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Identification of seizures among adults and children following influenza vaccination using health insurance claims data

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Abstract

Introduction: Post-licensure surveillance of adverse events following vaccination or prescription drug use often relies on electronic healthcare data to efficiently detect and evaluate safety signals. The accuracy of seizure-related diagnosis codes in identifying true incident seizure events in vaccine safety studies is influenced by factors such as clinical setting of diagnosis and age. To date, most studies of post-vaccination seizure have focused on pediatric populations. More information is needed on how well seizure can be identified in adults and children using algorithms that rely on electronic healthcare data.

Methods: This validation study was part of a larger safety study of influenza vaccination during the 2009–2010 and 2010–2011 influenza seasons. Children and adults receiving influenza vaccination were drawn from an administrative claims database of a large United States healthcare insurer. Potential seizure events were identified using an algorithm of ICD-9 diagnosis codes associated with an emergency department (ED) visit or hospitalization within pre-specified risk windows following influenza vaccination. Seizure events were confirmed through medical record review. The positive predictive value (PPV) of the algorithm was calculated within each diagnostic setting and stratified by age group, ICD-9 code group, and sex.

Results: Review confirmed 113 out of 176 potential seizure events. The PPVs were higher in the ED setting (93.9%) than in the inpatient setting (38.3%). The PPVs by age varied within the ED setting (98.2% in <7 years, 76.9% in 7–24 years, 92.3% in ≥25 years) and within the inpatient setting (64.7% in <7 years, 33.3% in 7–24 years, 32.3% in ≥25 years).

Conclusions: Our algorithm for identification of seizure events using claims data had a high level of accuracy in the emergency department setting in young children and older adults and a lower, but acceptable, level of accuracy in older children and young adults.

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Keywords

Vaccine safety; Seizure; ICD-9 diagnosis codes; Positive predictive value; Large electronic healthcare database

1. Introduction

In Western Australia, an increased risk of febrile convulsions was reported in children under 5 years of age following receipt of the 2010 trivalent inactivated influenza vaccine (TIV) manufactured by CSL Biotherapies (Fluvax®, Fluvax Junior®), leading to a temporary suspension of the Western Australia influenza vaccination program for children under 5 years of age [1]. An elevated risk of febrile seizures was also reported in a large United States (US) cohort in the 0–1 days following first dose TIV during the 2010–2011 season and in other studies in the short term following administration of vaccinations including diphtheria, tetanus, acellular pertussis, inactivated poliovirus, Haemophilus influenzae type B (DTaP-IPV-Hib), measles, mumps, rubella (MMR), and MMR plus varicella (MMRV) [2–11]. These studies highlight the risk of seizures in children following vaccine-induced fever. Although post-vaccination seizure is less common in adults, seizure has been reported as an adverse event (AE) in adults following influenza vaccination [12], which prompted the inclusion of seizures in adults as an outcome of interest in prospective influenza vaccine surveillance previously done in the US [13]. Monitoring for seizures as a potential AE in post-licensure vaccine safety studies in all age groups contributes to the robustness of the safety monitoring of the US influenza immunization program.

Post-licensure active surveillance of AEs following vaccination or prescription drug use often relies on electronic healthcare data to efficiently and effectively detect and evaluate potential safety signals [14,15]. The efficiency and validity of these surveillance programs are increased with an algorithm that reliably identifies adverse events using diagnosis codes recorded for medical visits.

Performance of seizure-related diagnosis codes in postlicensure safety studies is variable and may be influenced by several factors, including clinical diagnostic setting and age [16–19]. A systematic review commissioned by the US Food and Drug Administration (FDA) to validate seizure, convulsion, or epilepsy cases as part of its Mini-Sentinel program pilot found positive predictive values (PPVs) ranging from 21% to 98% [16]. Many of the studies included in the review focused on the pediatric population. Few published studies in adult populations were identified. The PPV of diagnosis codes suggestive of seizure in a study of adult tramadol users within a large US health insurance plan was 21%. [19]. More information is needed on how well seizures among vaccinated adults and children can be identified using electronic healthcare data.

