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The safety of live attenuated influenza vaccine in children and adolescents 2 through 17 years of age: A Vaccine Safety Datalink study

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Abstract

Purpose: To evaluate the safety of live attenuated influenza vaccine (LAIV) in children 2 through 17 years of age.

Methods: The study was conducted in 6 large integrated health care organizations participating in the Vaccine Safety Datalink (VSD). Trivalent LAIV safety was assessed in children who received LAIV between September 1, 2003 and March 31, 2013. Eighteen pre-specified adverse event groups were studied, including allergic, autoimmune, neurologic, respiratory, and infectious

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CONFLICT OF INTEREST
None declared.

ETHICS STATEMENT
The human subjects review board at each site approved the study; informed consent was not required.

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conditions. Incident rate ratios (IRRs) were calculated for each adverse event, using self-controlled case series analyses. For adverse events with a statistically significant increase in risk, or an IRR > 2.0 regardless of statistical significance, manual medical record review was performed to confirm case status.

Results: During the study period, 396 173 children received 590 018 doses of LAIV. For 13 adverse event groups, there was no significant increased risk of adverse events following LAIV. Five adverse event groups (anaphylaxis, syncope, Stevens-Johnson syndrome, adverse effect of drug, and respiratory failure) met criteria for manual medical record review. After review to confirm cases, 2 adverse event groups remained significantly associated with LAIV: anaphylaxis and syncope. One confirmed case of anaphylaxis was observed following LAIV, a rate of 1.7 per million LAIV doses. Five confirmed cases of syncope were observed, a rate of 8.5 per million doses.

Conclusions: In a study of trivalent LAIV safety in a large cohort of children, few serious adverse events were detected. Anaphylaxis and syncope occurred following LAIV, although rarely. These data provide reassurance regarding continued LAIV use.

Keywords

anaphylaxis; child; live attenuated influenza vaccine; pharmacoepidemiology; syncope; vaccine safety

1 | INTRODUCTION

Although intranasal live attenuated influenza vaccine (LAIV) was widely used after licensure in 2003, the US Advisory Committee on Immunization Practices (ACIP) made an interim recommendation against LAIV use for the 2016 to 2017 influenza season.[1] This decision was based on findings from US studies demonstrating decreased vaccine effectiveness, particularly against the 2009 pandemic influenza A(H1N1) strain.[2–4] However, several recent European studies found that LAIV remains effective,[5,6] and the vaccine continues to be administered in Canada, the United Kingdom,[5] and elsewhere.[6] LAIV remains licensed for use in the USA,[1,7] and ACIP recommendations could change to support LAIV use in the future.

The safety of LAIV in children has been evaluated in pre-licensure and post-licensure studies; commonly reported symptoms have included nasal congestion, headache, fever, vomiting, and abdominal pain.[8–12] Several studies have found an age-dependent effect of LAIV on wheezing, with asthma and medically attended wheezing reported in younger[10,13] but not older[10,13–17] children. Consequently, LAIV is not licensed for children <24 months of age, is contraindicated in children 2 through 4 years of age with asthma or recurrent wheezing, and has precautions regarding use in children ≥5 years of age with asthma.[1,7] Aside from an association with asthma and wheezing in young children, no serious adverse events have been attributed to LAIV in randomized[8–12,14,15] or observational[16,17] studies. Addition-ally, no unexpected serious adverse event reporting patterns have been found following LAIV in the Vaccine Adverse Events Reporting System (VAERS).[18,19]

Although existing LAIV safety data are reassuring, prior studies have certain limitations. Randomized trials of LAIV have not included adequate sample size to examine rare adverse events,[8–12] and VAERS data cannot be used for formal hypothesis testing.[20] The objective of this investigation was to examine LAIV safety in a large cohort of children 2 through 17 years of age.

