Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology

CBER Surveillance Program
Biologics Effectiveness and Safety Initiative

A Structured Review of Electronic Coding Algorithms for Febrile Seizure Using Administrative Claims and Electronic Health Records

Final Report

May 24, 2021

Prepared by: Patrick Saunders-Hastings[1], Sze Wing Heong[1], Timothy Burrell[2], Jeff Beers[3], Judith Cope[4], Deborah Thompson[4], Cindy Ke Zhou[4]

Author Affiliations:

[1] Gevity Consulting Inc., Ottawa, Ontario, Canada
[2] IBM Watson Health, Cambridge, Massachusetts, United States of America
[3] IBM Global Business Services, Issaquah, Washington, United States of America

[4] Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, United States of America

This page is intentionally left blank

Table of Contents

Table of Tables iv
Table of Figures iv
List of Acronyms v
A Summary 6
B Background 7
C Literature Review 8
C1 Methods 8
C2 Results 9
2.a Claims-based Algorithms With Validation 10
2.b Medical Records-based Algorithms With Validation 10
2.c Algorithm Application Without Validation 11
D Febrile Seizure Clinical Case Definition 11
E Febrile Seizure Coding Algorithm 12
F Assumptions and Decisions 13
G Algorithm Characterization 14
G1 Methods 14
G2 Results 15
H Discussion and Conclusion 25
I Acknowledgements 26
J References 27
Appendix A. Literature Review Extracted Results 28
Appendix B. Counts of Patients with Specific Codes Proposed for the Algorithm 32
Appendix C. Codes Excluded from Proposed Algorithm 35

Table of Tables

Table 1. Data elements records in the extraction spreadsheet. 9

Table 2. Inclusion and exclusion criteria for febrile seizure case adjudication. 12

Table 3. Febrile seizure algorithm. 13

Table 4. Overall counts of patients with febrile seizure (Option 1) by code set and year. 16

Table 5. Overall counts of patients (0–5 years of age) with febrile seizure (Option 1) by code set and year. 16

Table 6. Counts and proportions of patients with at least on ICD-9-CM or ICD-10-CM diagnosis for febrile seizure (Option 1),* stratified by time of year (2014–2018). 23

Table 7. Counts and proportions of patients 1–5 years of age with at least on ICD-9-CM or ICD-10-CM diagnosis for febrile seizure (Option 1),* stratified by time of year (2014–2018). 24

Table of Figures

Figure 1. Proportion of patients with febrile seizure (Option 1), by year (2014–2018). 17

Figure 2. Patients with at least one ICD-9-CM diagnosis code for febrile seizure (Option 1), January 1, 2014–September 30, 2015, stratified by age group. 18

Figure 3. Patients with at least one ICD-10-CM diagnosis code for febrile seizure (Option 1), October 1, 2015–December 31, 2018, stratified by age group. 19

Figure 4. Patients with at least one ICD-9-CM or ICD-10-CM diagnosis code for febrile seizure (Option 1), January 1, 2014–December 31, 2018, stratified by age group. 20

Figure 5. Proportion of patients with at least one ICD-9-CM or ICD-10-CM diagnosis code for febrile seizure (Option 1) per 1,000 population by age and gender, 1–85+ years (top) and 1–5 years (bottom) (January 1, 2014–December 31, 2018).* 21

Figure 6. Proportion of patients with at least one ICD-9-CM or ICD-10-CM diagnosis code for febrile seizure (Option 1) per 1,000 population by age and calendar year, 1–85+ years (top) and 1–5 years (bottom)(January 1, 2014–December 31, 2018).* 22

Figure 7. Proportion of patients with at least one ICD-9-CM or ICD-10-CM diagnosis code for febrile seizure (Option 1), stratified by time of year (2014–2018). 23

Figure 8. Proportion of patients 1–5 years of age with at least one ICD-9-CM or ICD-10-CM diagnosis code for febrile seizure (Option 1), stratified by time of year (2014–2018). 24

List of Acronyms

AFHSB	United States Armed Forces Health Surveillance Branch
AHRQ	Agency for Healthcare Research and Quality
BEST	Biologics Effectiveness and Safety
CBER	Center for Biologics Evaluation and Research
CMS	Centers for Medicare and Medicaid Services
CNS	Central Nervous System
CI	Confidence Interval
CPT	Current Procedural Terminology
EHR	Electronic Health Record
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GEM	General Equivalence Mapping
HCPCS	Healthcare Common Procedure Coding System
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
LOINC	Logical Observation Identifiers Names and Codes
NDC	National Drug Code
NPV	Negative Predictive Value
PICO	Population, Intervention, Comparator, Outcome
PPV	Positive Predictive Value
PRISM	Post-Licensure Rapid Immunization Safety Monitoring
SD	Standard Deviation
SME	Subject Matter Expert
U.S.	United States