This study objective was to evaluate an algorithm for identification of seizure events using an administrative claims database in a large health plan population of adults and children who received influenza vaccination in the US during the 2009–2010 and 2010–2011 seasons.

2. Methods

2.1. Data source and study population

The study population was derived from an electronic healthcare database of a large US insurer developed for research purposes. Accessible information includes demographics and pharmacy, medical, and facility claims, which provide dates on services, procedures, and their accompanying diagnoses. The insured population from which the data are drawn is geographically diverse, comprising approximately 3–4% of the US population. For a subset of approximately 6 million health plan members with medical coverage and pharmacy benefits, patient-identifiable information (PII) may be accessed for further inquiries, including medical chart review. The data undergo regular audits and quality control procedures by the insurer and are updated monthly.

This validation study was nested within a cohort study evaluating risk for adverse events following influenza vaccination during the 2009–2010 and 2010–2011 seasons. Eligible cohort study subjects included commercial health insurance plan members with complete medical coverage and pharmacy benefits. Cohort members received monovalent 2009 H1N1 or trivalent seasonal influenza vaccination from September 1 to March 31 during the 2009–2010 or 2010–2011 season, were aged 6 months or older at the time of the vaccination, and had at least 9 months of continuous health plan enrollment prior to vaccination. Individuals with vaccinations during both seasons entered the analysis more than once. This validation study included cohort members with potential seizure events identified using the algorithm described below and with administrative ability to access PII for medical record review.

2.2. Privacy and confidentiality

Approval of the study protocol and waiver of patient authorization were obtained from the New England Institutional Review Board and affiliated Privacy Board.

2.3. Algorithm for identification of potential seizure events

Potential seizure events met the following criteria: (1) presence of insurance claims associated with an emergency department (ED) visit or inpatient hospitalization with International Classification of Diseases, 9th Revision (ICD-9) codes 345.xx¹ (epilepsy) or 780.3x¹ (convulsions) occurring on days 0 through 29 following the index vaccination (day 0 = day of vaccination), and (2) absence of any of these ICD-9 codes in the 42 days prior to the potential seizure event, irrespective of the time since influenza vaccination. The restriction to the first occurrence of the code in a 42-day period was used in a prior evaluation of seizure signals following influenza vaccination [2] and was applied in the safety study to improve specificity in identifying new seizure events (e.g., as opposed to follow up visits for a previous seizure) while still maintaining adequate sensitivity for signal detection and evaluation.

¹The x represents any number.

2.4. Verification of potential seizure events

A research nurse reviewed listings of claims for healthcare services and treatments surrounding the potential seizure event date to select a healthcare provider most likely to yield records with information necessary to confirm the potential seizure events. Where possible, two providers were selected for each potential case so an alternate could be contacted if the first choice provider declined to participate.

Following a request letter to the selected providers, which included copies of the IRB approval and waiver of patient authorization, trained abstractors contacted the providers to retrieve medical records. Information on patient demographics, clinical characteristics and history, and state of consciousness and motor manifestations at the time of the event was abstracted. As complete information was unavailable in most medical records to classify cases using Brighton Collaboration criteria [20], potential cases were classified by the abstractors into (1) definite, (2) possible, or (3) no evidence of seizure based on the clinician diagnosis documented in the medical record. Definite seizures had medical record documentation of a clinical diagnosis of a seizure event. Possible seizures had medical record documentation by the treating clinician noting a possible seizure with further documentation unavailable to confirm. For records with no documentation of a new seizure event, reason(s) for non-confirmation were ascertained.

