HHS Public Access

Author manuscript

Vaccine. Author manuscript; available in PMC 2018 May 14.

Published in final edited form as:

Vaccine. 2017 January 23; 35(4): 529–535. doi:10.1016/j.vaccine.2016.12.033.

Hospitalizations within 14 days of vaccination among pediatric recipients of the live attenuated influenza vaccine, United States 2010–2012

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Abstract

Background—Live attenuated influenza vaccine (LAIV) is safe in healthy children ⩾2 years. The original clinical trials excluded individuals with underlying conditions; however, post-marketing data suggest LAIV may be safe for these populations.

Methods—We analyzed MarketScan Commercial Claims Databases from 2010 to 2012 to describe hospitalizations within 14 days of vaccination among LAIV recipients. We evaluated LAIV recipients aged 2–18 years and defined underlying conditions by presence of inpatient or outpatient ICD-9 code during the previous calendar year. We excluded asthma and immunocompromising conditions. We defined risk windows as 1–7 days and 8–14 days after vaccination; the control period was 12–4 days prior to and 15–23 days after vaccination. We conducted a self-controlled case series analysis using a conditional Poisson regression model to estimate incidence-rate ratios (IRR).

Results—1,216,123 children aged 2–18 years received LAIV from 2010 to 2012. 634 children met our inclusion criteria and were hospitalized during the observation period (12 days prior to vaccination to 23 days after vaccination). Of those hospitalized, 72 (11.4%) had non-asthma, non-immunocompromising underlying conditions. Children with non-asthma, non-immunocompromising underlying conditions had an all-cause hospitalization IRR of 1.1 (95% CI 0.6–2.0, p = 0.83) in the 1–7 day risk period and 0.9 (95% CI 0.4–1.7, p = 0.67) in the 8–14 day risk period. Children with no underlying conditions had an all-cause hospitalization IRR of 0.9

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Disclosure statement

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflicts of interest

The authors report no conflicts of interest.

(0.8–1.2, p = 0.60) in the 1–7 day risk period and 1.1 (95% CI 0.9–1.3, p = 0.53) in the 8–14 day risk period. There were no differences in all-cause hospitalization risk in individuals with non-asthma, non-immunocompromising underlying conditions compared to those without underlying conditions in the 1–7 day (p = 0.88) or 8–14 day (p = 0.24) risk period. *Conclusions:* We found no evidence of differences in post-LAIV hospitalization risk among children with non-asthma, non-immunocompromising underlying conditions compared to healthy children.

Keywords

Influenza; Vaccination; Live attenuated influenza vaccine; Pediatrics

1. Introduction

The Advisory Committee on Immunization Practices (ACIP) recommends that all children aged ≥6 months without contraindications receive an annual influenza vaccination [1]. Live attenuated influenza vaccine (LAIV) was approved in the United States for use in healthy individuals aged 5–49 years in 2003, and was subsequently approved for use in children 2–4 years of age in 2007. The original clinical trials for LAIV established that the vaccine was safe and associated with few adverse events in healthy children ⩾2 years [2–5]. However, the safety of LAIV was not established in children <2 years or in people with underlying medical conditions, such as pulmonary disease, cardiovascular disease, neurological disorders and metabolic disorders, at the time of licensure [1]. Thus, the LAIV package insert states the safety of LAIV in individuals with underlying medical conditions that may predispose them to complications following wild-type influenza infection has not been established and specifically includes a warning and precaution against use in children 24–59 months old with recurrent wheezing, any individuals with asthma, or altered immunocompetence [6]. Additionally ACIP recommends against the use of LAIV in individuals with conditions included in the “Warnings and Precaution” section of the package insert and also recommends precautions for the use of LAIV in children with underlying medical conditions predisposing them to complications of influenza due to lack of safety data [1]. However, children with non-immunocompromising underlying medical conditions are not excluded from receipt of other live virus vaccines, such as the measles, mumps and rubella vaccine [7]. Thus, the primary reason for precaution against the use of LAIV in children with non-immunocompromising underlying medical conditions is the lack of adequate safety data.

Our objective was to further evaluate the safety of LAIV use in pediatric patients, including children with non-asthma, non-immunocompromising underlying medical conditions. We used administrative health care claims data to describe recipients of LAIV and hospitalization events in the immediate two week period after vaccination.