2 | METHODS

2.1 | Study setting and population

This study was conducted in the Vaccine Safety Datalink (VSD), a collaboration between the Centers for Disease Control and Prevention (CDC) and 9 large integrated health care organizations (referred to as "sites").[21–23] The study population included all children 2 through 17 years of age with continuous health insurance enrollment at a VSD site for at least 1 influenza season (defined as September 1 through March 31) during the influenza seasons of 2003 to 2004 through 2012 to 2013. Age was defined as of the date of LAIV receipt, and children only contributed data for influenza seasons during which they received LAIV and were age eligible. This study period was chosen because the investigation focused exclusively on trivalent LAIV; quadrivalent LAIV replaced the trivalent vaccine beginning with the 2013 to 2014 season.[24] The Pediatric Medical Complexity Algorithm was used to define health status; using this algorithm, a condition such as asthma would be considered a non-complex chronic condition.[25] The human subjects review board at each site approved the study; informed consent was not required.

2.2 | Study design

Self-controlled case series (SCCS) analyses were used to examine the risk of adverse events following LAIV vaccination.[26–29] In SCCS analyses, which is a cases-only design, the incidence rate of adverse events in a risk period following vaccination is compared with the rate in control periods before and after the risk period.[26–29] Preliminary analyses were based upon diagnosis codes from electronic health records. Any adverse event with a positive signal in preliminary analyses underwent manual medical record review, and SCCS analyses were subsequently repeated using only cases confirmed by manual review.

2.3 | Vaccine exposure

Electronic health record data were used to identify all children in the study population who received LAIV. Children may have received LAIV in multiple influenza seasons; LAIV doses given in different influenza seasons were treated as independent exposures. Children may have received 2 LAIV doses within an influenza season;[24,30] only the first LAIV dose per season was included in analyses. The study focused on trivalent LAIV safety; monovalent A(H1N1)pdm09 LAIV and quad-rivalent LAIV were not included in analyses. Children may have received other vaccines on the same day as LAIV.

2.4 | Potential adverse events following immunization

Safety data from pre-licensure and post-licensure trials,[8–10,13–15] LAIV package inserts,[31] and reports to VAERS[18] were used to select the adverse events examined. Consistent with prior vaccine safety studies,[32–34] we selected potential adverse events which were (1)

biologically plausible to occur following vaccination; (2) serious enough to result in a medical encounter; and (3) thought to occur relatively acutely following vaccination. Adverse events were defined by International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes; ICD-10-CM codes were not yet in use. Most adverse events were defined using multiple codes, because in clinical practice, several different ICD-9-CM codes can be used for the same condition.

Eighteen potential adverse events were examined (Table 1). For each adverse event, we identified a risk period (the days following vaccination during which an individual was considered at risk for a particular adverse event) and the medical setting of the encounter. For most adverse events, we restricted encounters to inpatient and emergency department (ED) settings, because ICD-9-CM diagnosis codes from outpatient settings typically have poor accuracy for identifying incident cases of serious adverse events.[35,36] Guillain-Barré syndrome, venous thromboembolism, and thrombocytopenia were examined in all settings (inpatient, ED, outpatient), as these conditions are rare in children. Because angioneurotic edema and other non-anaphylactic allergic reactions may not result in inpatient or ED encounters, we examined this adverse event group, and each individual ICD-9-CM code within the group, in outpatient as well as inpatient and ED settings. To ensure that encounters were not for follow-up of previously diagnosed conditions, we required that events be the first in a pre-specified time period (Table 1, last column).

2.5 | Manual review of electronic health records

Any adverse event with a positive signal in preliminary analyses underwent manual medical record review to confirm case status. This step was necessary because diagnosis codes from electronic health records do not always represent true incident cases.[35,36] We defined a positive signal as (1) a statistically significant elevated risk of an adverse event following LAIV; or (2) a point estimate of risk exceeding a risk ratio of 2.0, even if not statistically significant. Using a standardized chart abstraction form, trained abstractors reviewed provider encounter notes of relevant visits. Prevalent cases, “ruled out” cases, and cases definitively attributed to another cause[37] (such as anaphylaxis after peanut consumption in someone known to be peanut-allergic) were excluded after manual record review.

Syncope was one of the adverse events for which manual medical record review was performed. Because it was not feasible to review all 543 syncope cases, a sample of 200 cases were reviewed: all syncope cases occurring in the risk window were reviewed, and a random sample of cases from the control period. The case confirmation rate was estimated from the sampled cases and then applied to the non- reviewed cases using multiple imputation as a means of addressing the uncertainty of the confirmation rate.