A Summary

The United States (U.S.) Food and Drug Administration (FDA) Biologics Effectiveness and Safety (BEST) Initiative conducted a structured literature review (through August 16, 2020) to identify validated coding algorithms for ascertaining cases of febrile seizure in large administrative healthcare databases. The studies selected for this targeted review used billing codes in claims, electronic health record (EHR), or electronic medical record (EMR) databases to derive electronic coding algorithms.

Seven studies were identified as being of relevance, of which five were U.S.-based validation studies that reported performance measures for proposed algorithms (e.g., positive predictive value [PPV], negative predictive value [NPV], sensitivity and/or specificity). However, only one U.S.-based validation study focused specifically on febrile seizures, while others focused on seizures more generally. Kawai and colleagues validated four algorithms to identify potential cases of post-vaccination febrile seizure in children 6–59 months of age.[1] Patients' medical records were reviewed to confirm cases and four algorithms were validated.

- **Algorithm A:** ICD-9-CM codes 780.31 (febrile convulsions [simple], unspecified), 780.32 (complex febrile convulsions), and 780.39 (other convulsions). Authors reported a PPV of 70% (95% confidence interval [CI] 64–76%).
- **Algorithm B:** ICD-9-CM codes 780.31 and 780.32. Authors reported a PPV of 91% (95% CI 85–95%).
- **Algorithm C**: ICD-9-CM codes 780.39 with 780.60 (fever, unspecified), 780.61 (fever presenting with conditions classified elsewhere), 780.62 (postprocedural fever), or 780.63 (postvaccination fever) on the same day. Authors reported a PPV of 20% (95% CI 1–72%).
- **Algorithm D**: ICD-9-CM codes 780.39 without 780.60 (fever, unspecified), 780.61 (fever presenting with conditions classified elsewhere), 780.62 (postprocedural fever), or 780.63 (postvaccination fever) on the same day. PPV of 19% (95% CI 10–32%).

The findings from this literature review were leveraged to develop a code-based algorithm for identifying cases of febrile seizure. Codes were mapped from ICD-9-CM to International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) via forward–backward mapping, using General Equivalence Mappings (GEMs) for reference.[i] The draft algorithm was then reviewed by clinical subject matter experts (SMEs) from IBM (TB, JB), FDA Center for Biologics Evaluation and Research (CBER [JC, DT]), and Acumen.

The algorithm proposes two options to identify potential cases of febrile seizure. Option 1 is more specific, while option 2 is more sensitive and includes additional codes. The algorithm can be tailored based on specific research questions.

- **Option 1** (more specific): ≥1 diagnosis code for febrile seizure (ICD-9-CM 780.31, 780.32; ICD-10-CM R56.00 [simple febrile convulsions], R56.01 [complex febrile convulsions])
- **Option 2** (more sensitive): Option 1 **OR**
  ≥1 diagnosis code for convulsion (ICD-9-CM 780.39; ICD-10-CM G40.89 [other seizures], R56.9 [unspecified convulsions]) **AND** ≥1 diagnosis code for fever (ICD-9-CM 780.60, 780.61, 780.62, 780.63; ICD-10-CM R50.81 [fever presenting with conditions classified elsewhere], R50.82 [postprocedural fever], R50.83 [postvaccination fever], R50.84 [fever presenting with conditions classified elsewhere], R50.9 [fever, unspecified]) **on the same day** among patients who cannot be identified by Option 1.

Note: Option 2 codes for convulsion and fever should be applied among a cohort of individuals that are not captured by codes in Option 1.

[i] Additional information about GEMs and the methodology for forward and backward mapping can be found at Centers for Medicaid and Medicare Services. (2017). 2018 ICD-10-CM and GEMs. Available at https://www.cms.gov/Medicare/Coding/ICD10/2018-ICD-10-CM-and-GEMs. Researchers used the following website to map ICD-9-CM codes to ICD-10-CM: https://www.icd10data.com.

