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Evaluating the safety of influenza vaccine using a claims-based health system☆

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Abstract

Introduction: As part of the Centers for Disease Control and Prevention's monitoring and evaluation activities for influenza vaccines, we examined relationships between influenza vaccination and selected outcomes in the 2009–2010 and 2010–2011 influenza seasons in a claims-based data environment.

Methods: We included patients with claims for trivalent influenza vaccine (TIV) and/or 2009 pandemic influenza A H1N1 vaccine (H1N1) during the 2009–2010 and 2010–2011 influenza seasons. Patients were followed for several pre-specified outcomes identified in claims. Seizures and Guillain–Barré Syndrome were selected a priori for medical record confirmation. We estimated incidence rate ratios (IRR) using a self-controlled risk interval (SCRI) or a historical comparison design. Outcomes with elevated IRRs, not selected a priori for medical record review, were further investigated with review of claims histories surrounding the outcome date to determine whether the potential event could be ruled-out or attributed to other causes based on the pattern of medical care.

Results: In the 2009–2010 season, no significant increased risks for outcomes following H1N1 vaccination were observed. Following TIV administration, the IRR for peripheral nervous system disorders and neuropathy was slightly elevated (1.07, 95% CI: 1.01–1.13). The IRR for anaphylaxis following TIV was 28.55 (95% CI: 3.57–228.44). After further investigation of claims histories, the majority of potential anaphylaxis cases had additional claims around the time of the event indicating alternate explanatory factors or diagnoses. In the 2010–2011 season following

☆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.

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TIV administration, a non-significant elevated IRR for anaphylaxis was observed with no other significant outcome findings.

Conclusion: After claims history review, we ultimately found no increased outcome risk following administration of 998,881 TIV and 538,257 H1N1 vaccine doses in the 2009–2010 season, and 1,158,932 TIV doses in the 2010–2011 season.

Keywords

Vaccine safety; Claims; Influenza; H1N1

1. Introduction

Safety monitoring and evaluation are critical components of vaccination programs. While pre-licensure studies are important for identifying potential vaccine-associated adverse events (AEs), rare AEs may go unrecognized until there is widespread use of the vaccine in the population. This was best demonstrated by the excess number of cases of Guillain–Barré Syndrome (GBS) occurring during the swine influenza vaccination program in 1976 [1].

AEs following influenza vaccines have been widely studied. Although causal associations have not been established for many, AEs have been reported to occur in temporal association with influenza vaccines [2–7]. Many of these AEs have been previously identified through passive surveillance systems such as the Vaccine Adverse Event Reporting System as well as through active surveillance and observational epidemiologic studies using the Vaccine Safety Datalink (VSD).

As part of Centers for Disease Control and Prevention's (CDC) ongoing monitoring and evaluation for influenza vaccine safety, we conducted evaluations of the relationship between 3 formulations of the influenza vaccine administered in the 2009–2010 and 2010–2011 seasons and the occurrence of selected outcomes in a large health plan population in the United States (U.S.).

2. Methods

2.1. Data source

The source population was derived from an electronic health care database of a large U.S. insurer developed for research purposes. The data includes information on health plan enrollment, demographics, pharmacy dispensing, facility, and medical claims. The data undergo regular audits and quality control procedures and are updated monthly. The insurer checks for completeness and accuracy before the data is extracted for research, and access to the data conforms to applicable Health Insurance Portability and Accountability Act (HIPAA) policies. The insured population from which the data are drawn is geographically diverse and comprises approximately 4% of the U.S. population. Data relating to approximately 12 million individuals with both medical and pharmacy benefit coverage were available at the time this study was conducted. For a subset of 6 million health plan members in the research database, health plan administrative approval was provided to access patient-identifiable information for further inquiries, including medical chart review.

2.2. Study population

This retrospective cohort study included individuals 6 months of age or older with complete medical and pharmacy benefits who were continuously enrolled in the health plan for at least 9 months prior to the date of influenza vaccination. Participants must have received at least one influenza vaccination between September 1st and March 31st during the 2009–2010 influenza season, 2010–2011 season, or one of the historical seasons from 2005–2006 to 2008–2009. We identified influenza vaccinations with Current Procedural Terminology codes and Healthcare Common Procedure Coding System codes on health insurance claims.