2.6 | Analytic methods

SCCS methods[26–29] were used to assess the risk of adverse events following LAIV. The incidence rate of adverse events in a risk period following vaccination was compared with the incidence rate in control periods before and after the risk period, with each individual acting as his or her own control. The risk period for each adverse event is shown in Table 1. The control period was defined as all person-time within a given influenza season that was

not within the risk period.[38] The 14 days immediately preceding LAIV vaccination were excluded from the control period, because adverse event rates immediately preceding vaccination are known to be lower than the baseline rate of disease.[39] Observation time was censored when an individual received monovalent A(H1N1)pdm09 LAIV or a second dose of trivalent LAIV.

Conditional Poisson regression analyses were used to calculate incident rate ratios (IRRs) for each adverse event group. Because vaccination and baseline disease incidence rates are seasonal (ie, likely to vary over time), we adjusted for calendar month of the adverse event. Unexposed cases (ie, individuals who did not receive LAIV that influenza season) were also included in adjusted analyses to control for changes in baseline disease incidence rates over calendar time. After preliminary analyses were completed, manual medical record review was performed, and conditional Poisson analyses were repeated using only cases confirmed by manual medical record review. Our primary analyses included all LAIV doses, whether or not other vaccines were received on the same day. In secondary analyses, we limited analyses to LAIV doses received with no other same-day vaccines. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

2.7 | Statistical power

In the VSD during the study period, 590 018 doses of trivalent LAIV were given to children 2 through 17 years of age. Based on 80% power and a significance level of 0.05, a study with this sample size was powered to detect an IRR of 1.2 for a 14-day risk window and 1.1 for a 42-day risk window for a disease with a background rate of 100 per 100 000 person-years. For a disease with a background rate of 1 per 100 000 person-years, the study was powered to detect an IRR of 4.8 for a 14-day risk window, and 3.3 for a 42-day risk window.

3 | RESULTS

3.1 | Description of study cohort and live attenuated influenza vaccine doses administered

During the 2003 to 2004 through 2012 to 2013 influenza seasons, 396 173 children and adolescents received a total of 590 018 doses of trivalent LAIV. Characteristics of the study cohort and vaccines received are presented in Table 2. Most LAIV was administered in September (13.1% of doses), October (38.9%), and November (26.5%) of each influenza season. Overall, 21.1% of LAIV doses were administered with other vaccines on the same day.

3.2 | Risk of pre-specified adverse events, not confirmed by medical record review

Risk estimates for 18 pre-specified adverse events following LAIV are shown in Table 3. The adjusted IRR was statistically significantly elevated for 4 adverse event groups: syncope; anaphylaxis; non-anaphylactic allergic reactions; and Stevens-Johnson syndrome. Risk estimates were not significantly elevated for the remaining 14 groups.

Multiple ICD-9-CM codes comprised the non-anaphylactic allergic reactions group (Table 1); each was examined individually in SCCS analyses. In inpatient and ED settings,

angioneurotic edema, unspecified allergy, and urticaria demonstrated no significant elevation in risk following LAIV administration. However, adverse effect of drug (ICD-9-CM code 995.2) was significantly elevated (adjusted IRR 16.68, 95% confidence interval [CI] 3.69–75.36).

3.3 | Manual medical record review

Manual medical record review was performed for the 4 adverse events with significantly elevated IRRs (syncope, anaphylaxis, adverse effect of drug, and Stevens-Johnson syndrome). A fifth adverse event group, respiratory failure, also met criteria for manual review, because greater than a 2-fold risk was detected, although the estimate was not statistically significant (adjusted IRR 2.42, 95% CI 0.87 to 6.72). For syncope, a total of 200 cases were reviewed: all 11 cases in the risk window, and a random sample of 189 cases from the control period.

