events were limited in the adult subgroup by the rarity of events and in the moderate and severe persistent severity subgroups by the small number of doses. Urticaria, which has been noted in spontaneous postmarketing reports, was the only outcome for which we observed a significantly increased risk.[3] The incidence of urticaria was low, and most cases were in the clinic setting, suggesting that these were not severe events. Severe hypersensitivity reactions such as anaphylaxis after vaccination are rare, with no cases detected after more than 800,000 doses of LAIV in a previous study.[26]

The asthma prevalence in our study population (5.9%) was lower than the 8.2% found in the United States by the National Health Interview Survey (NHIS) during 2008 through 2010. Previous studies have shown that administrative data tend to underestimate physician-diagnosed asthma.[27] The NHIS found influenza vaccine coverage of 39.9% in insured persons with asthma at least 2 years of age during 2005 through 2006.[28] Coverage in our study was higher than in the previous national estimate but still shows room for improvement in this high-risk group. We found that persons with greater asthma severity were more likely to receive an influenza vaccine but, as expected, were less likely to receive LAIV. This also was true during the 2009 H1N1 pandemic, although in the United States persons with asthma were one of the priority groups recommended to receive the pandemic vaccine first and LAIV was available somewhat sooner than IIV. Our safety findings for the 2009 H1N1 pandemic LAIV vaccine could help inform recommendations in a future pandemic if a similar LAIV formulation were to be available.

This study was subject to several potential limitations. First, the VSD sites might not receive records of all influenza vaccine doses received by their members, particularly doses given in nontraditional settings.[29,30] This could have resulted in an underestimation of influenza vaccine coverage in our study, but it would not have biased the SCRI safety study, which included only vaccinated individuals. Second, we had to exclude persons from the SCRI study who received 2 LAIV doses during the same influenza season because the second dose's risk interval could coincide with the first dose's control interval. Children younger than 9 years are recommended to receive 2 influenza vaccine doses in the same season if they have not received any influenza vaccine previously. During the 2009 to 2010 season, anyone could have received a seasonal and a pandemic LAIV dose. Third, our safety study was of medically attended outcomes; adverse events without a health care visit, such as self-

treated asthma exacerbations, were not studied. Fourth, we could not measure the level of asthma control, which might be an important factor in how well patients with asthma tolerate LAIV. Fifth, our study examined the trivalent seasonal formulation of LAIV. Quadrivalent LAIV was approved in the United States in 2012 based on 2 trials that found its safety and efficacy were similar to those of trivalent LAIV; the 2 trials excluded persons with a history of asthma.[31] Postmarketing reports of serious respiratory events have not increased since the change to quadrivalent LAIV.[32]

Our findings considered together with the results of previous studies suggest that the precaution in the United States about an increased risk of wheezing after LAIV in persons with intermittent or mild persistent asthma or children 2 to 4 years old with a history of recurrent wheezing might not be warranted. Our study lacked sufficient power to examine the risk of serious lower respiratory outcomes in persons with moderate or severe persistent asthma because of the low frequency of LAIV use in such patients in practice; larger observational studies or a clinical trial might be required to provide definitive safety evidence for LAIV use in groups with greater asthma severity.

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Table 1

Asthma Prevalence in the Study Population Averaged Over 3 Years, 2008 Through 2010

Age group (y)	Persons with asthma (person-years), n	Study population (person-years), n	Prevalence, %
2–4	34,766	656,246	5.3
5–8	83,748	944,339	8.9
9–17	164,299	2,559,576	6.4
18–49	358,239	7,601,158	4.7
≥50	468,175	7,160,770	6.5
All ages	1,109,227	18,922,089	5.9