2.5. Analysis

We calculated the positive predictive value (PPV) of the seizure algorithm as the number of definite seizure events divided by the number of medical records abstracted. For analytic purposes, medical records received without the requested date range of interest were not abstracted and not included in the PPV estimation. PPVs were calculated separately for the ED and inpatient settings and stratified by age group, gender, and ICD-9 diagnosis code groups (epilepsy and convulsion). These variables were previously observed to influence the PPV of claims-based seizure algorithms [16–19]. Patients with ED and inpatient claims on the day of the potential seizure were assigned to the inpatient setting. Patients were classified as children (<7 years), older children and young adults (7–24 years), and adults (≥ 25 years). As the study population includes patients administered monovalent 2009 H1N1 influenza vaccination, 24 years of age was chosen as the cutoff point between young adults and adults for consistency with administration recommendations for that vaccine [21]. Children younger than 1 year of age were initially evaluated separately but later combined with children through 7 years of age due to small sample size. Exact 95% confidence intervals (CI) were calculated using the Clopper–Pearson method [22]. Data analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

3. Results

224 potential seizure events following 1,091,181 influenza vaccinations were identified for medical record review in the main safety study and were thus eligible for inclusion in the algorithm validation analysis.

3.1. Characteristics of potential seizure events

Characteristics of the 224 potential seizure events by age group are described in Table 1. Potential events with claims for only convulsions occurred most frequently in children (85.9%) compared with the other age groups. Potential events with claims for only epilepsy occurred most frequently in adults (40.4%) versus the other age groups. Potential events in the ED setting were identified most frequently in children (74.1%) versus the other age groups, while potential events in the inpatient setting were identified most frequently in adults (84.8%) versus the other age groups.

3.2. Medical record retrieval and abstraction

Of the 224 medical records requested, 176 (78.6%) were obtained and abstracted. 48 records were not obtained due to provider non-response or unavailability of records within the requested date range for administrative reasons. The number of charts available for abstraction is presented in Table 2. The proportion of charts obtained and abstracted was highest in children (85.9%). The proportion of charts obtained and abstracted was higher for the ED setting (84.5%) than the inpatient setting (74.0%). Of the 73 charts abstracted in children, 56 (76.7%) were obtained and abstracted from the ED setting.

3.3. PPVs by clinical care setting

Of the 176 charts abstracted, 113 (64.2%) were classified as definite new seizure events, 6 (3.4%) were possible new seizure events, and 57 (32.4%) were non-seizure events.

The ED setting accounted for 82 (46.6%) of the 176 abstracted charts. The PPVs within the ED setting varied by age: 98.2% (95% CI: 90.5–100.0%) for seizure events in children, 76.9% (95% CI: 46.2–95.0%) in older children and young adults, and 92.3% (95% CI: 64.0–99.8%) in adults (Table 3). The PPV associated with the presence of claims for only convulsions varied by age group, with 98.1% (95% CI: 89.7–100.0%) in children, 66.7% (95% CI: 22.3–95.7%) in older children and young adults, and 88.9% (95% CI: 51.8–99.7%) in adults. For the small number of subjects with both epilepsy and convulsion claims, the PPVs were 100.0% (95% CI: 75.3–100.0%) for all age groups.

94 charts (53.4%) were abstracted from the inpatient setting. The PPVs within the inpatient setting were lower than in the ED setting, and varied by age group: 64.7% (95% CI: 38.3–85.8%) in children, 33.3% (95% CI: 9.9–65.1%) in older children and young adults, and 32.3% (95% CI: 21.2–45.1%) in adults (Table 4). PPVs associated with claims for epilepsy alone varied by age group (100.0%, 95% CI: 2.5–100.0% in children; 25.0%, 95% CI: 0.6–80.6% in older children and young adults; 17.6%, 95% CI: 6.8–34.5% in adults), as did the PPVs associated with claims for convulsions alone (72.7%, 95% CI: 39.0–94.0% in children; 40.0%, 95% CI: 5.3–85.3% in older children and young adults; 54.2%, 95% CI: 32.8–74.5% in adults) (Table 4). The PPVs did not improve with the presence of claims for both epilepsy and convulsions.