2. Methods

2.1. Population and data source

We performed our analysis using the MarketScan Commercial Claims Databases from 2010 to 2012 (Truven Health Analytics, Ann Arbor, MI). MarketScan collects deidentified

individual data from commercial health insurance claims (for ~40 million people per year) with wide geographical representation of the United States [8,9]. We evaluated children aged 2–18 years who had received LAIV in the 2010, 2011, or 2012 calendar years. We only included individuals who were enrolled in their insurance plan for a full year and individuals who were not missing service dates for their medical encounters. Receipt of LAIV was defined as the presence of *Current Procedural Terminology* (CPT) codes 90660 and 90672. We classified all underlying medical conditions by the presence of *International Classification of Diseases, Ninth Revision*, (ICD-9) discharge diagnoses from hospitalizations and outpatient visits during the prior one calendar year time period (Supplementary Table 1) [10]. We included the following underlying medical conditions: cardiac disease, pulmonary disease other than asthma, renal disease, diabetes, other metabolic disorders, liver disease, neurologic and neuromuscular disorders, cerebrovascular disease, and obesity. We excluded children with asthma, hemoglobinopathies, malignancy, pregnancy, HIV/AIDS, and immunodeficiencies due to conditions other than HIV.

We described the characteristics of the children identified meeting our inclusion and exclusion criteria in MarketScan. Medically-attended events were defined as an event associated with a known service date and an ICD-9 code.

2.2. Analysis

The primary outcome for our analysis was any hospitalization event that occurred within 14 days following vaccination with LAIV. Our secondary outcomes included hospitalizations with ICD-9 codes for specific categories of events which have been reported on the LAIV package insert and in the literature [6,11–13]. We categorized these secondary outcomes as neurological, respiratory, cardiac, head and neck, gastrointestinal, allergy, and constitutional hospitalization events (Table 1). Since diagnostic codes associated with hospitalizations can occasionally change for billing purposes and to avoid counting the same event more than once, we considered hospitalizations occurring within seven days of the first documented event as a single hospitalization event for the purpose of the analysis.

We conducted a self-controlled case series (SCCS) analysis using a conditional Poisson regression model to estimate incidence-rate ratios (IRR) for each of the two risk periods after vaccination compared to the control period with adjustment for seasonality [14]. Children with hospitalizations functioned as their own controls with implicit adjustment for unrecognized confounders [15]. Individuals who received LAIV but who did not have a hospitalization event were not included in the model. We defined our observation period as 12 days prior to vaccination through 23 days after vaccination. Our two risk windows were defined as occurring 1–7 days after vaccination and 8–14 days after vaccination. To control for the “healthy vaccinee effect,” we excluded days 3 through 1 prior to vaccination [16]; we also excluded the day of the vaccination because we were unable to evaluate the temporality between vaccination receipt and ICD-9 code associated with the service date. Therefore, our control period was defined as the 12 through 4 days prior to vaccination and 15–23 days after vaccination (Fig. 1).

We performed the SCCS analysis on the entire study population as well as by stratifying the population based on the presence or absence of underlying medical conditions. To determine

if there was increased risk of the outcomes of interest in individuals with underlying medical conditions compared with individuals with no underlying conditions, we performed the SCCS analysis in which we created a product term used to test for statistical interaction between the presence of an underlying medical condition on our primary and secondary outcomes in the two risk periods.

All analyses were conducted using SAS version 9.3 (SAS Institute Inc, Cary, NC) and p values of <0.05 were considered significant. To transform datasets for SCCS analyses, SAS macros developed by Farrington et al. were implemented (http://statistics.open.ac.uk/sccs).

This analysis was limited to existing claims data alone, and Institutional Review Board review was not required.

3. Results

A total of 1,216,123 children aged 2–18 years received LAIV from 2010 to 2012. Of these, 99,208 (8.2%) had a non-asthma, non-immunocompromising underlying medical condition of which neurological disorders and cardiovascular disorders were the most common (Table 2). Of the total population that received LAIV from 2010 to 2012, 634 children met our inclusion and exclusion criteria and had a hospitalization during the observation period (12–4 days prior to vaccination to 1–23 days after vaccination) (Fig. 2).