Results from manual medical record review are presented in Table 4. As shown, a number of cases were excluded because the cases could be clearly attributed to another etiology.[37] For example, we found 5 cases of anaphylaxis occurring after nut exposure in individuals known to be nut allergic. One case of Stevens-Johnson syndrome occurred in the risk period following LAIV: acetaminophen was considered the cause, although the subject had also been exposed to LAIV preceding development of Stevens-Johnson syndrome.

Five cases of syncope in the risk period following LAIV were con-firmed upon manual medical record review. The median age of confirmed syncope cases in the risk period was 14 years (range 10 to 17 years); 3 cases were female and 2 were male. Although documentation of the exact timing of the syncopal events was imprecise in the reviewed medical records, syncope symptoms appeared to occur within minutes following vaccination (for example, while walking from clinic after the vaccination visit). One confirmed syncope case occurred in an individual who received LAIV and no other vaccines; 4 cases occurred in individuals who received LAIV concurrent with injectable vaccines. One case of anaphylaxis occurred in the risk window: a 3-year-old developed wheezing, lip swelling, and hives 2 hours after receiving LAIV. Although a history of egg allergy was noted, the child had received injectable influenza vaccine in the past without an allergic reaction. The child recovered completely.

3.4 | Risk estimates using adverse events confirmed by medical record review

For the 5 adverse event groups with a positive signal in preliminary analyses, risk estimates were recalculated using only confirmed cases. As shown in Table 5, anaphylaxis and syncope were significantly associated with LAIV exposure, whereas adverse effect of drug, Stevens-Johnson syndrome, and respiratory failure were not.

The absolute risk of anaphylaxis and syncope were calculated based upon confirmed cases. During a 3-day risk period, 1 case of anaphylaxis was observed among 590 018 LAIV recipients, for an absolute risk of 1.7 per million LAIV doses. During a 1-day risk period (the day of vaccination), 5 cases of syncope were observed among 590 018 LAIV recipients, for an absolute risk of 8.5 per million doses. Excluding all subjects who received injectable

vaccines on the same day as LAIV, 1 case of syncope was observed among 465 489 LAIV recipients, for an absolute risk of 2.1 per million doses.

3.5 | Secondary analyses

All pre-specified adverse events were examined in secondary analyses, in which the study cohort was restricted to LAIV recipients who received no other vaccines on the same day. Results were similar to primary analyses, and no other significant associations were detected.

4 | DISCUSSION

Using well-established methods[26–28] in a multisite vaccine safety surveillance network,[21–23] the safety of trivalent LAIV was examined in more than 396 000 children and adolescents who received more than 590 000 doses of LAIV over a 10-year period. Based on cases confirmed by manual medical record review, 2 adverse events, anaphylaxis and syncope, were significantly associated with LAIV, although occurrences were rare. Anaphylaxis and syncope are known vaccine-associated adverse events,[40–42] which can be medically managed when they occur to minimize any long-term consequences.[43] These additional data regarding the safety profile of LAIV should provide reassurance for countries using LAIV,[5,6] as well as countries such as the United States that could recommend LAIV in the future.

Anaphylaxis was significantly associated with LAIV in the current study, with a single case occurring soon after LAIV vaccination in a 3-year-old with pre-existing egg allergy. It is plausible that vaccine-associated anaphylaxis occurs more commonly among individuals with allergic disease.[40] Although LAIV contains trace amounts of the egg white protein ovalbumin,[31] several open-label trials have found LAIV safe in egg-allergic patients; in these studies, small numbers of children had mild, resolving reactions that could have been allergic in nature.[44,45] In a recent VSD study, using anaphylaxis cases validated by manual medical record review, the rate of anaphylaxis following any vaccine was 1.3 per million vaccine doses, and all those with anaphylaxis recovered.[40] In this context, it is important to note that the absolute rate of confirmed anaphylaxis following LAIV in the current study (1.7 per million doses) was similar to the published rate following other vaccines.[40] Consequently, this finding supports the premise, articulated in ACIP influenza vaccine recommendations[1] and a recent review,[46] that hypersensitivity reactions following influenza vaccines are not necessarily related to the trace amounts of egg protein found in influenza vaccines.