As an initial step in assessing the feasibility of using the algorithm to identify febrile seizure, the algorithm was applied in the IBM MarketScan® Research Databases (Commercial and Medicare Supplemental), a large collection of commercially insured individuals in the U.S. Statistics describing the frequency and proportions of febrile seizure codes included in the algorithm for both options were generated.

B Background

Among other responsibilities, the U.S. FDA is mandated to protect public health by ensuring the safety and efficacy of drugs, biologics and medical devices.[ii] In support of this charge, the FDA Center for Biologics Evaluation and Research (CBER) has a mission to conduct policy and regulatory reviews of biologics and related products, including blood products, vaccines, allergenics, tissues, and cellular and gene therapies. CBER assesses the risks and benefits of new biologic products, as well as previously approved products that have been proposed for new indications. The CBER process emphasizes the pursuit of the maximum public benefit with the minimum risk to public safety associated with each biologic product. The BEST Initiative is a program initiated by CBER with the objective of assessing the safety and effectiveness of biologic products using large datasets of administrative healthcare data.

Febrile seizures affect 2–5% of children in the U.S. by the time they are five years old, leading to approximately 500,000 cases per year in the U.S. alone.[2] They are characterized as convulsions in a child without a history of seizures that are caused by a fever or increase in body temperature, often from an infection (e.g., colds, influenza, or ear infection) and are not associated with infections of the central nervous system (CNS) or acute symptomatic seizures (i.e., seizures occurring at the time of a systemic or brain insult) .[3] Symptoms can include loss of consciousness, rigidity or twitching in certain body parts, shaking of limbs, vomiting, or urination.[3] There are two types of febrile seizures, with simple febrile seizures accounting for 70–75% of cases and complex febrile seizures accounting for 9–35%.[3] Simple febrile seizures are defined as seizures that last under 10 minutes, include generalized features (e.g., twitching limbs or convulsions all over body), spontaneously resolve and do not recur within 24 hours. Complex febrile seizures last longer than 10 minutes, include focal features (e.g., seizure activity affecting only the fingers, or larger muscles in the arms and legs), and recur within 24 hours.[3] Although no deaths related to febrile seizures have been reported, they can result in self-injury, injury from surroundings, fluid aspiration, or repeat seizures and can be a frightening experience for the child and/or parents witnessing the event.[3]

Children aged 6–26 months are at highest risk for having a febrile seizure.[3] Risk factors for the first febrile seizure include family history, viral infection, difficult birth, neonatal asphyxia, and developmental delay.[3,4] Another reported risk factor is receipt of vaccinations.[3] Prior studies have found that some vaccines — including the measles, mumps and rubella vaccine — increase the risk for febrile seizure.[3]

The objective of this review was to assess and understand the validity of electronic coding algorithms using billing codes for identifying febrile seizure from administrative claims and EHRs. These coding algorithms could be drawn from a variety of standard code sets, including the International Classification of Diseases (ICD), the Healthcare Common Procedure Coding System (HCPCS), Current Procedural Terminology (CPT®), National Drug Codes (NDCs), and Logical Observation Identifiers Names and Codes (LOINC).

A structured literature review of coding algorithms for identifying potential cases of febrile seizure using administrative claims and EHRs was conducted, leveraging findings from U.S. and international studies to inform algorithm development. The focus of the review was on algorithms derived from administrative claims data (i.e., claims-based), while algorithms derived from EHRs that used standard billing code sets (i.e., EHR-based) were also considered. The draft algorithm was then subject to review by clinical SMEs from IBM (TB, JB), FDA CBER (JC, DT), and Acumen, and testing in the IBM MarketScan® Research Databases (Commercial and Medicare Supplemental), a large collection of U.S. administrative insurance

[ii] U.S. Food and Drug Administration. What We Do. March 28, 2018. https://www.fda.gov/aboutfda/whatwedo/

claims data accessed via the Treatment Pathways online analytic platform. **Section C** summarizes the literature review methodology and findings; **Section D** provides a clinical case definition for febrile seizure, which could be of value in further assessing the performance of the proposed algorithm via chart review in validation studies; **Sections E** and **F** present the algorithm and its associated assumptions and decisions, respectively; **Section G** presents the results of the initial application of the algorithm to characterize the population with febrile seizure in a claims database; and **Section H** provides discussion and concluding thoughts.