3.4. Availability of clinical information for definite seizure events

Information on motor manifestations, state of consciousness, and febrile status was abstracted from the medical records of the 113 definite seizure events. Information on motor

manifestations was missing from 30.3% of records for children, 14.2% of records for older children and young adults, and 33.3% of records for adults. Information on state of consciousness was missing from 72.7% of records for children, 42.9% of records for older children and young adults, and 57.6% of records for adults. The majority of records therefore did not have adequate information to classify definite seizure events using the Brighton Collaboration criteria. Data on febrile status based on report of fever at the time of seizure occurrence noted in the medical record or temperature of >38.0 °C (100.4 °F) recorded upon presentation at the ED or inpatient hospital was available in the majority of records; 84.8% of definite seizure events in children were likely febrile compared with only 3% of definite seizure events in adults. No evidence of febrile seizure events were found in older children and young adults. When examining febrile status of definite seizure events by ICD-9 diagnosis code, 11.1% with claims for epilepsy only, 60.5% with claims for convulsions only, and 22.2% claims for both epilepsy and convulsions were likely to be febrile.

3.5. Reasons for non-confirmation among non-cases

Reasons for non-confirmation for the 57 non-seizure cases included one or more of the following: (1) visit for another reason, but the patient had documented history of seizure disorder (72.0%), (2) visits for seizure-related testing but not involving a seizure event on that day (i.e., seizure diagnosis claim was a justification for neurological tests such as electroencephalogram (EEG) or magnetic resonance imaging (MRI)) (21.0%), (3) visit for a suspected seizure that was ruled out (14.0%), and (4) indicated management of a known seizure disorder (7.0%). Of the 57 cases, 41 (72.0%) were in adults, 6 (10.5%) in children, and 10 (17.5%) in older children and young adults. Of the 41 adult cases, 34 (82.9%) had a visit for another reason but with a documented history of seizure disorder. No significant differences in reasons for non-confirmation were observed among the other age groups.

4. Discussion

This study validated an algorithm to identify seizures in vaccinated children and adults within a health insurance claims database using a combination of ICD-9 diagnosis codes, diagnostic setting, and pre-specified lookback and risk periods relative to vaccination. Our findings suggest higher PPVs with ICD-9 codes associated with ED visits (76.9–98.2%) and lower PPVs for the same claimsbased criteria when associated with inpatient visits (32.3–64.7%). Lower PPVs were observed in older children and young adults in the ED setting and in older children and young adults and adults in the inpatient setting. The majority of non-confirmed cases were in adults with a prior history of seizure disorder.

Previous studies within vaccinated populations relying on health insurance claims or electronic healthcare data have focused on performance of seizure diagnosis codes in children. Our pediatric population findings of higher PPVs in the ED setting and lower PPVs in the inpatient setting are consistent with findings by Shui and colleagues (2009), who reported a PPV of 97% in an ED setting and 64% in an inpatient setting in children aged 6–23 months. The limited availability of Brighton Collaboration classification criteria

information and febrile status in medical charts is also consistent with previous findings [18,23].

The differences in PPVs by clinical care setting and age group are likely due to several factors. The higher PPVs in children may be a function of disease incidence and prevalence, as children, particularly under the age of 2, are at higher risk for a seizure event [24]. Most charts abstracted and confirmed in the ED setting were in children. Parents of a young child with a seizure are likely to seek immediate medical attention at an emergency department. Seizure diagnosis codes for older children and adults may represent a personal history of seizures and/or a follow-up visit rather than a new event. Of the 78 cases obtained in adults, 65 were abstracted from an inpatient setting. The differences in PPV by diagnostic setting may be a function of the age of the health plan members and the underlying disease pattern in different age groups.

The PPVs by ICD-9 diagnosis code varied by age group within the ED and inpatient settings. Convulsion diagnosis codes are typically used to code isolated seizure events, while epilepsy codes are used to code recurrent seizure events [25]. This may be reflected in the higher PPVs with convulsions in children in both the ED (98.1%) and inpatient (72.7%) settings. The presence of epilepsy claims alone was rarely seen in the ED setting. The presence of epilepsy claims alone was seen more frequently in the inpatient setting, but gave rise to lower PPVs in older children/young adults and adults. In the small number of records with both epilepsy and convulsions claims, high PPVs were observed in the ED setting, but the presence of both codes did not consistently translate into higher PPVs in the inpatient setting. Since the diagnosis of seizures is generally made after the event occurs outside of the medical care setting, availability of clinical information in the Brighton collaboration classification scheme was limited in the medical record.