Syncope and near-syncope are also known to occur following vaccination, particularly in adolescents,[41,42] and we found an association between LAIV and syncope. While post-vaccination syncope typically occurs without long-term consequences, serious injuries such as head injuries from falls during syncopal episodes can occur.[47] The pain and anxiety associated with receiving an injection are thought to trigger syncope, and 4 of the 5 cases of syncope in the current study received injectable vaccines at the same time as LAIV. However, 1 case of syncope occurred in an individual who received LAIV only; it is possible that anxiety, discomfort, or pain with intranasal administration triggered syncope in this individual. To help prevent syncope-related injuries, the ACIP recommends that vaccine

recipients be seated or laying down during vaccination and be observed for 15 minutes post-vaccination,[43] although this often does not occur in routine practice.[48]

Several additional findings are important to highlight. We did not find a significantly increased rate of asthma encounters in ED and inpatient settings following LAIV. While this is reassuring, it is important to note the vast majority (91.7%) of patients in our study population did not have asthma or another complex or chronic condition. However, several recent VSD studies examined LAIV safety specifically among individuals with asthma; no increased risk of asthma exacerbations was found.[49,50] Finally, a single case of Stevens-Johnson syndrome was observed in an individual exposed to acetaminophen as well as LAIV. Because acetaminophen is thought to cause Stevens-Johnson syndrome,[51] but the evidence for this association is not definitive,[52] the case is best described as "indeterminate."[37] In other words, while acetaminophen may have caused this case of Stevens-Johnson syndrome, with the information available it is not possible to exclude LAIV as a potential cause.

The investigation has several potential limitations, many of which are common to studies using electronic health record data for research purposes. Misclassification of vaccination status could have occurred, for example if an injectable influenza vaccine was miscoded as LAIV. Misclassification of adverse events could have occurred and could have led to false-negative as well as false-positive findings. This risk was mitigated for the 5 outcome groups with a positive signal in preliminary analyses, which underwent manual medical record review to confirm case status. However, among the 307 medical records selected for manual review, 28 records (9.1%) were not available, typically because care was received outside of the respective VSD site. Additionally, not all syncope cases underwent manual review; this could have influenced results if the reviewed cases were not representative of all cases of syncope in the study population. Although the sample size was large (n = 590 018), the study may not have been adequately powered to detect very rare but serious adverse events such as Guillain-Barré syndrome. This study focused exclusively on trivalent LAIV, which has been replaced by a quadrivalent vaccine.[24] While this is a limitation, trivalent and quadrivalent LAIV are manufactured using the same processes and have very similar compositions,[7,31] suggesting that safety findings regarding trivalent LAIV are directly relevant to the quadrivalent formulation. Finally, SCCS methods are susceptible to time-varying confounding.[28] While we controlled for month in our analyses, it is possible that our results were confounded by unmeasured factors which changed over the observation period.

In conclusion, the safety of trivalent LAIV was evaluated in a large cohort of children and adolescents; anaphylaxis and syncope were rarely but significantly associated with vaccination. These data provide reassurance regarding vaccine use in countries that continue to recommend LAIV.

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CLINICAL TRIAL REGISTRATION

Not applicable.

Abbreviations:

ACIP	Advisory Committee on Immunization Practices
CDC	Centers for Disease Control and Prevention
ED	emergency department
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
IRR	incident rate ratio
KP	Kaiser Permanente
VAERS	Vaccine Adverse Events Reporting System
VSD	Vaccine Safety Datalink

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KEYPOINTS

- Although existing data regarding the safety of live attenuated influenza vaccine are reassuring, prior studies have not had adequate sample size to examine rare adverse events.
- The safety of trivalent live attenuated influenza vaccine was evaluated in more than 396 000 children and adolescents.
- Anaphylaxis and syncope were significantly associated with live attenuated influenza vaccine, although occurrences were rare.
- These data provide reassurance regarding continued use of live attenuated influenza vaccine.