C Literature Review

C1 Methods

The workgroup developed a literature review search strategy based upon a Population, Intervention, Comparator, and Outcome (PICO) framework. The PICO framework for this review can be summarized as follows:

- **Population:** *any population group (human)*
- **Intervention:** *any intervention or no intervention*
- **Comparator:** *any comparator, placebo*
- **Outcome:** *febrile seizure*

The setting for eligible studies was any clinically observable environment that led an individual to seek care.

The review process began with conducting comprehensive searches of existing publications available in the CBER[iii] and Center for Drug Evaluation and Research Sentinel[iv] databases, however no articles were retrieved from either. Next, a structured review of the peer-reviewed literature was conducted, using PubMed, Medline, and Google Scholar to identify relevant resources. Only English language publications were selected for review. No restriction was imposed on publication date for the PubMed search (inception to August 16, 2020). The Google Scholar search was limited to January 2000 through August 16, 2020. The PubMed search strategy, which is not case-sensitive, is summarized below:

- **Search 1: "**febrile seizure" AND "icd" – **retrieved 11 results**
- **Search 2:** "febrile seizure" AND "validat*****" – **retrieved 70 results**
- **Search 3:** "febrile seizure" AND "PPV" – **retrieved 3 results**
- **Search 4:** "febrile seizure" AND "claim*****" – **retrieved 19 results**

Targeted and *ad hoc* searches of the gray literature were conducted, including clinical guidelines and reports from organizations such as the United States Armed Forces Health Surveillance Branch (AFHSB) and the Agency for Healthcare Research and Quality (AHRQ). A snowballing technique was also applied, wherein the bibliographies of relevant studies were scanned for additional publications. Abstract review was subsequently conducted for these publications. No restriction was imposed on publication date. Since this was not a systematic review, authors did not track the total number of abstracts screened after de-duplication.

All abstracts were reviewed, and 10 articles were reviewed in full text. Of these, seven were retained for extraction and informed algorithm development. A Microsoft® Excel spreadsheet was developed to extract relevant data. The data elements collected are provided in **Table 1**. A relevance ranking was assigned based on the judgement of the reviewer and the available information on study location ("Country"), the

[iii] U.S. Food and Drug Administration. Innovation and Regulatory Science. Accessed on July 10, 2020. https://www.fda.gov/vaccines-blood-biologics/science-research-biologics/innovation-and-regulatory-science
[iv] Sentinel. Publications and Presentations. https://www.sentinelinitiative.org/communications/publications

algorithm specifications ("Algorithm"), and the measures of validity and diagnostic accuracy (e.g., PPV and NPV). Relevance rankings were assigned based on the following criteria:

- ***Ranking 1:*** U.S. claims- or EHR-based validation study (i.e., reporting measures of validity and diagnostic accuracy);
- ***Ranking 2:*** U.S. study that reported a claims- or EHR-based coding algorithm but no independent validation OR a non-U.S. validation study;
- ***Ranking 3:*** Non-U.S. study that reported a claims- or EHR-based coding algorithm but no independent validation

Table 1. Data elements records in the extraction spreadsheet.

Data Element
Author
Publication Year
Article Relevance (Ranking 1-3)
Full Citation
Country of Study
Data Source
Years Included
Population Eligibility Criteria
Validation Method
Disease Definition
Algorithm Incidence Rules
ICD-9/ICD-9-CM Codes
ICD-10/ICD-10-CM Codes
Other Codes
PPV % (95% Confidence Interval [CI])
NPV % (95% CI)
Other Performance Measures
Comments

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; PPV, Positive predictive value; NPV, Negative predictive value; 95% CI, 95% confidence interval

C2 Results

Following title and abstract screening, full-text review, and data extraction, a total of seven publications (six from the U.S., one from France) were identified as being of greater relevance for identifying febrile seizures using administrative healthcare datasets (additional information in **Appendix A**).[1,5-10] No studies reporting the use of ICD-10-CM codes were found. Each publication reported either measures of diagnostic accuracy associated with claims-based algorithms (i.e., febrile seizure codes derived from administrative insurance claims databases) or EHR-based algorithms (i.e., febrile seizure codes derived from admission or discharge medical records). An additional publication identified approaches for identifying cases of febrile seizure using administrative claims data but did not validate their approach.

Of the seven papers, six were subject to validation and included measures of performance.[1,5,6,8-10] Measures of diagnostic accuracy varied across these six studies but were generally strong.[1,5,6,8-10] We have summarized the literature below by the data source that the coding algorithms was derived from

(i.e., insurance claims or EHRs), validation with medical charts (i.e., yes or no), and the location of the study (i.e., U.S. or international).