This study does have certain limitations. Approximately 15% of ED records and 26% of inpatient records were not procured due to provider non-response. The higher non-procurement rate of inpatient records may be attributed to administrative barriers that are often present when requesting records from an inpatient hospital. To maximize abstraction rates, charts were procured from an alternate provider where possible if the first choice provider declined to participate. The small sample size precluded an assessment of predictors of definite seizures using a multivariate logistic regression model. All cohort members received influenza vaccination. Our findings are consistent with PPVs reported in other vaccinated health plan populations [18] and may therefore be useful to other vaccine safety studies. A brief evaluation of the PPVs in mutually exclusive time windows (0–1, 2–7, 8–14, 15–29 days) following vaccination showed no variation based on time since influenza vaccination. As seizures occurring in later time windows could reasonably be attributed to non-vaccine exposures, the algorithm may also be useful in non-vaccine safety studies. This warrants further investigation.

This study examined the performance of an algorithm to identify seizure events in influenza-vaccinated adults and children in a claims data environment. We restricted outcome identification in claims to ED and inpatient settings to improve specificity, as previous publications have reported low predictive values of diagnosis codes for seizures identified in

outpatient settings [16,18]. Our algorithm had a high level of accuracy in the ED setting in young children and older adults and a lower, but acceptable, level of accuracy in older children and young adults. This study adds to the literature supporting the reliability of electronic healthcare data in accurately identifying seizures associated with an ED visit. The low predictive value in the inpatient setting, particularly with epilepsy claims, suggests the continued need for medical record confirmation of claims-identified seizure events in this setting.

5. Conclusions

This study evaluated the performance of an algorithm to identify seizures in influenza-vaccinated adults and children using health insurance claims data. This study adds to the literature supporting the reliability of electronic healthcare data in accurately identifying seizure events in the ED setting in vaccinated populations.

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Ms. Thyagarajan and Dr. Lin are employees of Optum. Ms. Su and Dr. Chan were employees of Optum at the time this study was conducted. Ms. Gee, Dr. Duffy, Ms. McCarthy, and Mr. Weintraub are employees of the Centers for Disease Control and Prevention.

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Characteristics of potential seizure events identified in health insurance claims data by age group.

Table 1

ICD-9 diagnosis code ^a	<7years (N =85)		7–24 years (N = 40)		25 years (N = 99)		Total (N =224)	
	n	%	n	%	n	%	n	%
345.xx only	3	3.5	13	32.5	40	40.4	56	25.0
780.3x only	73	85.9	18	45.0	45	45.5	136	60.7
Both 345.xx and 780.3x	9	10.6	9	22.5	14	14.1	32	14.3
Setting of diagnosis								
Emergency Department	63	74.1	19	47.5	15	15.2	97	43.3
Inpatient	22	25.9	21	52.5	84	84.8	127	56.7
Sex								
Male	55	64.7	22	55.0	38	38.4	115	51.3
Female	30	35.3	18	45.0	61	61.6	109	48.7
Simultaneous vaccination received								
No	39	45.9	37	92.5	88	88.9	164	73.2
Yes	46	54.1	3	7.5	11	11.1	60	26.8

^aCodes included all digits. ICD-9 345.xx = epilepsy, ICD-9 780.3x = convulsions.

Table 2

Number of charts available for abstraction.

	Charts requested	Complete charts obtained and abstracted	
	<i>N</i>	<i>N</i>	%
Overall	224	176	78.6
Age			
<7 years	85	73	85.9
7–24 years	40	25	62.5
≥25 years	99	78	78.8
Setting of diagnosis			
ED	97	82	84.5
Inpatient	127	94	74.0
Sex			
Male	115	88	76.5
Female	109	88	80.7
ICD-9 diagnosis code ^a			
345.xx only	56	41	73.2
780.3xx only	136	107	78.7
Both 345.xx and 780.3x	32	28	87.5

^aCodes included all digits. ICD-9 345.xx = epilepsy, ICD-9 780.3x = convulsions.