For the 2009–2010 season, we conducted separate evaluations of the trivalent influenza virus vaccine (TIV) and 2009 pandemic influenza A H1N1 vaccines (H1N1). We created 1 cohort of patients who received at least one dose of TIV and another cohort of patients who received at least one dose of H1N1 vaccine (live attenuated or inactivated formulations). As this was a retrospective study, we chose to focus the analyses on TIV and either form of H1N1, but did not include seasonal live attenuated influenza vaccine (LAIV) in the analyses. Patients who received both TIV and H1N1 vaccines during the 2009–2010 season were included in both cohorts. For the 2010–2011 season, we included patients who received at least one dose of TIV. For individuals who received more than one dose of TIV (or more than one dose of H1N1 vaccine) during a single season, only their first vaccine dose was included in the analysis.

2.3. Adverse events

For each patient, pre-specified AEs were identified on the basis of specific ICD-9 codes through an initial screening of the claims data. These outcomes were clinically well defined, serious, and had previously been temporally associated with seasonal influenza vaccine or other pandemic influenza vaccine candidates in clinical trials (Table 1). Events based on diagnoses associated with inpatient, emergency department, and/or outpatient visits were identified during outcome-specific risk and control windows relative to the date of influenza vaccination. For improved specificity, an AE was considered only if it was the first event of its type to occur within a certain period of time, irrespective of the timing of the influenza vaccination. This restriction ensured that multiple events of the same type could not be counted for a given individual during a single observation period.

Claims-identified GBS and seizure events were chosen a priori for medical record confirmation, regardless of whether an elevated risk was detected during analysis of the health care claims. Medical record review was performed among the subset of the patient population with health plan administrative approval to access patient-identifying information. Trained research staff abstracted clinical information from medical records using standardized forms and also provided confirmation of the seizure events. A neurologist reviewed the abstracted clinical information to confirm GBS cases.

2.4. Analysis

For each of the influenza seasons, we estimated the incidence rate ratios (IRR) and 95% confidence intervals (CI) for each outcome following influenza vaccination. We implemented different analytic approaches for each pre-specified outcome depending on the

nature of the outcome, number of cases of that outcome, and the availability of appropriate self-controlled time windows.

Bell's palsy, other cranial nerve disorders, central demyelinating disease, disorders of the peripheral nervous system and neuropathy, and seizures, were analyzed using the Self Controlled Risk Interval (SCRI) design. In the SCRI analysis, time intervals within the same person are used to classify the case as either in the risk or control period. The period time following vaccination is designated as the risk period, and time intervals before and after vaccination outside of the risk period are designated as the control periods. The day of vaccination (Day 0) was included in the risk window for AEs for which a same-day diagnosis was deemed biologically plausible. The incident rates for cases in the risk and control windows are compared to give an IRR [8,9]. The historical comparison analysis was conducted for ataxia, encephalitis/myelitis/transverse myelitis, hemorrhagic stroke, narcolepsy and cataplexy, ischemic stroke, anaphylaxis and other allergic reactions (including angioneurotic edema and urticaria) outcomes. Patients with seasonal influenza vaccination claims during the 2005–2006 through 2008–2009 influenza seasons served as the comparison group, with adjustment for age, sex, region, and administrative ability to request medical records. In both analyses, Poisson regression was used to calculate IRR and 95% CIs. We implemented both methods when analyzing GBS due to the increased concern of the risk of GBS following influenza vaccination.

In all analyses, to examine any effect of the difference in populations with and without medical record availability, we tested for interaction, and stratified by patient age. We chose to stratify by ages above and below 25 years based on the recommendations for H1N1 vaccine during the 2009–2010 season, and to keep the age groups consistent throughout the study [10]. For seizures, we limited analyses to cases occurring among patients aged 6–59 months because prior studies have indicated this age group is at higher risk [11]. We conducted additional SCRI analyses for chart-confirmed seizures and GBS cases where possible.