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TABLE 1

Definitions of potential adverse events examined following trivalent live attenuated influenza vaccine (LAIV)

Potential Adverse Event	ICD-9-CM CODES[a]	Post-Vaccination Period Considered at Risk (Days)[b]	Medical Setting	First Diagnosis Recorded in What Time Period?[c]
Seizures	345, 780.3 (excluding 780.33)	0–14	Inpatient, ED	42 days
Stroke	433, 434, 435.0, 435.1, 435.8, 435.9, 436, 437.1, 437.9	0–42	Inpatient, ED	42 days
Syncope	780.2	0	Inpatient, ED, outpatient	2 days
Guillain-Barré syndrome	357.0	1–42	Inpatient, ED, outpatient	42 days
Venous thromboembolism	415.1, 452, 453, 451.1, 451.81, 451.89, 325	1–42	Inpatient, ED, outpatient	1 year
Anaphylaxis	995.0, 999.4 (excluding 999.41)	0–2	Inpatient, ED	2 days
Angioneurotic edema and other non-anaphylactic allergic reactions	995.1, 995.27, 995.3, 708.0, 708.1, 708.9	1–2	Inpatient, ED, outpatient	42 days
Stevens-Johnson syndrome	695.1[d]	1–28	Inpatient, ED	42 days
Asthma	493, 519.1, 786.07	1–28	Inpatient, ED	42 days
Lower respiratory tract infections	079.6, 466, 466.0, 466.1, 466.11, 466.19, 490, 491, 033, 480, 481, 482, 483, 484, 485, 486	1–28	Inpatient, ED	42 days
Specified upper respiratory tract infections	383, 464.30, 462, 463, 475, 461, 473	1–28	Inpatient, ED	42 days
Lymphadenitis and lymphadenopathy	289.3, 457.2, 785.6	1–14	Inpatient, ED	42 days
Abdominal pain	789.0, 789.4, 789.6	1–14	Inpatient, ED	42 days
Meningitis, encephalitis, and myelitis	047.8, 047.9, 049.9, 321.2, 322, 323	1–42	Inpatient, ED	42 days
Unspecified adverse event following immunization	909.0, 909.5, 977.9, 979.6, 979.9, 995.2 (excluding 995.21, 995.22, 995.23, 995.24, 995.27), 997.09, 999.3, 999.5, 999.9, E949.6, E949.9	1–42	Inpatient, ED	42 days
Thrombocytopenia	287.3	1–42	Inpatient, ED, outpatient	42 days
Respiratory failure	518.8	0–7	Inpatient, ED	42 days
Hypotension	458.9	0–7	Inpatient, ED	42 days

Abbreviations: ED, emergency department; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; LAIV, live attenuated influenza vaccine.

[a] For 3-digit ICD-9-CM codes, all 4-digit and 5-digit codes with the same first 3 digits were included; for 4-digit codes, all 5-digit codes with the same first 4 digits were included.

[b] The day of vaccination was defined as Day 0.

[c] To ensure that a visit was not for follow-up of a previously diagnosed condition, the event was required to be the first in a pre-specified time period.

[d] A 5-digit code (695.13), more specific for Stevens-Johnson syndrome, has been added to ICD-9-CM, but was not in use early in the study period; therefore, the 4-digit code was used.

TABLE 2

Characteristics of the study cohort and vaccines received, influenza seasons 2003–2004 through 2012–2013, Vaccine Safety Datalink (VSD)[a]

Characteristic	Value
Total subjects who received 1 or more doses of LAIV, *n*	396 173
Sex, *n* (%)	
Male	192 433 (48.6%)
Female	203 740 (51.4%)
Total number of doses of LAIV, *n*	590 018
Age in years when received LAIV, mean (SD)	8.7 (4.3)
Health status in 12 months prior to receiving LAIV, *n* (%)[b]	
No chronic condition	540 936 (91.7%)
Non-complex chronic condition	41 340 (7.0%)
Complex chronic condition	7742 (1.3%)
LAIV doses by influenza season, *n* (%)	
2003–2004	459 (0.1%)
2004–2005	5945 (1.0%)
2005–2006	8333 (1.4%)
2006–2007	8661 (1.5%)
2007–2008	23 807 (4.0%)
2008–2009	65 374 (11.1%)
2009–2010	80 314 (13.6%)
2010–2011	104 730 (17.8%)
2011–2012	135 944 (23.0%)
2012–2013	156 451 (26.5%)
LAIV doses by month administered, *n* (%)	
September	77 237 (13.1%)
October	229 311 (38.9%)
November	156 427(26.5%)
December	71 323(12.1%)
January	42 103(7.1%)
February	11 412(1.9%)
March	2205(0.4%)
Concomitant vaccination, *n* (%)	
Received only LAIV on vaccination date	465 489(78.9%)
Received LAIV plus other vaccines on vaccination date[c]	124 529(21.1%)

Abbreviations: LAIV, live attenuated influenza vaccine; SD, standard deviation; VSD, Vaccine Safety Datalink.