2.a Claims-based Algorithms With Validation

In the U.S., Kawai and colleagues studied febrile seizures among children 6–59 months of age who enrolled in an insurance health plan and had received an inactivated influenza vaccine, diphtheria tetanus acellular pertussis-containing vaccines, or 13-valent pneumococcal conjugate vaccine.[1] The authors developed four electronic coding algorithms to identify potential febrile seizures in the risk window of 0–1 or 14–20 days post-vaccination using ICD-9-CM codes in the inpatient and emergency department settings from claims within the FDA Post-Licensure Rapid Immunization Safety Monitoring (PRISM) Program, followed with validation via medical records review for confirmed cases. No information on diagnosis position was reported.

- **Algorithm A** included ICD-9-CM codes 780.31 (febrile convulsions [simple], unspecified), 780.32 (complex febrile convulsions), and 780.39 (other convulsions)
- **Algorithm B** included ICD-9-CM codes 780.31 and 780.32
- **Algorithm C** included ICD-9-CM codes 780.39 with 780.60 (fever, unspecified), 780.61 (fever presenting with conditions classified elsewhere), 780.62 (postprocedural fever), or 780.63 (postvaccination fever) on the same day.
- **Algorithm D** included ICD-9-CM codes 780.39 without 780.60 (fever, unspecified), 780.61 (fever presenting with conditions classified elsewhere), 780.62 (postprocedural fever), or 780.63 (postvaccination fever) on the same day.[1]

Among the 216 potential febrile seizure cases identified with one or more seizure codes, 152 were chart-confirmed. Authors reported that Algorithm A had a PPV of 70% (95% confidence interval [CI] 64–76%), Algorithm B had a PPV of 91% (95% CI 85–95%), Algorithm C had a PPV of 20% (95% CI 1–72%) and Algorithm D had a PPV of 19% (95% CI 10–32%).[1] Based on the performance of the four different algorithms, the authors concluded that having a narrower definition comprised only of codes for febrile seizures resulted in the best PPV in comparison to broader algorithms that include paired fever and convulsion codes.[1]

Another U.S. study by Thyagarajan and colleagues sought to validate an algorithm for seizure events in children (85.9% were less than seven years in age) and adults who received an influenza vaccine using data from a large administrative claims database.[10] Potential seizure events were identified using ICD-9-CM 345.xx (epilepsy and recurrent seizures) or 780.3x (convulsions) reported within 29 days of vaccine receipt, with no codes reported in the 42 days prior to the potential seizure. The PPV in the emergency department setting (93.9% [95% CI 86.3–98.0%]) was much higher than that in the inpatient setting (38.3% [95% CI 28.5–48.9%]).

2.b Medical Records-based Algorithms With Validation

Three U.S. studies used Vaccine Safety Datalink to validate their algorithms.[5,6,9] First, Klein and colleagues validated an algorithm using billing codes from EHRs to identify potential seizure events (including febrile seizures) in 712,507 children aged 12–23 months, who had received the measles-mumps-rubella-varicella vaccine.[5] ICD-9-CM 345.xx (epilepsy and recurrent seizures) or 780.3x (convulsions) were used to identify potential seizure events in an inpatient or emergency department setting occurring during a 0-42 day risk window post-vaccination.[5] Fever events in outpatient settings were identified using ICD-9-CM 780.6x (fever and other physiologic disturbances of temperature regulation).[5] The authors reported that 87% of the potential cases were febrile seizures based on chart review.[5]

Second, Tse and colleagues identified seizures (including febrile seizures) from the emergency department or inpatient setting among 206,174 patients aged 6–59 months, who had received a trivalent inactivated influenza vaccine in the U.S..[6] The authors used ICD-9-CM 780.31, 780.32, and 780.39 to identify potential seizures and only considered cases that were the first seizure event in the past six

months. Of the 32 and 31 potential cases identified in the risk (0-1 days post-vaccination) and control windows (14–15 days post-vaccination), respectively, 25 (83%) and 22 (71%) were confirmed as febrile seizure following chart review.[6]

Third, Shui and colleagues sought to identify potential seizures with a broader set of codes in children six weeks to 23 months of age within a 0–30-day risk window following pneumococcal vaccination. The authors used ICD-9-CM codes 333.2 (myoclonus), 345.xx, 780.3x, and 779.90 (convulsions in newborn).[9] Among 859 medical charts reviewed, 483 (56%) were classified as having no evidence of seizure; 314 (37%) were classified as having a definite[v] seizure event; 62 (7%) were classified as having a probable[vi] seizure event. PPV ranged widely across healthcare settings, from 2% in the outpatient setting to 97% in the emergency department.