2.5. Claims profile reviews

For AEs not selected a priori for medical record review but with an observed elevated risk in the claims data, we conducted claims profile review to further characterize the potential events in a timely manner and to determine if medical record review was warranted for further validation. Claims profiles provide a chronological claims history of all diagnoses, procedures, services, and medication dispensings and administrations surrounding the date of the potential claims-identified AE. Review of the claims profiles are an efficient way to determine whether a potential AE can be attributed to alternate causes or represent a rule-out diagnosis based on the pattern of medical care. If there is a possibility of a new onset event or the claims history is unclear, then medical record review is necessary to validate the outcome. This approach was taken in a previous study of seizures in pediatric patients [12].

We reviewed claims profiles to further investigate hemorrhagic stroke in the 2009–2010 and historical seasons, and anaphylaxis in the 2009–2010, 2010–2011, and historical seasons. Two reviewers reviewed claims histories ranging from 1 year before through 1 year after the claims-identified event date, with discrepancies resolved by a third reviewer.

2.6. Privacy and confidentiality

This study followed the HIPAA guidelines for protection of patient confidentiality. The New England Institutional Review Board and affiliated Privacy Board approved the study protocol and granted a waiver of patient authorization to request medical records.

3. Results

3.1. H1N1: 2009–2010 influenza season

Table 2 presents the SCRI and historical comparison analyses for the claims-identified outcomes following administration of 538,257 doses of H1N1 vaccine in the 2009–2010 season. No significant findings of an increased risk for claims-identified outcomes following H1N1 vaccination were observed.

Among patients 6–59 months, there were 14 seizure events identified in claims following H1N1 administration. Of those, 1 case had the medical record available for request, and it was not a confirmed seizure. Among the 9 GBS events identified in claims, medical records were available for 4 cases. 2 of the 4 cases were confirmed as Brighton level 2 GBS cases [13], with 1 case in the risk window and 1 in the control window.

3.2. TIV: 2009–2010 influenza season

Table 3 presents the SCRI and Poisson regression analyses for the claims-identified outcomes following administration of 998,881 doses of TIV in the 2009–2010 season. A slightly elevated IRR was observed for peripheral nervous system disorders and neuropathy following administration of TIV (IRR = 1.07, 95% CI: 1.01–1.13). After stratifying by age group, the IRR was 1.34 (95% CI: 0.95–1.90) in patients younger than 25 years and 1.06 (95% CI: 1.00–1.12) in patients aged 25 years and older. In the historical comparison analysis, the IRR for claims-identified anaphylaxis following TIV administration was 28.55 (95% CI: 3.57–228.44) when compared with the historical cohort. In patients less than 25 years of age, the IRR for claims-identified hemorrhagic stroke following TIV was 2.37 (95% CI: 0.95–5.65); the risk was higher among patients with medical records available for request (IRR = 3.79, 95% CI: 0.87–16.49). A decreased risk of encephalitis/myelitis/encephalomyelitis following TIV was observed (IRR = 0.28, 95% CI: 0.09–0.92). The profile reviews for patients with claims-identified anaphylaxis and hemorrhagic stroke cases are described at the end of this section.

Among patients 6–59 months, there were 28 claims-identified seizure events following TIV administration in the 2009–2010 season, of which 12 cases had medical records that could be requested. There were 8 confirmed cases, 1 in the risk window and 7 in the control window (IRR = 0.50, 95% CI: 0.62–4.06). Among the 18 claims-identified GBS events, records were available for 7 cases. 1 case of GBS was confirmed in the risk window and none in the control windows. The confirmed case did not meet the case definition for Brighton levels 1–3. However, the GBS case was confirmed by a neurologist in the medical record, and was considered a probable case by Brighton criteria [13].

3.3. TIV: 2010–2011 influenza season

There were no significant findings in either the SCRI or historical comparison analyses for outcomes following administration of 1,158,932 doses of TIV in the 2010–2011 season. Although, an elevated IRR of 6.70 (95% CI: 0.60–74.74) was observed for anaphylaxis following TIV (Table 4).