[a]Children may have received LAIV in multiple influenza seasons; LAIV doses given in different influenza seasons were treated as independent exposures.

[b]Health status within the 12 months prior to receipt of LAIV was deter-mined using a previously published algorithm, the Pediatric Medical Complexity Algorithm.[25]

[c]Children could have received multiple other vaccines on the same date as LAIV; in order of frequency, the 5 most frequently received vaccines included human papillomavirus (*n* = 34 181 doses), meningococcal conjugate (*n* = 32 953), varicella (*n* = 30 872), hepatitis A (*n* = 26 796), and tetanus and reduced diphtheria and acellular pertussis (*n* = 25 475) vaccines.

TABLE 3

Risk of a potential adverse event following LAIV, prior to manual medical record review, influenza seasons 2003–2004 through 2012–2013, Vaccine Safety Datalink (VSD)

Medically Attended Event	Post-Vaccination Period Considered at Risk (Days)	Number of Cases in Risk Window[a]	Number of Cases in Control Period[a]	Adjusted Incident Rate Ratio (95% CI)[b]	*P* Value
Seizures	0–14	53	691	1.06 (0.80–1.41)	0.66
Stroke	0–42	2	10	0.77 (0.17–3.55)	0.74
Syncope	0	11	532	4.49 (2.47–8.16)	<0.001
Guillain-Barré syndrome	1–42	0	3	NE[c]	NE
Venous thromboembolism	1–42	8	18	1.88 (0.81–4.35)	0.14
Anaphylaxis	0–2	2	19	7.34 (1.70–31.61)	<0.01
Angioneurotic edema and other non-anaphylactic allergic reactions	1–2	95	6566	1.58 (1.29–1.93)	<0.001
Stevens-Johnson syndrome	1–28	8	14	4.54 (1.88–10.96)	<0.01
Asthma	1–28	225	1321	1.14 (0.99–1.31)	0.08
Lower respiratory tract infections	1–28	185	1214	1.11 (0.95–1.30)	0.19
Specified upper respiratory tract infections	1–28	239	1514	1.12 (0.97–1.28)	0.12
Lymphadenitis and lymphadenopathy	1–14	12	140	1.26 (0.70–2.28)	0.44
Abdominal pain	1–14	276	3559	1.12 (0.99–1.26)	0.08
Meningitis, encephalitis, and myelitis	1–42	7	23	1.26 (0.54–2.97)	0.59
Unspecified adverse event following immunization	1–42	57	178	1.28 (0.95–1.74)	0.11
Thrombocytopenia	1–42	9	45	0.88 (0.43–1.80)	0.72
Respiratory failure	0–7	4	46	2.42 (0.87–6.72)	0.09
Hypotension	0–7	0	13	NE	NE

Abbreviations: CI, confidence interval; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; LAIV, live attenuated influenza vaccine; NE, not estimated; VSD, Vaccine Safety Datalink.

[a]The number of events in risk and control periods were based upon ICD-9-CM diagnosis codes from electronic health records, among subjects who had received LAIV at any time during the influenza season.

[b]Self-controlled case series analyses, adjusted for seasonality; unexposed cases (ie, individuals who did not receive LAIV in a given influenza season) were also included in adjusted analyses to control for changes in baseline disease incidence rates over calendar time.

[c]The incident rate ratio was noted as not estimated (NE) if there were no observed events among the vaccine recipients in the risk window.

