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

Veena Thyagarajan[a,*], Sue Su[a], Julianne Gee[b], Jonathan Duffy[b], Natalie L. McCarthy[b], K. Arnold Chan[c], Eric S. Weintraub[b], Nancy D. Lin[d]

[a] Optum Epidemiology, 315 E. Eisenhower Parkway Suite 305, Ann Arbor, MI 48108, USA
[b] Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, 1600 Clifton Road NE, MS-D26, Atlanta, GA 30333, USA
[c] Department of Medical Research, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan
[d] Optum Epidemiology, 950 Winter Street Suite 3800, Waltham, MA 02451, USA

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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.

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

* Corresponding author. Tel.: +1 734 205 1807; fax: +1 734 205 1840.
E-mail addresses: veena.thyagarajan@optum.com (V. Thyagarajan), dzg2@cdc.gov (J. Gee), jduffy@cdc.gov (J. Duffy), gvz7@cdc.gov (N.L. McCarthy), k.a.chan@post.harvard.edu (K.A. Chan), eiw8@cdc.gov (E.S. Weintraub), nancy.lin@optum.com (N.D. Lin).

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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 post-licensure 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.xx[1] (epilepsy) or 780.3x[1] (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.

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] The x represents any number.