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Validation of febrile seizures identified in the Sentinel Post-Licensure Rapid Immunization Safety Monitoring Program

Alison Tse Kawai [a,*,1], David Martin [b], Sarah E. Henrickson [c], Ashleigh Goff [a], Megan Reidy [a], Diana Santiago [a], Nandini Selvam [d], Mano Selvan [e], Cheryl McMahill-Walraven [f], Grace M. Lee [a,g]

[a] Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, United States
[b] FDA, Center for Drug Evaluation and Research, Silver Spring, MD, United States
[c] Division of Allergy-Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA, United States
[d] HealthCore, Alexandria, VA, United States
[e] Comprehensive Health Insight, Humana, Louisville, KY, United States
[f] Aetna, Blue Bell, PA, United States
[g] Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA, United States

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ABSTRACT

Background: The Sentinel Initiative was established in 2008 to monitor the safety of FDA-regulated medical products. We evaluated the positive predictive value (PPV) of ICD-9 codes for post-vaccination febrile seizures to identify optimal algorithms for use in post-market safety surveillance.
Methods: We identified ICD-9 diagnosis codes for fever and seizures in the emergency department or inpatient setting after vaccinations of interest from July 1, 2010 to June 30, 2011. Medical record review was conducted to verify febrile seizure events.
Results: Of 216 potential febrile seizures identified with one or more seizure codes (the broadest algorithm), 152 were chart-confirmed (i.e., documentation of fever within 24 h of seizure or clinician diagnosis of febrile seizure; PPV 70%, 95% CI 64, 76%). Two codes specific for febrile seizures produced the highest PPV (PPV 91%, 95% CI 85, 95%) and accounted for 140 confirmed febrile seizures. In the absence of febrile seizure codes, other seizure codes yielded much lower PPVs, regardless of the presence of fever codes.
Conclusions: Our results indicate that ICD-9 diagnosis codes in the inpatient and emergency department settings have high predictive value for identifying febrile seizures within the Sentinel Distributed Database. While the PPV of the algorithm based on any diagnosis code for seizure is moderate, the algorithm limited to febrile seizure codes has a high PPV (>90%) and captures the vast majority of confirmed cases identified by the broadest algorithm, suggesting that the narrower algorithm limited to febrile seizure codes may be preferred.

1. Introduction

The Food and Drug Administration's (FDA) Sentinel Initiative was developed in response to a congressional mandate to create a national post-market safety monitoring system for FDA-approved medical products using electronic health-care data. The Post-Licensure Rapid Immunization Safety Monitoring (PRISM) Program is the vaccine safety monitoring component of this system and is currently the largest cohort in the US general population for vaccine safety surveillance [1,2]. PRISM includes data from 5 partners, 4 of which include claims-based data from large, national health insurers. Claims-based data from each of these partners is transformed into a distributed database, which follows a common data model [3]. Additionally, investigators have the capability to perform medical record review on a subset of patients [3]. A crucial component of PRISM's success is the accurate and efficient identification of key adverse health outcomes. One such outcome of interest to the FDA and others interested in vaccine safety is febrile seizure.

To date, most of the studies validating computerized algorithms for febrile seizure in the U.S. have been conducted in the Vaccine Safety Datalink [4–6], whose data are largely comprised of electronic health records of several regional managed care

* Corresponding author at: RTI Health Solutions, 307 Waverley Oaks Road, Suite 101, Waltham, MA 02452, United States. Tel.: 781-434-1787.
E-mail address: akawai@rti.org (A.T. Kawai).
[1] Current affiliation: RTI Health Solutions, Waltham, MA, United States.

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organizations with integrated healthcare delivery systems [7]. In contrast, PRISM data are largely based on claims from multiple providers in community care settings throughout the U.S. [2]. We sought to examine the accuracy of a number of ICD-9 coded algorithms for febrile seizure in the Sentinel PRISM Program. This would facilitate evaluation of the risk of febrile seizure associated with vaccinations of interest for post-market surveillance within the Sentinel PRISM Program.

