Vaccine 31 (2013) 5975–5982

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

Natalie L. McCarthy[a,*], Julianne Gee[a], Nancy D. Lin[b], Veena Thyagarajan[c], Yi Pan[a], Sue Su[c], Bruce Turnbull[b], K. Arnold Chan[d], Eric Weintraub[a]

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

ARTICLE INFO

Article history:
Received 20 June 2013
Received in revised form
30 September 2013
Accepted 8 October 2013
Available online 19 October 2013

Keywords:
Vaccine safety
Claims
Influenza
H1N1

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 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.

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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

☆ 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.

* Corresponding author at: CDC, 1600 Clifton Road, MS-D26, Atlanta, GA 30333, USA. Tel.: +1 404 543 0463; fax: +1 404 639 8834.
E-mail addresses: nmccarthy@cdc.gov, gvz7@cdc.gov, nattyd21@gmail.com (N.L. McCarthy), dzg2@cdc.gov (J. Gee), nancy.lin@optum.com (N.D. Lin), veena.thyagarajan@optum.com (V. Thyagarajan), jnu5@cdc.gov (Y. Pan), yingsue@yahoo.com (S. Su), bruce.turnbull@optum.com (B. Turnbull), k.a.chan@post.harvard.edu (K.A. Chan), eiw8@cdc.gov (E. Weintraub).

0264-410X/$ – see front matter. Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.vaccine.2013.10.031

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