In a French validation study using administrative databases of 10 hospitals, Quantin and colleagues sought to validate the following four algorithms of ICD-10 codes to identify potential cases of febrile convulsions among 695 children aged one month to three years:[8]

- **Algorithm 1** used R56.0 (febrile convulsions) or R56.8 (other and unspecified convulsions)[vii] in any diagnosis position. Authors reported a PPV of 80.1% (95% CI 77.8–83.7%) and sensitivity of 98.5% (95% CI 96.6–99.9%).
- **Algorithm 2** only used R56.0 (febrile convulsions) as the principal diagnosis. The authors reported a PPV of 95.0% (95% CI 93.1–96.9%) and sensitivity of 89.1% (95% CI 83.8–94.3%).
- **Algorithm 3** required R56.0 as the principal diagnosis with admission to an emergency department. The authors reported a PPV of 96.3% (95% CI 94.7–98.0%) and sensitivity of 86.9% (95% CI 81.2–92.5%).
- **Algorithm 4** required R56.0 as the principal diagnosis with admission to an emergency department and a neurological investigation. The authors reported a PPV of 98.3% (95% CI 96.6–100.0%) and sensitivity of 47.5% (95% CI 39.1–55.8%).

The authors concluded that Algorithm 2 was the preferred choice as it was achieved the best balance between PPV and sensitivity.[8]

2.c Algorithm Application Without Validation

Baker and colleagues used electronic coding algorithms in the U.S.-based PRISM claims data to identify febrile seizure cases following exposure to inactivated influenza vaccines or 13-valent pneumococcal conjugate vaccines.[7] A total of 735,525 patients included in the study were aged 6–23 months, received either vaccines, and were enrolled in an insurance health plan with medical coverage for at least 180 days before and 20 days after vaccination.[7] Patients were excluded if they had another seizure code within 42 days of the febrile seizure code in any settings.[7] The risk and control windows were 0–1 days and 14–20 days post-vaccination, respectively. The authors used two algorithms to identify potential cases of febrile seizures in the emergency department or inpatient setting.[7] The primary (and more specific) algorithm included ICD-9-CM 780.31 and 780.32, while their secondary algorithm included ICD-9-CM 780.31, 780.32 and 780.39.[7] The primary and secondary algorithms were based on the previous study by Kawai and colleagues summarized in **Section C2.a**.[7]

D Febrile Seizure Clinical Case Definition

Febrile seizure refers to the co-occurrence (within 24 hours) of a seizure and fever (≥38°C) among individuals <60 months of age. Possible exclusion criteria include metabolic disorders, CNS infection/trauma, or a history of afebrile seizures (i.e., seizures unrelated to fever). Convulsions generally last a minute or less but can last up to 15 minutes, and rarely recur within 24 hours.

[v] Definite seizures included any clinician diagnoses of seizure.
[vi] Probable seizures included those in which the clinician could neither exclude nor confirm a seizure.
[vii] This code translates approximately to ICD-10-CM R56.9 (unspecified convulsions).

As part of the FDA Sentinel Initiative, Kawai and colleagues used medical record review in order to validate their algorithms and reported case adjudication criteria (**Table 2**) that could be used in future validation studies using ICD-9-CM and/or ICD-10-CM codes.[1]

Table 2. Inclusion and exclusion criteria for febrile seizure case adjudication.

Inclusion Criteria	Exclusion Criteria
Seizure AND evidence of a fever in medical record which can include: - Temperature of 38°C or above or reported fever within 24 hours before or after a seizure OR - Physician diagnosis of concomitant febrile illness and seizure OR - Physician diagnosis of febrile seizure	- Visits due to known seizure, non-seizure related issue, or seizure that has been ruled out - Cases with underlying metabolic disorder - Cases with CNS infection/trauma - Cases with history of afebrile seizures - Seizures with focal features that are not associated with a complex febrile seizure - Insufficient documentation - Uncertain seizure diagnosis by attending physician