2. Methods

2.1. Study population

This validation study was nested within a larger assessment that examined the association between 2010–2011 inactivated influenza vaccine (IIV) and risk of febrile seizure in the PRISM program. In brief, it consisted of children ages 6–59 months who were enrolled in a health plan associated with a PRISM Data Partner (Aetna, HealthCore, and Humana) between July 1, 2010 and June 30, 2011 [8]. Using a self-controlled risk interval design (SCRI), we identified febrile seizures in the 0–1 or 14–20 day periods following IIV, diphtheria tetanus acellular pertussis-containing vaccines, and 13-valent pneumococcal conjugate vaccine. Vaccinations were identified in claims or immunization registry data, the latter of which was only available in 8 states and New York City. Febrile seizures and vaccinations were subsequently verified via retrospective medical record review. Results on the validation of vaccinations were published previously [8].

Data presented in this paper were collected as part of a public health surveillance activity conducted under the auspices of the FDA Sentinel Initiative. Therefore, collection and analyses of these data did not qualify as human subjects research under the Common Rule and were not subject to IRB review. The study consisted of a secondary analysis of existing health records and obtaining informed consent from the included patients was not required.

2.2. Febrile seizure identification

Potential febrile seizures occurring in the 0–1 or 14–20 days after vaccination were identified in claims-based data using ICD-9 codes for seizures, as part of the larger SCRI described previously. We considered four algorithms ranging from the broadest, which prioritized capture over predictive value, to the most restrictive, which we anticipated would increase the PPV but reduce capture of true cases. We characterized the PPV of each algorithm, and for the more restrictive algorithms, the percent of all confirmed cases that were identified with the algorithm.

In primary algorithm A (Table 1), which was the broadest, potential febrile seizures were identified using ICD-9 codes 780.3 [*convulsions*], 780.31 [*simple febrile convulsions, unspecified*], 780.32 [*complex febrile convulsions*], or 780.39 [*other convulsions*] in the emergency department (ED) or inpatient setting. Of note, we did not include ICD-9 code 780.33 [*post-traumatic convulsions*]. We excluded events with a prior seizure code in any setting occurring in the 42-days prior in order to avoid including events with onset prior to vaccination [4,6]. Codes in the ambulatory setting were also excluded because they often represent follow-up care or management of seizure disorders, rather than acute seizures [5]. All potential febrile seizure events were validated by review of medical records when available.

2.3. Comparison of febrile seizure algorithms

Algorithm A, the broadest algorithm, prioritized capture over predictive value. To inform future studies, we also examined alternative algorithms, including one restricted to more specific codes, which could potentially minimize the number of false positives; on the other hand, the use of overly specific codes could also substantially reduce the number of true cases captured. In studies incorporating medical record review, the best algorithm would capture the vast majority of confirmed cases to maximize statistical power and avoid systematic exclusion of cases; at the same time, a high confirmation rate would be optimal to minimize the number of potential cases to be later ruled out after chart review. In the absence of chart review, the choice of algorithm for the outcome of interest no longer depends on the number of potential cases (both confirmed and not confirmed) that need to be reviewed to yield true cases. However, in case-based studies (e.g., SCRI or self-controlled case series) based on electronic only data, an algorithm that optimizes both capture and predictive value would still be ideal to maximize validity and minimize loss of statistical power.

In addition to evaluating the PPV of the broadest algorithm (algorithm A, which included all seizure codes except those for post-traumatic convulsions), we also evaluated a number of alternative definitions, each a mutually exclusive subset of cases identified by algorithm A. The first of these, algorithm B (Table 1), identified the subset of potential cases with ICD-9 diagnosis code 780.31 or 780.32 (i.e., codes for febrile convulsions). Next, we evaluated the PPVs of algorithms C and D (Table 1), both of which required the absence of ICD-9 diagnosis codes 780.31 or 780.32. In addition, algorithm C required ICD-9 diagnosis code 780.39 [*other seizure*] and one of the following ICD-9 diagnosis codes used to identify medically attended fever on the same day: 780.6 [*fever and other physiologic disturbances of temperature regulation*], 780.61 [*fever presenting with conditions classified elsewhere*], 780.62 [*post-procedural fever*], or 780.63 [*postvaccination fever*]. Algorithm D required ICD9 diagnosis code 780.39 without any of the following

Table 1
Algorithms for febrile seizures based on ICD-9 diagnosis codes in the inpatient and emergency department settings.