Among patients 6–59 months, there were 25 seizure events identified in claims following TIV administration in the 2010–2011 season, of which 6 cases had medical records that could be requested. There were 4 confirmed cases, 1 confirmed in the risk window and 3 confirmed in the control window (IRR = 1.17, 95% CI: 0.02–14.5). Among the 28 GBS events identified in claims, 4 events had medical records available for request. Of those, no cases were confirmed GBS.

3.4. Claims profile review results

Given the potential increased risks for anaphylaxis and hemorrhagic stroke identified in the 2009–2010 season, we conducted a profile review for patients with diagnostic claims for hemorrhagic stroke or anaphylaxis following either TIV or H1N1 to further characterize the claims-identified potential events. The potential risk of anaphylaxis during the 2010–2011 season was not statistically significant (IRR = 6.70, 95% CI: 0.60–74.74); however the elevated IRR supported further investigation.

Claims profile review was conducted for 11 patients with claims-identified anaphylaxis in the 2009–2010, 2010–2011, and 2005–2008 seasons. Patients ranged in age from 6 months through 64 years. Five case profiles included diagnostic claims for allergic reactions attributed to non-medicinal causes (e.g. food allergy). One case profile included diagnostic claims for an allergic reaction attributed to another medication or anesthesia. Two case profiles had anaphylaxis diagnosis codes associated with procedure claims or evaluation visits that resulted in an alternate diagnosis. One case appeared to be a miscode as the remainder of the profile did not contain claims indicative of a possible anaphylaxis event. The remaining 2 case profiles did not include diagnoses suggestive of alternate factors in the claims; 1 case occurred in the control window the 2009–2010 season and 1 case occurred in the risk window in the 2010–2011 season.

There were 12 claims-identified cases of hemorrhagic stroke in the 2009–2010 and historical seasons ranging in age from 6 months through 15 years. Nine case profiles included diagnostic claims for physical trauma or fall associated with head injury and/or epilepsy. Two case profiles had accompanying diagnoses representing potential alternate factors (e.g., neoplasm, surgical procedures). One case profile included claims consistent with a cerebrovascular accident or potential event with no alternative diagnoses in the claims profile available, which occurred in the 2008–2009 historical season.

4. Discussion

We utilized a large claims-based health system to conduct a retrospective analysis of the safety of influenza vaccines among a population of 12 million individuals. After claims profile reviews, we did not find any increased risk for the pre-specified outcomes following

998,881 TIV and 538,257 H1N1 vaccine doses administered in the 2009–2010 season, and 1,158,932 TIV doses in the 2010–2011 season.

We found an elevated risk of claims-identified anaphylaxis following TIV in the 2009–2010 season in the claims data. Another analysis using health insurance claims conducted in the Post-Licensure Rapid Immunization Safety Monitoring system also found an elevated risk for allergic reactions following TIV in the 2009–2010 season [14]. In the present study, a profile review of the healthcare claims suggested that 9 of the 11 potential cases had alternate contributory factors. Of the 2 profiles that did not have alternate contributory claims present, 1 case occurred in the 2009–2010 season, and 1 case occurred in the 2010–2011 season. This equates to approximately 1 anaphylaxis case per million influenza doses, which is a similar estimate found in previous studies [15].

The risk of claims-identified hemorrhagic stroke was also elevated following TIV immunization in the 2009–2010 season. However, claims profile review suggested that only one case in the historical cohort was consistent with a potential stroke, and the remaining cases had alternate contributory factors. Thus, there is no measured risk of hemorrhagic stroke following 2009–2010 TIV administration. Analysis of other outcomes did not suggest any clinically significant safety concerns.

Although other studies, though not all, found a significant increased risk of GBS after H1N1 vaccination [8,14], we did not find any increased risk of GBS following H1N1 influenza vaccination. Additionally, we did not find an increased risk of seizures following TIV vaccination in the 2010–2011 season as was found in a previous VSD study [11]. Medical record review of the subset of both GBS and seizure cases with administrative approval for medical record requests further decreased the IRR.