TABLE 4

Findings from manual medical record review, including reasons for exclusion of potential cases

Medically Attended Event	Total Number of Medical Records Reviewed[a]	Reasons for Exclusion after Medical Record Review, in Order of Frequency	Number of Confirmed Cases
Syncope	200	Medical record not available for review (*n* = 17); syncope during or while observing medical procedure, eg, blood draw (*n* = 16); no syncope (*n* = 9); seizure (*n* = 5); follow-up of prior syncopal episode (*n* = 6); trauma (*n* = 2); exercise (*n* = 2); prior to vaccination (*n* = 1); breath-holding (*n* = 1); severe anemia (*n* = 1); helium inhalation (*n* = 1); smoke inhalation (*n* = 1); anaphylaxis (*n* = 1); adrenal insufficiency (*n* = 1); arrhythmia (*n* = 1)	135
Anaphylaxis	21	Anaphylaxis attributed to nut exposure, in someone known to be nut-allergic (*n* = 5); medical record not available for review (*n* = 4); local reaction attributed to injection (*n* = 2); anaphylaxis attributed to intravenous contrast (*n* = 1); anaphylaxis attributed to insect sting (*n* = 1)	8
Adverse effect of drug[b]	14	Allergic reaction attributed to oral antibiotic (*n* = 6); medical record not available for review (*n* = 3); local reaction to injection (*n* = 2); allergic reaction attributed to oral acetylsalicylic acid (*n* = 1); drug intolerance attributed to oral antibiotic (*n* = 1); allergic reaction attributed to oral codeine (*n* = 1)	0
Stevens-Johnson syndrome	22	Erythema multiforme (*n* = 17); urticaria (*n* = 2); mucositis with minimal skin involvement (*n* = 1); drug rash from phenytoin exposure (*n* = 1); Stevens-Johnson syndrome attributed to acetaminophen exposure (*n* = 1)	0
Respiratory failure	50	No respiratory failure (*n* = 14); seizure (*n* = 5); medical record not available for review (*n* = 4); traumatic brain injury (*n* = 3); malignancy (*n* = 2); medication overdose (*n* = 1); subarachnoid hemorrhage (*n* = 1); tonsillar and adenoidal hypertrophy (*n* = 1); non-accidental trauma (*n* = 1); Stevens-Johnson syndrome (*n* = 1); anaphylaxis attributed to nut exposure (*n* = 1)	16

[a] With the exception of syncope, all cases from risk and control periods were reviewed; for syncope, a total of 200 cases were reviewed, including all *n* = 11 cases in the risk window and a sample of *n* = 189 cases in the control period.

[b] Multiple ICD-9-CM codes comprised the non-anaphylactic allergic reactions group; each was examined individually in SCCS analyses; adverse effect of drug was the only ICD-9-CM code which was significantly elevated.

TABLE 5

Risk of a potential adverse event following LAIV, based upon cases confirmed by manual medical record review, influenza seasons 2003– 2004 through 2012–2013, Vaccine Safety Datalink (VSD)

Medically Attended Event	Number of Confirmed Cases in Risk Window[a]	Number of Confirmed Cases in Control Period[a]	Adjusted Incident Rate Ratio[b] (95% CI)	*P* Value
Syncope	5	130	2.52 (1.04–6.10)[c]	0.04
Anaphylaxis	1	7	19.98 (1.73–230.29)	0.02
Adverse effect of drug	0	0	NE	NE
Stevens-Johnson syndrome	0	0	NE	NE
Respiratory failure	1	15	2.57 (0.28, 23.22)	0.40

Abbreviations: CI, confidence interval; LAIV, live attenuated influenza vaccine; NE, not estimated.

[a]With the exception of syncope, all cases from risk and control periods were reviewed; for syncope, a total of 200 cases were reviewed, including all $n = 11$ cases in the risk window and a sample of $n = 189$ cases in the control period.

[b]Self-controlled case series analyses, adjusted for seasonality; the incident rate ratio was denoted as not estimated (NE) if there were no observed events among the vaccine recipients in the risk window.

[c]Because not all syncope cases from the control period underwent manual medical record review, the case confirmation rate was estimated from sampled cases, and then applied to non-reviewed cases using multiple imputation to generate the incident rate ratio and confidence interval.

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