Algorithm	Status of inclusion of ICD-9 codes for convulsions in algorithms for febrile seizures			
	780.3 [Convulsions]	780.31 [Simple febrile convulsions]	780.32 [Complex febrile convulsions]	780.39 [Other convulsions]
Algorithm A	Included	Included	Included	Included
Algorithm B	Not included	Included	Included	Not included
Algorithm C	Included if 780.6 or 780.60–780.63[1] present on the same day	Not included	Not included	Included if 780.6 or 780.60–780.63[1] present on the same day
Algorithm D	Included if 780.6 or 780.60–780.63[1] not present on the same day	Not included	Not included	Included if 780.6 or 780.60–780.63[1] not present on the same day

[1] The following codes were used to identify medically attended fever: 780.6 [fever and other physiologic disturbances of temperature regulation], 780.61 [Fever presenting with conditions classified elsewhere], 780.62 [Postprocedural fever], or 780.63 [Postvaccination fever].

ICD-9 diagnosis codes on the same day: 780.6, 780.60, 780.61, 780.62, or 780.63.

2.4. Medical record review

Medical record review was conducted on all potential cases of febrile seizure identified using the primary and broadest definition, algorithm A (ICD-9 diagnosis code for convulsions, with the exception of those specified as post-traumatic). Medical records were no longer pursued if after a minimum of 5 requests (using a combination of letters, emails, faxes, or phone calls), we received no response from the provider. Records were also no longer pursued if (1) the provider declined participation; (2) the provider was reached but the chart could not be found at the provider site (e.g., no record for the date of service of interest existed or the charts had been destroyed or lost); or (3) the provider could not be contacted using the information available to the health plan at the time of chart requests (e.g., provider had since relocated or lost affiliation with the clinic or hospital, had retired, or was deceased). The percentage of unobtainable charts ranged from 10% to 28% for each of the three Data Partners (Table 2).

Case status was determined based on review of redacted full text medical records. Cases were not considered confirmed if the medical record revealed that the visit was due to management of a known seizure or other non-seizure related issue or if the examining physician ruled out a suspected seizure. Each of the remaining potential febrile seizure cases was independently reviewed by two pediatricians blinded to vaccination status. A third pediatrician adjudicator, also blinded, reviewed cases where discrepancies in febrile seizure status were identified. These cases were rediscussed by the three adjudicators until consensus was achieved.

Cases were considered confirmed if documentation in the medical records described a seizure and evidence of fever (i.e., a measured temperature $\geq$ 38C or report of fever within 24 h before or after of a seizure by a caregiver or healthcare provider, a physician's diagnosis of concomitant febrile illness and a seizure, or a physician's diagnosis of a febrile seizure). Potential cases were excluded if they had an underlying metabolic disorder, CNS infection/trauma, or had a history of afebrile seizures [9]. Seizures were excluded if they were described as having focal features, unless they were part of complex febrile seizure (which are defined as lasting more than 15 min and/or having focal features). They were also excluded if documentation was insufficient to confirm the seizure or if the treating physician recorded uncertainty regarding a seizure diagnosis in the medical records.

3. Results

3.1. Characteristics of potential febrile seizures

Table 2 shows the characteristics of the 252 potential febrile seizure cases identified in ICD-9-coded data using primary algorithm A, the broadest algorithm that included all seizure codes except those specified as post-traumatic. The majority of potential cases were less than 2 years of age (71%) and diagnosed in the ED setting (82%). Cases with charts available were more likely to come from Data Partner A and less likely to come from Data Partner B. No differences were found in age at diagnosis or medical care setting between potential cases with and without medical charts available for review.

3.2. Positive predictive value of algorithms for febrile seizure

The majority of potential cases identified by algorithm A, the broadest algorithm that included any ICD9 diagnosis code for seizure except those identified as post-traumatic, had ICD-9 diagnosis code 780.31 [*simple febrile convulsions, unspecified*] or 780.32 [*complex febrile convulsions*] (Table 3; 71%). No potential cases were identified with ICD-9 diagnosis code 780.3 [*convulsions*].

Of the 252 potential febrile seizure cases identified using primary algorithm A (any ICD-9 diagnosis code for seizures, except post-traumatic seizures), 216 (86%) had medical records of seizure-related visits obtained from healthcare providers (Table 3). Of those with medical records available, 152 cases were confirmed, for a PPV of 70% (95% CI 64, 76%). The PPVs were numerically higher in younger children (6–25 months vs. 26–59 months) and in the risk interval; however confidence intervals overlapped (Supplementary Appendix A).