The ability to request medical records for only a portion of the population is a barrier to conducting vaccine safety analyses in this administrative claims database. This may contribute to the difference in findings between the present study and other systems, such as the VSD, where medical records are more readily available. However, our ability to conduct claims profile reviews was valuable in further investigating and characterizing potential signals in a timely manner where medical record review was not feasible. Additionally, there was a relatively low number of influenza vaccinations captured given the size of the population. Although this study utilized a vaccinated cohort, which eliminates the potential misclassification of the vaccine exposure, and had ample power for the AEs studied, capture of a larger proportion of could potentially influence generalizability. We were also unable to distinguish between live attenuated and inactivated H1N1 in the claims-based system. Vaccine capture and classification may vary between claims-based systems and medical record based systems such as the VSD. Lastly, the positive predictive value of ICD-9 codes varies by AE, and misclassification may occur resulting in possible type II error. This limitation may be present whenever ICD-9 codes are used as a proxy for AEs.

There are strengths and limitations for both the SCRI and the historical comparison methods used to analyze the risk of AEs following influenza vaccination. The SCRI method can control for individual-level confounders that are fixed over time, but not for time-varying

confounders such as seasonality; though more recent self-controlled methods do have this capability. The historical comparison method has increased statistical power by using multiple years of data, which is particularly useful for rare outcomes. The main limitation to this method is the increased risks occurring in the historical cohort have the potential to mask associations when used as a control; although any differences between the present cohort and the historical cohort would be discernible. Additionally, the safety of TIV in the historical seasons of the present study, 2005 through 2008, was examined in a previous VSD study [16], and no AEs were found to be associated with influenza vaccination.

We utilized a claims-based data source to evaluate the safety of TIV and H1N1 vaccines. We ultimately found no increased outcome risk following 998,881 TIV and 538,257 H1N1 vaccine doses administered in the 2009–2010 season, and 1,158,932 TIV doses in the 2010–2011 season. The large number of vaccines in this health plans' database allowed for precise risk estimates of most outcomes, although claims profile reviews were critical in excluding cases with alternate explanations. This study adds to the body of evidence supporting the safety of influenza vaccines.

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Table 1

Pre-specified adverse event definitions and risk and control windows.

Outcome, exclusion period	ICD-9 codes	Risk window (days)	Control window (days)
Guillain-Barré Syndrome, 1st in 9 months	357.0	1 to 42	43 to 84
Demyelinating disease, 1st in 6 months	340[a]	1 to 42	−98 to −15
	341.0		
	341.8		
	341.9		
	377.30		
	377.31		
	377.32		
	377.34		
	377.39		
	357.81		
Disorders of the peripheral nervous system and neuropathies, 1st in 6 months	337.0	1 to 42	−98 to −15
	337.9		
	354.1–354.9		
	355[a]		
	356.4		
	356.8		
	357.6		
	357.7		
	357.82		
	357.89		
	357.9		
Seizures, 1st in 42 days (ages 6–59 months only)	345.0[a] to 345.9[a]	0 to 1	14 to 20
	780.3		
	780.31		
	780.39		
Encephalitis/myelitis/encephalomyelitis, 1st in 6 months	323.5[a]	1 to 21	Historical comparison

Outcome, exclusion period	ICD-9 codes	Risk window (days)	Control window (days)
	323.6[a]		
	323.8[a]		
	323.9		
	341.2		
Bell's palsy, 1st in 6 months	351.0	1 to 42	−56 to −15
Other cranial nerve disorders, 1st in 6 months	350[a]	1 to 42	−98 to −15
	351.1		
	351.8		
	351.9		
	352[a]		
Ataxia, 1st in 6 months	334.3	1 to 42	Historical comparison
Anaphylaxis, 1st in 6 months	995.0	0 to 2	Historical comparison
	999.4		
Angioneurotic edema. Allergic Reaction, Urticaria, 1st in 6 months	995.1	1 to 2	Historical comparison
	995.3		
	708.0		
	708.1		
	708.9		
Hemorrhagic stroke, 1st in 9 months	430[a]	1 to 42	Historical comparison
	431[a]		
	432[a]		
Ischemic stroke, 1st in 9 months	433.01	1 to 42	Historical comparison
	433.11		
	433.21		
	433.31		
	433.81		
	433.91		
	434[a]		
Myocarditis, pericarditis, 1st in 6 months	420.90	1 to 42	−56 to −15

Outcome, exclusion period	ICD-9 codes	Risk window (days)	Control window (days)
	420.91		
	422.0		
	422.90		
	422.91		
	422.99		
Narcolepsy and cataplexy, 1st in 9 months	347[a]	1 to 90	Historical comparison

[a]All ICD9 sub-codes included.