Table 2

Influenza Vaccination Rates in Persons With Asthma by Season and Age

Influenza season	Age group (y)	Persons with asthma	Received IIV, n (% vaccinated)	Received LAIV, n (% vaccinated)	Received any flu vaccine, n (% vaccinated)
2008–2009	2–4	10,934	5,532 (50.6)	320 (2.9)	5,852 (53.5)
	5–8	26,079	11,047 (42.4)	785 (3.0)	11,832 (45.4)
	9–17	52,078	18,827 (36.2)	738 (1.4)	19,565 (37.6)
	18–49	118,660	38,593 (32.5)	566 (0.5)	39,159 (33.0)
	≥50	151,648	96,817 (63.8)	388 (0.3)	97,205 (64.1)
	all ages	359,399	170,816(47.5)	2,797 (0.8)	173,613 (48.3)
2009–2010	2–4	11,198	6,245 (55.8)	325 (2.9)	6,570 (58.7)
	5–8	26,939	13,429 (49.9)	821 (3.1)	14,250 (53.0)
	9–17	53,047	22,197 (41.9)	906 (1.7)	23,103 (43.6)
	18–49	115,074	42,026 (36.5)	742 (0.6)	42,768 (37.1)
	≥50	151,245	96,154 (63.6)	65 (0.0)	96,219 (63.6)
	all ages	357,503	180,051 (50.4)	2,859 (0.8)	182,910 (51.2)
2009 H1N1 pandemic	2–4	11,198	4,560 (40.7)	468 (4.2)	5,028 (44.9)
	5–8	26,939	9,426 (35.0)	1,313 (4.9)	10,739 (39.9)
	9–17	53,047	13,530 (25.5)	1,823 (3.4)	15,353 (28.9)
	18–49	115,074	22,751 (19.8)	1,272 (1.1)	24,023 (20.9)
	≥50	151,245	44,140 (29.2)	342 (0.2)	44,482 (29.4)
	all ages	357,503	94,407 (26.4)	5,218 (1.5)	99,625 (27.9)
2010–2011	2–4	12,634	6,526 (51.7)	462 (3.7)	6,988 (55.4)
	5–8	30,730	13,863 (45.1)	1,239 (4.0)	15,102 (49.1)
	9–17	59,174	23,683 (40.0)	1,336 (2.3)	25,019(42.3)
	18–49	124,505	45,798 (36.8)	624 (0.5)	46,422 (37.3)
	≥50	165,282	109,482 (66.2)	42 (0.0)	109,524 (66.2)
	all ages	392,325	199,352 (50.8)	3,703 (0.9)	203,055 (51.7)

Abbreviations: IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine.

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Table 3.

Influenza Vaccination Rates in Persons With Asthma by Asthma Severity

Vaccine	Asthma severity[a]	Person-years[b]	Received IIV, n (% vaccinated)	Received LAIV, n (% vaccinated)	Received any flu vaccine, n (% vaccinated)
Trivalent LAIV (2008–2009 through 2010–2011)	intermittent	531,843	262,446 (49.4)	4,995 (0.9)	267,441 (50.3)
	mild persistent	434,809	208,958 (48.1)	3,684 (0.9)	212,642 (49.0)
	moderate persistent	98,531	52,053 (52.8)	494 (0.5)	52,547 (53.3)
	severe persistent	44,044	26,762 (60.8)	186 (0.4)	26,948 (61.2)
Monovalent LAIV (2009 H1N1 pandemic)	intermittent	170,219	42,609 (25.0)	2,800 (1.6)	45,409 (26.6)
	mild persistent	141,770	37,976 (26.8)	2,053 (1.5)	40,029 (28.3)
	moderate persistent	31,581	9,205 (29.2)	274 (0.9)	9,479 (30.1)
	severe persistent	13,933	4,617 (33.1)	91 (0.7)	4,708 (33.8)

Abbreviations: IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine.

[a] Severity assigned according to the criteria of Leidy et al.[16]

[b] Includes those at least 2 years old who met the asthma case definition.

Table 4.

Self-controlled Risk Interval Safety Study Results for Lower Respiratory Adverse Events After LAIV in Persons With Asthma[a]

Subgroup analysis	Subgroup category	Doses	Inpatient and ED			Clinic		
			Risk interval events[c]	Control interval events[d]	IRR (95% CI)	Risk interval events[c]	Control interval events[d]	IRR (95% CI)
All persons	N/A	12,354	40	41	0.98 (0.63–1.51)	388	477	0.81 (0.71–0.93)
Vaccine type	trivalent LAIV[b]	8,413	27	28	0.96 (0.57–1.64)	274	373	0.73 (0.63–0.86)
	2009 H1N1 LAIV	3,941	13	13	1.00 (0.46–2.16)	114	104	1.10 (0.84–1.43)
Age group (y)	2–8	4,800	14	16	0.88 (0.43–1.79)	196	246	0.80 (0.66–0.96)
	9–17	4,494	17	16	1.06 (0.54–2.10)	119	155	0.77 (0.60–0.97)
	18 –49	3,060	9	9	1.00 (0.40–2.52)	73	76	0.96 (0.70–1.32)
Asthma severity	intermittent	6,611	21	18	1.17 (0.62–2.19)	171	207	0.83 (0.67–1.01)
	mild persistent	4,888	15	16	0.94 (0.46–1.90)	170	191	0.89 (0.72–1.09)
	moderate persistent	645	4	4	1.00 (0.25–4.00)	37	53	0.70 (0.46–1.06)
	severe persistent	210	0	3	0	10	26	0.38 (0.19–0.80)

Abbreviations: CI, confidence interval; ED, emergency department; IRR, incidence rate ratio; LAIV, live attenuated influenza vaccine; N/A, not applicable.