Of the 64 unconfirmed cases, 56 were not confirmed due to the following reasons: seizure without fever documentation (N = 8), possible seizure without adequate evidence to confirm that it occurred (N = 7), seizure determined not to have occurred (N = 19), or were a seizure with a documented absence of fever (N = 22). An additional 8 were not considered confirmed because they were associated with metabolic disorder, CNS inflammation/infection, history of afebrile seizures, or were described as having focal features but were not part of a complex febrile seizure.

When we restricted to ICD-9 codes for simple or complex febrile seizure (algorithm B), we observed a higher PPV (Table 3, PPV 91%, 95% CI 85, 95%), accounting for 140 of the 152 (92%) total confirmed cases identified by the broadest algorithm (algorithm A).

Table 2
Characteristics of potential febrile seizure cases identified in electronic data.

Characteristic	Number potential cases identified N = 252	Number medical records obtained N = 216	Number medical records not obtained N = 36
Data partner[1]			
A	187 (74%)	169 (78%)	18 (50%)
B	53 (21%)	38 (18%)	15 (42%)
C	12 (5%)	9 (4%)	3 (8%)
Age (months)[2]			
6–11	34 (13%)	30 (14%)	4 (11%)
12–23	145 (58%)	124 (57%)	21 (58%)
24–35	41 (16%)	37 (17%)	4 (11%)
36–47	14 (6%)	9 (4%)	5 (14%)
48–59	18 (7%)	16 (7%)	2 (5%)
Setting of diagnosis[3]			
Emergency department	207 (82%)	177 (82%)	30 (83%)
Inpatient	45 (18%)	39 (18%)	6 (17%)

[1] P-value for chi-square = 0.002.
[2] P-value for Fisher's exact test = 0.25.
[3] P-value for Fisher's exact test = 0.91.

Table 3
Positive predictive value of ICD-9 Code definitions for febrile seizures.

Definition based on ICD-9 diagnosis codes identified in the inpatient or ED setting	Number potential cases with medical records available	Number chart-confirmed cases	% of total chart-confirmed cases identified by algorithm	Positive predictive value (95% CI)
Algorithm A: 780.3 [*convulsions*], 780.31 [*simple febrile convulsions, unspecified*], 780.32 [*complex febrile convulsions*], or 780.39 [*other convulsions*][1,2]	216	152	100%	70% (64, 76%)
Algorithm B: 780.31 or 780.32	154	140	92%	91% (85, 95%)
Algorithm C: In the absence of 780.31 or 780.32, meets the following on the same day:(i) 780.39 [*other seizure*] and (ii) 780.6 [*fever and other physiologic disturbances of temperature regulation*], 780.61 [*fever presenting with conditions classified elsewhere*], 780.62 [*postprocedural fever*], or 780.63 [*postvaccination fever]*	5	1	0.7%	20% (1, 72%)
Algorithm D: In the absence of 780.31 or 780.32, meets the following on the same day: (i) 780.39 without (ii) 780.6, 780.60, 780.61, 780.62, or 780.63	57	11	7%	19% (10, 32%)

[1] No potential cases were identified with ICD-9 code 780.3.
[2] Two potential cases were identified with ICD-9 code 780.32 while 152 potential cases were identified with ICD-9 code 780.31 and 62 potential cases were identified with ICD-9 code 780.39.

Only 1 of 5 cases identified by algorithm C (codes for seizure or other seizure and for medically attended fever, without codes for febrile seizure on the same day) was confirmed (PPV 20%, 95% CI 1, 72%). Of the 4 potential cases identified by algorithm C that were not subsequently confirmed, 1 was caused by CNS infection/inflammation, 1 had a history of afebrile seizures, 1 did not have any evidence of a seizure at the visit, and 1 had insufficient documentation to determine whether a seizure occurred. Likewise, only 11 of 57 cases identified by algorithm D (codes for seizure or other seizure, without codes for medically attended fever or febrile seizure on the same day) were confirmed (PPV 19%, 95% CI 10, 32%). Of the 46 potential cases identified with algorithm D and not subsequently confirmed, the most common reasons for exclusion were afebrile seizure (n = 22), no evidence of a seizure at the visit (n = 10), and insufficient documentation to determine whether a seizure occurred (n = 5).