Table 2

Self-controlled risk interval and historical comparison analyses for pre-specified claims-identified outcomes following H1N1 vaccine in the 2009–2010 influenza season.

Outcome	Age	Cases in the risk window (N)	Cases in the comparison window (N)	Incidence rate ratio	95% confidence limits		Doses administered	Doses administered in historical cohort
Self-controlled risk interval analysis								
Seizure	6–59 months	2	12	0.58	0.06	2.62	133,872	NA
Bell's Palsy	All ages	43	37	1.16	0.75	1.84	538,257	NA
	≤24 years	9	7	1.29	0.43	4.06	312,914	NA
	≥25 years	34	30	1.13	0.67	1.92	225,343	NA
Other cranial nerve disorders	All ages	82	151	1.09	0.83	1.42	538,257	NA
	≤24 years	13	28	0.92	0.48	1.79	312,914	NA
	≥25 years	69	123	1.12	0.84	1.51	225,343	NA
Central demyelinating disease	All ages	82	141	1.16	0.87	1.53	538,257	NA
	≤24 years	7	6	2.33	0.78	6.94	312,914	NA
	≥25 years	75	135	1.11	0.84	1.47	225,343	NA
Guillain-Barré Syndrome	All ages	6	3	2.00	0.50	8.00	538,257	NA
	≤24 years	3	0	–	–	–	312,914	NA
	≥25 years	3	3	1.00	0.20	4.95	225,343	NA
Disorders of the peripheral nervous system and neuropathy	All ages	656	1370	0.96	0.87	1.95	538,257	NA
	≤24 years	29	46	1.26	0.79	2.01	312,914	NA
	≥25 years	627	1324	0.95	0.86	1.42	225,343	NA
Historical comparison analysis								
Anaphylaxis	All ages	0	1	–	–	–	538,257	3,508,144
	≤24	0	0	–	–	–	312,914	1,559,970
	≥25	0	1	–	–	–	225,343	1,948,174
Ataxia	All ages	4	43	0.68	0.24	1.89	538,257	3,508,144
	≤24	2	7	1.35	0.28	6.52	312,914	1,559,970
	≥25	2	36	0.45	0.11	1.88	225,343	1,948,174
Encephalitis/myelitis/ encephalomyelitis	All ages	0	36	–	–	–	538,257	3,508,144

Outcome	Age	Cases in the risk window (N)	Cases in the comparison window (N)	Incidence rate ratio	95% confidence limits		Doses administered	Doses administered in historical cohort
	24	0	10	–	–	–	312,914	1,559,970
	≥25	0	26	–	–	–	225,343	1,948,174
Guillain-Barré Syndrome	All ages	6	33	1.42	0.59	3.42	538,257	3,508,144
	≤24	3	4	3.79	0.85	17.02	312,914	1,559,970
	≥25	3	29	0.91	0.28	3.10	225,343	1,948,174
Angioneurotic edema, allergic reaction and urticaria	All ages	66	510	0.77	0.60	1.00	538,257	3,508,144
	≤24	47	304	0.77	0.57	1.05	312,914	1,559,970
	≥25	19	206	0.78	0.49	1.24	225,343	1,948,174
Hemorrhagic stroke	All ages	18	193	0.74	0.46	1.20	538,257	3,508,144
	≤24	5	15	1.56	0.44	4.54	312,914	1,559,970
	≥25	13	178	0.62	0.35	1.09	225,343	1,948,174
Ischemic stroke	All ages	59	589	0.85	0.65	1.11	538,257	3,508,144
	≤24	1	14	0.37	0.05	2.85	312,914	1,559,970
	≥25	58	575	0.87	0.66	1.14	225,343	1,948,174
Narcolepsy and cataplexy	All ages	25	234	0.90	0.59	1.36	538,257	3,508,144
	≤24	2	19	0.53	0.12	2.27	312,914	1,559,970
	≥25	23	215	0.95	0.62	1.46	225,343	1,948,174

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Table 3

Self-controlled risk interval and historical comparison analyses of pre-specified claims-identified outcomes following trivalent influenza virus vaccine in the 2009–2010 influenza season.