[a]Lower respiratory outcomes included health care visits with the following *International Classification of Diseases, Ninth Revision* codes: acute bronchitis and bronchiolitis (466.xx), bronchitis, not specified as acute or chronic (490.xx), asthma (493.xx), respiration, insufficiency, acute (518.82), other disease of trachea/bronchi (519.1x), respiration, disorder of (786.00), shortness of breath (786.05), wheezing (786.07), other respiratory distress, insufficiency (786.09), and cough (786.2x).

[b]The results for LAIV were similar across the 3 influenza seasons studied, so pooled results are shown.

[c]Risk interval 1 to 14 days after vaccination.

[d]Control interval 29 to 42 days after vaccination.

Table 5.

Self-controlled Risk Interval Safety Study Results for Upper Respiratory Adverse Events After LAIV in Persons With Asthma[a]

Subgroup analysis	Subgroup category	Doses	Inpatient and ED			Clinic		
			Risk interval events[c]	Control interval events[d]	IRR (95% CI)	Risk interval events[c]	Control interval events[d]	IRR (95% CI)
All persons	N/A	12,354	16	17	0.94 (0.48–1.86)	250	308	0.81 (0.69–0.96)
Vaccine type	trivalent LAIV[b]	8,413	7	15	0.47 (0.19–1.14)	193	227	0.85 (0.70–1.03)
	2009H1N1 LAIV	3,941	9	2	4.50 (0.97–20.8)	57	81	0.70 (0.50–0.99)
Age group (y)	2–8	4,800	10	12	0.83 (0.36–1.93)	120	156	0.77 (0.61–0.98)
	9–17	4,494	3	5	0.60 (0.14–2.51)	83	109	0.76 (0.57–1.01)
	18–49	3,060	3	0	undefined	47	43	1.09 (0.72–1.65)
Asthma severity	intermittent	6,611	10	6	1.67 (0.61 −4.59)	114	146	0.78 (0.61–1.00)
	mild persistent	4,888	6	10	0.60 (0.22–1.65)	111	136	0.82 (0.64–1.05)
	moderate persistent	645	0	0	N/A	20	19	1.05 (0.56–1.97)
	severe persistent	210	0	1	0	5	7	0.71 (0.23–2.25)

Abbreviations: CI, confidence interval; ED, emergency department; IRR, incidence rate ratio; LAIV, live attenuated influenza vaccine; N/A, not applicable.

[a]Upper respiratory outcomes included health care visits with the following *International Classification of Diseases, Ninth Revision* codes: acute nasopharyngitis (460.xx), acute sinusitis (461.xx), acute pharyngitis (462.xx), acute tonsillitis (463.xx), acute laryngitis and tracheitis (464.xx), acute upper respiratory infections of multiple or unspecified sites (465.xx), rhinorrhea/nasal congestion (478.19), otalgia (388.7x), and epistaxis (784.7).

[b]The results for LAIV were similar across the 3 influenza seasons studied, so pooled results are shown.

[c]Risk interval 1 to 14 days after vaccination.

[d]Control interval 29 to 42 days after vaccination.

Table 6.

Self-controlled Risk Interval Safety Study Results for Respiratory Adverse Events After LAIV in Children 2 Through 4 Years Old With Recurrent Wheezing

Outcome			Inpatient and ED			Clinic		
Subgroup analysis	**Subgroup category**	**Doses**	**Risk interval events[b]**	**Control interval events[c]**	**IRR (95% CI)**	**Risk interval events[b]**	**Control interval events[c]**	**IRR (95% CI)**
Lower respiratory outcomes								
All persons	N/A	2,139	6	5	1.20 (0.37–3.93)	52	77	0.68 (0.48–0.96)
Vaccine type	trivalent LAIV[a]	1,709	5	4	1.25 (0.34–4.65)	39	66	0.59 (0.40–0.88)
	2009 H1N1 LAIV	430	1	1	1.00 (0.06–16)	13	11	1.18 (0.53–2.64)
Upper respiratory outcomes								
All persons	N/A	2,139	4	2	2.00 (0.37–11)	60	81	0.74 (0.53–1.03)
Vaccine type	trivalent LAIV[a]	1,709	4	1	4.00 (0.45–36)	47	71	0.66 (0.46–0.96)
	2009 H1N1 LAIV	430	0	1	0	13	10	1.30 (0.57–2.96)

Abbreviations: CI, confidence interval; ED, emergency department; IRR, incidence rate ratio; LAIV, live attenuated influenza vaccine; N/A, not applicable.

[a]The results for LAIV were similar across the 3 influenza seasons studied, so pooled results are shown.

[b]Risk interval 1 to 14 days after vaccination.

[c]Control interval 29 to 42 days after vaccination.