In total, the 634 children in our study population accounted for 642 hospitalizations during the observation period. Pneumonia (ICD-9 code 486) was the most frequent primary discharge diagnosis among the hospitalized patients, occurring in 67 (10.4%) of all hospitalization events, and acute appendicitis without mention of peritonitis (ICD-9 code 540.9) was the second most frequent primary discharge diagnosis occuring in 38 (5.9%) hospitalization events during in the observation period. The median age of hospitalized individuals who had received LAIV was 8 years (IQR 5–12), and 72 (11.4%) had a non-asthma, non-immunocompromising underlying medical condition. Neurological disorders, diabetes and metabolic conditions, and cardiovascular conditions were the most common underlying medical conditions (Table 3).

We found no increased risk for all-cause hospitalization (primary outcome) among children with and without underlying medical conditions in the 1–7 day risk period or the 8–14 day risk period from the SCCS analysis (Table 4). Children with underlying medical conditions had an incidence rate ratio (IRR) for all-cause hospitalization of 1.1 (95% CI 0.6–2.0, p = 0.83) in the 1–7 day risk period and 0.9 (95% CI 0.4–1.7, p = 0.67) in the 8–14 day risk period compared to the control period. All-cause hospitalization in children with no underlying conditions had an IRR of 0.9 (0.8–1.2, p = 0.60) in the 1–7 day risk period and 1.1 (95% CI 0.9–1.3, p = 0.53) in the 8–14 day risk period compared to the control period. Using the product term based on the presence of underlying medical conditions used to test for statistical interaction with the entire study population in the SCCS analysis, we found no differences in risk for all-cause hospitalization in individuals with underlying medical conditions compared to those with no underlying conditions in the 1–7 day risk period (p = 0.88) or in the 8–14 day risk period (p = 0.24).

For our analysis of the secondary outcomes among the 642 hospitalization events in the observation period, we identified 140 (21.8%) respiratory events, 21 (3.3%) neurological events, 12 (1.9%) gastrointestinal events, 5 (<0.1%) constitutional events, and 4 head and neck events (<0.1%). We found no hospitalizations for allergy or cardiac events in the discharge diagnoses occurring within the study population during the observation period. The IRR for hospitalization with respiratory ICD-9 codes was 0.5 (95% CI 0.3–0.9, p = 0.02) in the 1–7 day risk period, but was not statistically significant in the 8–14 day risk period (IRR: 1.2, 95% CI 0.7–1.6, p = 0.77). There were no statistically significant differences in IRRs observed for our population related to neurological, gastrointestinal, constitutional, head and neck events (Table 4). The most frequent diagnosis in each category of hospitalization was as follows: pneumonia (ICD-9 code 486) was the most frequent respiratory event occurring in 67/140 (47.9%); abdominal pain (ICD-9 code 789.xx) was the most frequent gastrointestinal event occurring in 9/12; headache/migraine (ICD-9 codes 784, and 346.00–346.99) was the most frequent medically-attended neurological event occurring in 12/21 (57.01%); fever (ICD-9 code 780.6) was the most frequent medically-attended constitutional event occurring in 5/5 (100%); unspecified otitis media (ICD-9 code 382.9) was the most frequent medically-attended head and neck event occurring in 2/4 (50%). There were no cases of Guillain-Barrie syndrome (GBS) (ICD-9 code 357.0) in our population of LAIV recipients during the observation period. Other hospitalization events not classified as secondary outcomes occurring in the observation period are listed in Supplementary Table 2.

4. Discussion

From 2010 to 2012, hospitalizations after administration of LAIV were rare in our study population. We found no evidence of a different risk for all-cause hospitalization after LAIV receipt among children with non-asthma, non-immunocompromising underlying medical conditions compared to healthy children.

The original clinical trials for LAIV established that the vaccine is safe and associated with few adverse events in healthy children ⩾2 years [2–5]. Additional clinical trials and post-marketing surveillance have supported the safety profile of LAIV [3,5,11–13]. Using a large healthcare claims database, we were able to identify children with underlying medical conditions who received LAIV. We found no increased risk of adverse events resulting in hospitalizations in this population. Our findings are supported by other reports suggesting that there is not an increased frequency of adverse events in recipients of LAIV from populations ⩾2 years with underlying medical conditions [12,13,17]. Previous studies using data from The Vaccine Adverse Event Reporting System also did not find an increase in hospitalizations in individuals following receipt of LAIV [12,13]. Similarly, using administrative data to compare recipients of LAIV and trivalent inactivated influenza vaccine among children younger than 5 years with underlying medical conditions such as asthma or altered immunocompetence, Tennis et al. found similar rates of emergency department visits and hospitalizations in both groups [17]. Our study population included older children and excluded several of the underlying medical conditions in Tennis et al.; however, we similarly did not find an increased rate of hospitalization in children with non-asthma, non-immunocompromising underlying medical conditions in the 1–7 or 8–14 days