Table 3

PPV of claims-identified seizures diagnosed in an emergency department setting by age group.

	<7 years (<i>n</i> abstracted = 56)			7–24 years (<i>n</i> abstracted = 13)				
	Chart-confirmed cases (<i>n</i>)	Charts abstracted (<i>n</i>)	PPV (%)	95% CI	Chart-confirmed cases (<i>n</i>)	Charts abstracted (<i>n</i>)	PPV (%)	95% CI
All visits	55	56	98.2	90.5–100.0	10	13	76.9	46.2–95.0
ICD-9 diagnosis code ^a								
345.xx	1	1	100.0	2.5–100.0	0	1	0.0	0.0–97.5
780.3x	51	52	98.1	89.7–100.0	4	6	66.7	22.3–95.7
Both 345.xx and 780.3x	3	3	100.0	29.2–100.0	6	6	100.0	54.1–100.0
Gender								
Male	36	36	100.0	90.3–100.0	6	7	85.7	42.1–99.6
Female	19	20	95.0	75.1–99.9	4	6	66.7	22.3–95.7
25 years (<i>n</i> abstracted = 13)								
All visits	12	13	92.3	64.0–99.8	77	82	93.9	86.3–98.0
ICD-9 diagnosis code ^a								
345.xx	0	0	0.0	-	1	2	50.0	1.3–98.7
780.3x	8	9	88.9	51.8–99.7	63	67	94.0	85.4–98.4
Both 345.xx and 780.3x	4	4	100.0	39.8–100.0	13	13	100.0	75.3–100.0
Gender								
Male	5	6	83.3	35.9–99.6	47	49	95.9	86.0–99.5
Female	7	7	100.0	59.0–100.0	30	33	90.9	75.7–98.1

Abbreviations: PPV, positive predictive value.

^aCodes included all digits. ICD-9 345.xx = epilepsy, ICD-9 780.3x = convulsions.

Table 4

PPV of claims-identified seizures diagnosed in an inpatient setting by age group.

	<7 years (<i>n</i> abstracted = 17)				7–24 years (<i>n</i> abstracted = 12)			
	Chart-confirmed cases (<i>n</i>)	Charts abstracted (<i>n</i>)	PPV (%)	95% CI	Chart-confirmed cases (<i>n</i>)	Charts abstracted (<i>n</i>)	PPV (%)	95% CI
All visits	11	17	64.7	38.3–85.8	4	12	33.3	9.9–65.1
ICD-9 diagnosis code ^a								
345.xx	1	1	100.0	2.5–100.0	1	4	25.0	0.6–80.6
780.3x	8	11	72.7	39.0–94.0	2	5	40.0	5.3–85.3
Both 345.xx and 780.3x	2	5	40.0	5.3–85.3	1	3	33.3	0.8–91.0
Gender								
Male	7	9	77.8	40.0–97.2	2	7	28.6	3.7–71.0
Female	4	8	50.0	15.7–84.3	2	5	40.0	5.3–85.3
25 years (<i>n</i> abstracted = 65)								
	Chart-confirmed cases (<i>n</i>)	Charts abstracted (<i>n</i>)	PPV (%)	95% CI	Chart-confirmed cases (<i>n</i>)	Charts abstracted (<i>n</i>)	PPV (%)	95% CI
All visits	21	65	32.3	21.2–45.1	36	94	38.3	28.5–48.9
ICD-9 diagnosis code ^a								
345.xx	6	34	17.6	6.8–34.5	8	39	20.5	9.3–36.5
780.3x	13	24	54.2	32.8–74.5	23	40	57.5	40.9–73.0
Both 345.xx and 780.3x	2	7	28.6	3.7–71.0	5	15	33.3	11.8–61.6
Gender								
Male	12	23	52.2	30.6–73.2	21	39	53.8	37.2–69.9
Female	9	42	21.4	10.3–36.8	15	55	27.3	16.1–41.0

Abbreviations: PPV = positive predictive value.

^aCodes included all digits. ICD-9 345.xx = epilepsy, ICD-9 780.3x = convulsions.