Abbreviation: CNS, Central Nervous System

E Febrile Seizure Coding Algorithm

The aim of this review was to develop an algorithm to identify cases of febrile seizure that could be of potential interest following exposure to a biologic product. To form a comprehensive list of febrile seizure codes for clinical consideration, all ICD-9-CM and ICD-10 codes for febrile seizures, convulsions, and fever were extracted from the seven articles identified in the literature review (**Appendix A**). To expand the draft code list and reflect current coding practice, ICD-10-CM diagnosis codes were generated from ICD-9-CM codes using forward-backward mapping via the Centers for Medicare and Medicaid Services (CMS) GEMs files. The expanded draft code list, which included ICD-9-CM and ICD-10-CM codes, was subsequently reviewed by clinical SMEs from IBM (TB, JB), FDA CBER (JC, DT), and Acumen. Specific decisions and assumptions related to construction of the algorithm are summarized in **Section F**. Overall, the clinical SMEs recommended the inclusion of additional codes or exclusion of codes from the expanded draft code list based on clinical relevance and optimizing the balance between specificity and sensitivity. A list of excluded codes is provided in **Appendix C**. These codes were ultimately determined by the clinical SMEs to be too general and could potentially increase the risk of misclassification. As such, while they were not applied as exclusion criteria, the codes in **Appendix C** were left out of the algorithm options to identify cases of febrile seizure.

The proposed algorithm is presented in **Table 3** and includes the diagnosis codes for febrile seizure (Inclusion Category 1) as well as codes combining convulsions and fever (Inclusion Category 2). The algorithm and exclusions proposed in **Table 3** and **Appendix C**, respectively, are consistent with approaches identified in the peer-reviewed literature. This algorithm may need to be adjusted or tailored for specific research questions that arise in the future. Annual counts of patients with individual diagnosis codes are provided in **Appendix B**.

Briefly, the proposed algorithm can be summarized as follows:

INCLUDE: ANY (“either–or” logic) of the codes listed below, regardless of health care setting or coding position (only one code required).

Option 1: ≥1 diagnosis code for febrile seizure (Inclusion Category 1: ICD-9-CM 780.31, 780.32; ICD-10-CM R56.00, R56.01)

Option 2: Option 1 **OR**

≥1 diagnosis code for convulsion (Inclusion Category 2: ICD-9-CM 780.39; ICD-10-CM G40.89, R56.9) **AND** ≥1 diagnosis code for fever (Inclusion Category 2. ICD-9-CM

780.60, 780.61, 780.62, 780.63; ICD-10-CM R50.81, R50.82, R50.83, R50.84, R50.9) **on the same day** among patients who cannot be identified by Option 1**.**

Note: If applying both inclusion categories, Inclusion Category 2 should be applied among a cohort of individuals that are not captured by Inclusion Category 1 for that event (i.e., Inclusion Category 2 should EXCLUDE febrile seizure diagnosis codes).

Table 3. Febrile seizure algorithm.

Code	Description	Code Category	Code Type	Inclusion Category
780.31	Febrile convulsions (simple), unspecified	DX	9	1
780.32	Complex febrile convulsions	DX	9	1
R56.00	Simple febrile convulsions	DX	10	1
R56.01	Complex febrile convulsions	DX	10	1
780.39	Other convulsions	DX	9	2
780.60	Fever, unspecified	DX	9	2
780.61	Fever presenting with conditions classified elsewhere	DX	9	2
780.62	Postprocedural fever	DX	9	2
780.63	Postvaccination fever	DX	9	2
G40.89	Other seizures	DX	10	2
R50.81	Fever presenting with conditions classified elsewhere	DX	10	2
R50.82	Postprocedural fever	DX	10	2
R50.83	Postvaccination fever	DX	10	2
R50.84	Fever presenting with conditions classified elsewhere	DX	10	2
R50.9	Fever, unspecified	DX	10	2
R56.9	Unspecified convulsions	DX	10	2

Abbreviation: DX, ICD-CM diagnosis.

F Assumptions and Decisions

The algorithm presented in **Section E** was reviewed internally as well as with CBER stakeholders and partners. Decisions and assumptions related to algorithm construction are summarized below. Some of these assumptions may be adjusted for future research questions.