after receipt of LAIV. Overall, our results in healthy children are consistent with the favorable safety profile for LAIV reported from the literature; and, more importantly, our results in children with certain underlying medical conditions provide additional evidence to support a favorable safety profile for LAIV in children with non-asthma, non-immunocompromising underlying medical conditions [11,17].

The majority of studies reporting on the safety of LAIV in healthy children found few medically-attended adverse events. The most commonly reported adverse event types from analyses on the safety of LAIV included neurological and respiratory adverse events and in some instances GBS, seizures, and wheezing [5,11–13]. Our analysis only focused on hospitalizations, and we found that pneumonia was the most common reason documented for hospitalization in our population. Additionally, we found no hospitalization events for GBS during our observation period and no hospitalizations with a discharge code for anaphylaxis in our population. These results were expected since these are rare events, and there were few overall hospitalizations in the risk window. Similarly, the frequency of anaphylaxis and GBS following receipt of LAIV reported from data from the Vaccine Safety Data-link in the 2012–2013 influenza season was low [18]; however, it is possible we may have missed cases of GBS occurring in days 24–42 after receipt of the vaccine since those days were not in our observation period. Importantly, children with non-asthma, non-immunocompromising underlying medical conditions had no differences in risk of all-cause hospitalization compared to healthy children, with IRRs of 1 or less in both groups. In fact, the upper limit of the confidence interval of the IRR for children with underlying medical conditions for all hospitalizations was 2.0, which represents less than a doubling of the risk of hospitalization events in this population. Thus, our results were similar to other studies which have evaluated adverse events from LAIV in populations with underlying medical conditions further supporting the safety of LAIV in a population excluded from the original phase three clinical trials [5,11–13,19].

Several countries, including Canada, Germany, the United Kingdom, and Israel, have preferential recommendations for LAIV use for healthy children [20–22]. During the 2014–2015 influenza season, ACIP issued a preferential recommendation for LAIV for healthy children aged 2–8 years citing improved efficacy in this population compared to inactivated influenza vaccine (IIV) [23]. However, ACIP did not renew the preferential recommendation for LAIV for the 2015–2016 influenza season based on additional vaccine effectiveness data related to the influenza A(H1N1)pdm09 virus [24]. In June 2016, ACIP made an interim recommendation that LAIV should not be used in 2016–2017 influenza season in the United States due to concerns related to poor effectiveness against A(H1N1)pdm09 during the 2013–14 and 2015–16 influenza seasons [25].

Our analysis has limitations. First, we only analyzed results from healthcare claims data and could not perform chart review. Therefore, some adverse events and underlying medical conditions in our database may have been misclassified. Additionally, children included in MarketScan databases may not be representative of the US population, and we only evaluated commercially insured individuals. Second, we only evaluated children with events requiring hospitalization and are therefore unable to evaluate the frequency of reported medically-attended events for individuals not requiring hospitalization (outpatient or

emergency room). Although evaluating outpatient medically-attended adverse events would have been useful, our inability to perform chart review and the lack of a primary diagnostic code for outpatient visits would have posed challenges to our accurate interpretation of those events since it would be impossible to verify incident adverse events if a diagnostic code had previously been used for a particular individual. Third, we did not evaluate adverse events in children with asthma because the administrative dataset limited our ability to determine the clinical severity of an individual's asthma; therefore, we are unable to comment on hospitalization events in this group. Finally, we do not know if children with underlying medical conditions who received LAIV in our study population are different from children with underlying medical conditions who did not receive it.

Currently, underlying medical conditions that predispose persons to complications of influenza virus infection including chronic pulmonary, cardiovascular, neurologic, and metabolic disorders are considered precautions for the use of LAIV because of limited safety data. These limited data are the reason many government immunization programs recommend use of LAIV only in healthy children. Our analysis supports the growing evidence for a favorable safety profile of LAIV for children with non-asthma, non-immunocompromising underlying medical conditions [5,11–13,19].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2016.12.033.