Outcome	Age	Cases in the risk window (N)	Cases in the control window (N)	Incidence rate ratio	95% confidence limits		Doses administered	Doses administered in historical cohort
Self-controlled risk interval analysis								
Seizure	6–59 months	8	20	1.40	0.53	3.32	189.980	NA
Bell's Palsy	All Ages	74	89	0.83	0.60	1.15	998,881	NA
	≤24 years	9	11	0.82	0.30	2.17	430,879	NA
	≥25 years	65	78	0.83	0.60	1.16	568,002	NA
Other cranial nerve disorders	All Ages	187	356	1.05	0.88	1.25	998,881	NA
	>24 years	20	29	1.38	0.78	2.44	430,879	NA
	≥25 years	167	327	1.02	0.85	1.23	568,002	NA
Central demyelinating disease	All Ages	170	358	0.95	0.79	1.14	998,881	NA
	≤24 years	10	20	0.39	0.47	2.14	430,879	NA
	≥25 years	160	338	0.95	0.78	1.14	568,002	NA
Guillain-Barré Syndrome	All Ages	11	7	1.57	0.61	4.05	998,881	NA
	≤24 years	3	1	3.00	0.31	28.84	430,879	NA
	≥25 years	8	6	1.33	0.46	3.84	568,002	NA
Disorders of the peripheral nervous system and neuropathy	All Ages	1926	3614	1.07	1.01	1.13	998,881	NA
	≤24 years	53	79	1.34	0.95	1.90	430,879	NA
	≥25 years	1873	3535	1.06	1.00	1.12	568,002	NA
Historical comparison analysis								
Anaphylaxis	All Ages	8	1	28.55	3.57	228.44	998,881	3,508,144
	≤24	5	0	–	–	–	430,879	1,559,970
	≥25	3	1	10.92	1.13	105.37	568,002	1,948,174
Ataxia	All Ages	5	43	0.39	0.15	0.98	998,881	3,508,144
	≤24	1	7	0.52	0.06	4.26	430,879	1,559,970
	≥25	4	36	0.37	0.13	1.03	568,002	1,948,174
Encephalitis/myelitis/ encephalomyelitis	All Ages	3	36	0.28	0.09	0.92	998,881	3,508,144

Outcome	Age	Cases in the risk window (N)	Cases in the control window (N)	Incidence rate ratio	95% confidence limits		Doses administered	Doses administered in historical cohort
	≤24	0	10	–	–	–	430,879	1,559,970
	≥25	3	26	0.39	0.12	1.28	568,002	1,948,174
Guillain-Barré Syndrome	All Ages	11	33	1.16	0.58	2.29	998,881	3,508,144
	≤24	3	4	2.72	0.61	12.17	430,879	1,559,970
	≥25	8	29	0.95	0.44	2.09	568,002	1,948,174
Angioneurotic edema, allergic reaction and urticaria	All Ages	135	510	0.92	0.76	1.11	998,881	3,508,144
	≤24	80	304	0.94	0.74	1.21	430,879	1,559,970
	≥25	55	206	0.89	0.66	1.20	568,002	1,948,174
Hemorrhagic stroke	All Ages	70	193	1.24	0.94	1.63	998,881	3,508,144
	≤24	10	15	2.37	0.95	5.65	430,879	1,559,970
	≥25	60	178	1.14	0.86	1.54	568,002	1,948,174
Ischemic stroke	All Ages	157	589	0.91	0.76	1.08	998,881	3,508,144
	≤24	4	14	1.07	0.35	3.25	430,879	1,559,970
	≥25	153	575	0.90	0.76	1.08	568,002	1,948,174
Narcolepsy and cataplexy	All Ages	73	234	1.09	0.84	1.41	998,881	3,508,144
	≤24	4	19	0.77	0.26	2.28	430,879	1,559,970
	≥25	69	215	1.11	0.85	1.46	568,002	1,948,174

Table 4

Self-controlled risk interval and historical comparison analysis of pre-specified claims-identified outcomes following trivalent influenza virus vaccine in the 2010–2011 influenza season.