4. Discussion

In this study, we validated an ICD-9 based algorithm for febrile seizure that included post-immunization seizures and compared its positive predictive value (PPV) to alternative algorithms that considered seizure in the context of fever. We found that the PPV was moderate (PPV 70%) when including all seizure codes except post-traumatic seizures. However, when we restricted to ICD-9 codes for simple or complex febrile seizure (780.31 or 780.32), the PPV increased substantially to 91%; these codes map to ICD-10 codes R56.00 (simple febrile convulsions) and R56.01 (complex febrile convulsions). In contrast, the PPV was very low when seizures were only identified with codes for seizure or other seizure, regardless if codes for fever were required (PPV 20%) or not (PPV 19%).

A number of studies have validated the use of ICD-9 codes for identifying post-immunization seizures [4–6,10]. Our PPV estimate of 70%, based on all seizure codes except post-traumatic seizures is nearly equivalent to that of a similar study conducted in the Vaccine Safety Datalink (VSD); the study included 61 potential cases and found a PPV of 77% when using the same codes in the ED and inpatient settings following influenza vaccinations in the same age group [6]. The VSD study did not examine the PPV of ICD-9 codes specific to febrile seizure. To our knowledge, an important contribution of our study was the evaluation of algorithms that incorporate fever within the context of seizure. Our chart confirmation rate when restricting to codes specific for febrile seizure (91%) is similarly high when compared to that of a study conducted in France (95%) [11]. That study, which used ICD-10 codes from the administrative databases of ten hospitals, also concurred with our finding that restricting to febrile seizure codes led to a higher confirmation rate when compared to using a broader algorithm that included less specific convulsion codes. Importantly, we found that restricting to codes specific to febrile seizure does not result in a large decrease in the number of confirmed cases from that identified by the broadest algorithm.

Our study had several strengths. First, we included data from several large national commercial health plans that covered medical care in community settings across the U.S. This likely enhances the generalizability of our findings to other US commercial health plans and claims-based data systems. Second, we were able to obtain the records of the majority of cases (86%). Third, each case was adjudicated independently by two pediatricians blinded to vaccination timing, and by a third in instances of disagreement, therefore minimizing the likelihood of misclassification of cases.

The study also had some limitations. First, we were unable to obtain medical records for a portion of cases (14%). If confirmation status was related to whether charts were available, we could have misestimated the PPV of our case finding algorithms. Second, because we only chart reviewed potential cases identified by the algorithm, we are unable to evaluate the sensitivity or negative predictive value of the algorithm. However, given the frightening nature of febrile seizures for parents and other caregivers, it is likely that the vast majority of febrile seizures would be medically attended and therefore captured in the claims database. While it is possible that some febrile seizure events might not be captured by the algorithm (i.e., captured by other codes), we anticipate that any such misclassification would be non-differential with respect to exposure status, which would bias relative risk estimates in safety evaluations towards the null. Third, this study analyzed data from the ICD-9 era, and it is unclear whether the validity of electronic algorithms will remain the same in the ICD-10 era. We anticipate that these results will remain relevant because there is a near equivalence between the two coding systems in coding for seizures, as convulsions codes in the ICD-10 include R56.00 [*simple febrile* convulsions], R56.01 [*complex febrile convulsions]*, R56.1 [*post-traumatic convulsions*], and R56.9 [*unspecified convulsions*]. However, further studies are needed to confirm the validity of ICD-10 based algorithms for febrile seizure. Fourth, because the study was limited to post-vaccination events, the PPV of the febrile seizure algorithms may not be generalizable to all febrile seizures occurring in children ages 6–59 months, including those potentially in association with other exposures.

Our results indicate that ICD-9 diagnosis codes in the inpatient and emergency department settings have high predictive value for identifying febrile seizures within the Sentinel Distributed Database. While the PPV of the algorithm based on any ICD-9 diagnosis code for seizure is moderate, the algorithm limited to febrile seizure codes (780.31 or 780.32) has a high PPV (>90%) and captures the vast majority of confirmed cases identified by the broadest algorithm, suggesting that the latter algorithm may be preferred for ICD-9 based studies; further an algorithm limited to ICD-10 codes that map to these codes (R56.00 or R56.01) may be preferred for more recent studies.

Declaration of Competing Interest

A Kawai is currently an employee of RTI Health Solutions, a business unit of Research Triangle Institute, which conducts work for government, public, and private organizations, including pharmaceutical companies. The work described in this manuscript was completed while A. Kawai was an employee of the Harvard Pilgrim Health Care Institute before she became an employee of RTI Health Solutions.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.05.042.

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