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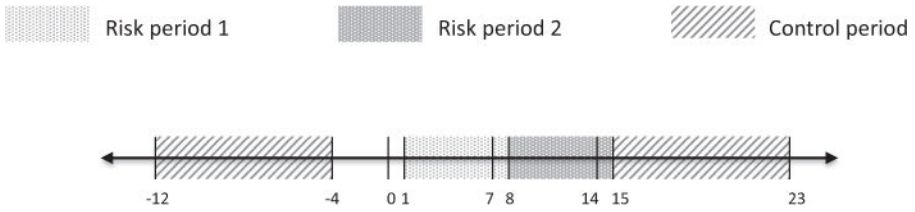

Fig. 1.

Graphical representation of the observation period used in the self-controlled case series analysis to evaluate for hospitalizations after live attenuated influenza vaccine receipt. Legend: The observation period is defined as 12 days prior to vaccination through 23 days after vaccination. Day 0 represents the day of live attenuated influenza vaccine receipt. The two risk windows are defined 1–7 days after vaccination and 8–14 days after vaccination. The control period was defined as 12 through 4 days prior to vaccination and 15 to 23 days after vaccination. Days 3 through 1 prior to vaccination were excluded to control for the "healthy vaccine effect."

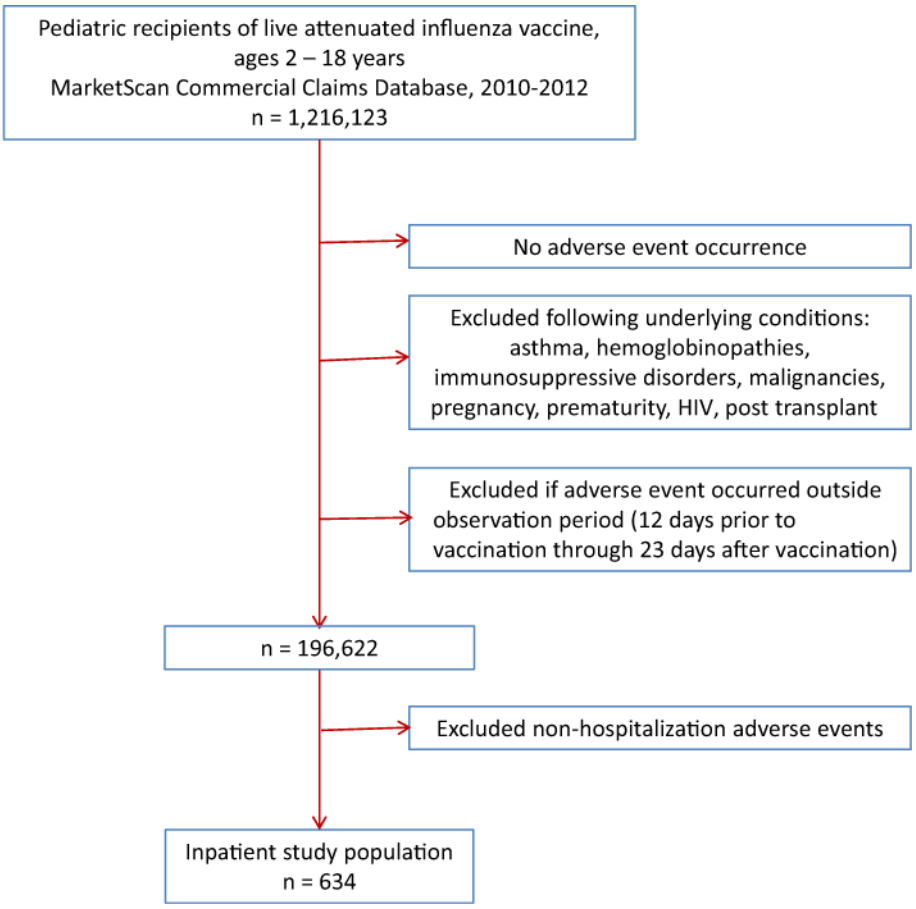

Fig. 2.

Children receiving live attenuated influenza vaccine hospitalized in the 12 days prior to vaccination to 23 days after vaccination from the total population of children receiving live attenuated influenza vaccine, MarketScan Commercial Claims Databases, 2010–2012.