Outcome	Age	Cases in the risk window (N)	Cases in the comparison window (N)	Incidence rate ratio	95% confidence limits		Doses administered	Doses administered in historical cohort
Self-controlled risk interval analysis								
Seizure	6–59 months	5	20	0.88	0.26	2.40	185,144	NA
Bell's Palsy	All Ages	80	91	0.88	0.65	1.19	1,158,932	NA
	≤24 years	7	9	0.78	0.29	2.09	436,905	NA
	≥25 years	73	82	0.89	0.65	1.22	722,027	NA
Other cranial nerve disorders	All Ages	226	395	1.14	0.97	1.35	1,158,932	NA
	≤24 years	15	28	1.07	0.57	2.01	436,905	NA
	≥25 years	221	367	1.15	0.97	1.36	722,027	NA
Central demyelinating disease	All Ages	184	355	1.04	0.87	1.24	1,158,932	NA
	≤24 years	5	26	0.38	0.15	1.00	436,905	NA
	≥25 years	179	329	1.09	0.91	1.31	722,027	NA
Guillian-Barré Syndrome	All Ages	14	14	1.00	0.45	2.23	1,158,932	NA
	≤24 years	2	0	–	–	–	436,905	NA
	≥25 years	12	14	0.86	0.40	1.85	722,027	NA
Disorders of the peripheral nervous system and neuropathy	All Ages	2239	4325	1.04	0.98	1.09	1,158,932	NA
	≤24 years	64	100	1.28	0.94	1.75	436,905	NA
	≥25 years	2175	4225	1.03	0.98	1.08	722,027	NA
Historical comparison analysis								
Anaphylaxis	All Ages	2	1	6.70	0.60	74.74	1,158,932	3,508,144
	≤24	1	0	–	–	–	436,905	1,559,970
	≥25	1	1	–	–	–	722,027	1,948,174
Ataxia	All Ages	11	43	0.69	0.35	1.34	1,158,932	3,508,144
	≤24	3	7	1.49	0.39	5.78	436,905	1,559,970
	≥25	3	36	0.56	0.26	1.21	722,027	1,948,174
Encephalitis/myelitis/ encephalomyelitis	All Ages	5	36	0.39	0.15	1.01	1,158,932	3,508,144

Outcome	Age	Cases in the risk window (N)	Cases in the comparison window (N)	Incidence rate ratio	95% confidence limits		Doses administered	Doses administered in historical cohort
	≤24	2	10	0.69	0.15	3.16	436,905	1,559,970
	≥25	3	26	0.30	0.09	1.00	722,027	1,948,174
Guillain-Barre Syndrome	All Ages	14	33	1.17	0.62	2.19	1,158,932	3,508,144
	≤24	2	4	1.78	0.32	9.73	436,905	1,559,970
	≥25	12	29	1.10	0.56	2.17	722,027	1,948,174
Angioneurotic edema, allergic reaction and urticaria	All Ages	141	510	0.86	0.71	1.03	1,158,932	3,508,144
	≤24	82	304	0.95	0.75	1.21	436,905	1,559,970
	≥25	59	206	0.75	0.56	1.00	722,027	1,948,174
Hemorrhagic stroke	All Ages	72	193	1.01	0.77	1.33	1,158,932	3,508,144
	≤24	3	15	0.70	0.20	2.42	436,905	1,559,970
	≥25	69	178	1.04	0.78	1.37	722,027	1,948,174
Ischemic stroke	All Ages	180	589	0.82	0.69	0.97	1,158,932	3,508,144
	≤24	6	14	1.58	0.61	4.11	436,905	1,559,970
	≥25	174	575	0.80	0.68	0.95	722,027	1,948,174
Narcolepsy and cataplexy	All Ages	67	234	0.80	0.62	1.06	1,158,932	3,508,144
	≤24	1	19	0.19	0.03	1.42	436,905	1,559,970
	≥25	66	215	0.85	0.65	1.13	722,027	1,948,174