Legend: Inpatient study population only represents individuals with events occuring 12–4 days prior to vaccination and 1–23 days after vaccination. As described in methods, days 3–1 prior to vaccination and day of vaccination were excluded from the analysis.

Table 1

ICD9 codes used to classify hospital discharge diagnoses for medically-attended events following receipt of live attenuated influenza vaccine in the Marketscan Commercial Claims Databases, 2010–2012.

Event Category	ICD9 condition name	ICD9 Code(s)
Respiratory	Wheezing	786.07
	Acute bronchitis and bronchiolitis	466.xx
	Asthma	493.xx
	Bronchitis	490.xx
	Bronchiectasis	494.xx
	Extrinsic allergic alveolitis	495.xx
	Chronic airway obstruction NOS	496.xx
	Respiratory conditions due to fumes vapors	506.xx
	Respiratory conditions due to unspecified agents	508.xx
	Cough	786.2x
	Acute upper respiratory infection	465.xx
	Shortness of breath	786.05
	Acute laryngotracheitis/tracheitis	462.x, 464.1x–464.59
	Influenza/pneumonia	480.0–487.8
Allergy	Anaphylaxis	995.00–995.29
	Urticaria	708.xx
Neurological	Headache	784.0–784.09, 346–346.99
	Other specified meningitis and viral meningitis not otherwise specified	047.8–047.99
	Meningitis of unspecified cause	322–322.9.x (exclude 322.2)
	Encephalitis, myelitis, and encephalomyelitis following immunization procedures	323.5x
	Febrile convulsions	780.31, 780.32
Gastrointestinal	Diarrhea	787.91
	Abdominal pain	789.09
	Nausea and vomiting	787.00–787.09
Head and Neck	Acute nonsuppurative otitis media	381.0x
	Nonsuppurative otitis media, not specified as acute or chronic	381.4x, 382.9
	Acute suppurative otitis media	382.0x,
	Mastoiditis	383.0x
	Other disease of nasal cavity and sinuses	478.1x
	Retinal hemorrhage	362.81
	Pain in or around eye	379.91
	Epistaxis	784.7x
	Acute sinusitis	461.xx
	Corneal edema	371.2x
	Orbital edema or congestion	376.33
	Swelling or mass of eye	373.13, 376.01, 379.92
Cardiac	Acute pericarditis, unspecified	420.90
	Acute idiopathic pericarditis	420.91

Event Category	ICD9 condition name	ICD9 Code(s)
	Acute myocardial infarction	410.xx
	Chest pain	786.5x
Constitutional	Fever	780.6x (exclude 780.64, 780.65,780.66)
	Anorexia	783.0x
	Irritability	799.22
	Malaise and fatigue	780.7 (exclude 780.71)
	Myalgia and myositis, unspecified	729.1x
	Dizziness and giddiness	780.4x
	Pain in joint	719.4x
	Stiffness of joint not elsewhere classified	719.5x

Table 2

Characteristics of all children receiving live attenuated influenza vaccine, MarketScan Commercial Claims Databases, 2010–2012.

Characteristic	Overall (n = 1,216,123)	2010 (n = 365,725)	2011 (n = 412,347)	2012 (n = 438,051)
Age, years (median, IQR)	7 (4–11)	7 (4–10)	7 (4–11)	7 (4–11)
Any underlying condition	99,208 (8.2)	29,780 (8.1)	33,130 (8.0)	36,298 (8.3)
Cardiovascular	11,482 (0.9)	3504 (1.0)	3781 (0.9)	4197 (1.0)
Respiratory (non-asthma)	1805 (0.2)	624 (0.2)	640 (0.2)	541 (0.1)
Diabetes/metabolic	5223 (0.4)	1576 (0.4)	1701 (0.4)	1946 (0.4)
Liver	201 (0.02)	53 (0.01)	69 (0.02)	79 (0.02)
Neurological	18,720 (1.5)	5539 (1.5)	6296 (1.5)	6885 (1.6)
Obesity	7473 (0.6)	1862 (0.5)	2555 (0.6)	3056 (0.7)
Renal	1017 (0.08)	291 (0.08)	364 (0.09)	362 (0.08)

Individuals may have more than one underlying condition.

Table 3

Characteristics of children receiving live attenuated influenza vaccine hospitalized in the 12 days prior to vaccination to 23 days after vaccination, MarketScan Commercial Claims Databases, 2010–2012.

Characteristic	Overall (n = 634)	2010 (n = 153)	2011 (n = 213)	2012 (n = 268)
Age, years (median, IQR)	8 (5–12)	9 (5–12)	8 (5–12)	8 (5–12)
Any underlying condition	72 (11.4)	15 (9.8)	19 (8.9)	38 (14.2)
Cardiovascular	13 (2.1)	4 (2.6)	5 (2.4)	4 (1.5)
Respiratory	1 (0.2)	0 (0)	1 (0.5)	0 (0)
Diabetes/metabolic	14 (2.2)	1 (0.7)	4 (1.9)	9 (3.4)
Liver	2 (0.3)	0 (0)	0 (0)	2 (0.8)
Neurological	42 (6.6)	9 (5.9)	7 (3.3)	26 (9.7)
Obesity	2 (0.3)	0 (0)	2 (0.9)	0 (0)
Renal	2 (0.3)	0 (0)	1 (0.5)	1 (0.4)

Individuals may have more than one underlying condition.

Table 4

Self-controlled case series analysis of hospitalizations among children receiving live attenuated influenza vaccine, MarketScan Commercial Claims Databases, 2010–2012.

	Number of hospitalizations (observation period)[a]	Risk period (days after vaccination)	Number of hospitalizations (risk period)	Incidence-rate ratio (95% CI)	p-value
All Hospitalizations					
All population	642	1–7	129	1.0 (0.8–1.2)	0.65
		8–14	140	1.0 (0.9–1.3)	0.66
Underlying condition	73	1–7	15	(0.6–2.0)	0.83
		8–14	12	0.9 (0.4–1.7)	0.67
No underlying conditions	569	1–7	114	(0.8–1.2)	0.60
		8–14	128	1.1 (0.9–1.3)	0.53
Respiratory Events					
All population	140	1–7	18	0.5 (0.3–0.9)	0.02
		8–14	31	1.1 (0.7–1.6)	0.76
Underlying conditions	5	1–7	0	Undefined	Undefined
		8–14	0	Undefined	Undefined
No underlying conditions	135	1–7	18	0.6 (0.3–1.0)	0.04
		8–14	31	1.1 (0.7–1.6)	0.62
Neurological events					
All population	21	1–7	1	0.6 (0.1–5.8)	0.69
		8–14	2	1.3 (0.2–7.0)	0.77
Underlying condition	4	1–7	1	Undefined	Undefined
		8–14	2	Undefined	Undefined
No underlying conditions	17	1–7	3	0.9 (0.2–3.7)	0.93
		8–14	3	1.2 (0.3–5.0)	0.83
Gastrointestinal events					
All population	12	1–7	1	0.6 (0.4–1.0)	0.07
		8–14	2	1.1 (0.7–1.7)	0.70
Underlying conditions	0	1–7	0	Undefined	Undefined
		8–14	0	Undefined	Undefined
No underlying conditions	12	1–7	1	0.6 (0.4–1.0)	0.07

	Number of hospitalizations (observation period)[a]	Risk period (days after vaccination)	Number of hospitalizations (risk period)	Incidence-rate ratio (95% CI)	p-value
		8–14	2	1.1 (0.7–1.7)	0.70
Constitutional events					
All population	5	1–7	1	0.5 (0.04–5.1)	0.53
		8–14	0	Undefined	Undefined
Underlying conditions	0	1–7	0	Undefined	Undefined
		8–14	0	Undefined	Undefined
No underlying conditions	5	1–7	1	0.5 (0.04–5.1)	0.53
		8–14	0	Undefined	Undefined
Head and neck events					
All population	4	1–7	1	Undefined	Undefined
		8–14	2	Undefined	Undefined
Underlying conditions	0	1–7	0	Undefined	Undefined
		8–14	0	Undefined	Undefined
No underlying conditions	4	1–7	1	Undefined	Undefined
		8–14	2	Undefined	Undefined

[a]Observation period defined as 12 days prior to vaccination to 23 days after vaccination. Day 3 through 1 prior to vaccination, and the day of the vaccination were excluded from the analysis as described in the methods.