- As informed by approaches in the published literature and on the basis of clinical consultation, it was decided that methods for diagnosing and treating febrile seizure — as would be reflected in procedural and prescription coding standards — were too variable and general to be included in the code-based definition. The proposed algorithm has therefore been restricted to ICD diagnosis codes.
- The limited information identified in the literature suggests that PPV is higher and sensitivity lower for algorithms with a coding position restriction (i.e., principal position codes only).[8] Queries presented in **Section G** did not restrict based on coding position, out of concern that queries based solely on primary-position codes could exclude possible febrile seizure cases. Users may adjust this approach to include primary, secondary or unspecified position codes. Such specification is likely better done on a study basis, when a specific research question has been formulated.
- Algorithms identified in the literature applied different restrictions on code lists, settings, and risk windows used to determine the association of febrile seizure with a particular exposure. An inclusive approach to code list development has been taken here, while further tailoring and restriction of settings and risk windows are likely better determined at the study planning stage.

- The PPV of seizure algorithms varied widely across healthcare settings, with lower performance in the outpatient setting. As such, users may consider restricting cases to inpatient and emergency department settings and excluding those reported in the outpatient setting.
- Febrile seizure generally occurs in those six months to five years of age. Users may wish to limit queries to a specified age range, especially if applying Inclusion Category 2 (as outlined in **Table 3**).
- To define an incident occurrence, consideration could be given to including a "washout period" (to be defined depending on the study question), wherein individuals would be excluded from the study if they had a febrile seizure event within a certain time period (e.g., six months) prior to the exposure of interest.
- Dravet syndrome (ICD-9-CM 345.1/ICD-10-CM G40.83), may be associated with febrile seizures, but it is a rare genetic condition which affects those under one year old with complex seizures, myoclonus, and encephalopathy. It was considered outside of scope and were excluded from the algorithm.
- Codes for epilepsy were considered distinct from convulsions related to febrile seizure and were excluded from the algorithm.
- Codes for convulsions among newborns (ICD-9-CM 779.0; ICD-10-CM P90) were excluded from the algorithm. The newborn period extends to 28 days, while febrile seizure occurs in infancy or childhood usually at >6 months to <5 years of age. Neonates with seizures most often have a neurological etiology, encephalopathy, brain injury or metabolic disturbance. Given this, clinical SMEs recommended excluding these codes.

G Algorithm Characterization

G1 Methods

To characterize febrile seizure among a commercially insured population in the U.S., the workgroup used the IBM MarketScan Research Databases (Commercial and Medicare Supplemental), accessed via the Treatment Pathways[viii] online analytic platform, to query and analyze the diagnostic codes included in the febrile seizure algorithm (**Table 3**). Recognizing the higher diagnostic accuracy performance reported for specific codes associated with febrile seizure, queries were restricted to codes listed in Option 1. However, the impact of including Option 2 on overall counts was assessed, and code-specific queries for codes listed in Options 1 and 2 are summarized in **Appendix B**. To gather the broadest range of cases to support a descriptive analysis, the analyses presented herein did not require exposure to a biologic product and did not restrict based on coding position. Queries also did not set a lower and upper age limit for the population experiencing febrile seizure, as the focus was on characterizing the use of codes in the MarketScan Research Databases. However, understanding that febrile seizure is generally viewed as occurring between six months and five years of age, additional charts that tailor findings to this age cohort have been included. It is recommended that the proposed algorithm undergo a validation study prior to use, though future analytical studies should also tailor the algorithm specifications according to the study question of interest.

The figures presented below have been drawn from a large patient dataset during the study period of January 1, 2014–December 31, 2018. For all analyses, authors queried ICD-9-CM codes for January 1, 2014–September 30, 2015 and ICD-10-CM codes for October 1, 2015–December 31, 2018. This was done out of recognition of the transition to ICD-10-CM on October 1, 2015 and an effort to exclude codes that were reported in error.

Counts of individual patients who had a diagnosis code related to febrile seizure within a given calendar year, rather than counts of febrile seizure codes, were presented. As such, counts relate to the first

[viii] IBM MarketScan Research. Insight for Better Healthcare. https://marketscan.truvenhealth.com/marketscanportal/Portal.aspx

diagnosed febrile seizure event for an individual during a given surveillance period (e.g., January 1–December 31, 2014), and individuals could only be counted once per surveillance period. Since we did not estimate the incidence of febrile seizure in the study population, no washout period was applied.

Individuals had to be continuously enrolled to be included in the analysis for a particular year. For example, patients had to be continuously enrolled from January 1 to December 31, 2014, to be included in the "2014" dataset. Age is calculated in Treatment Pathways as if each individual was born on July 1 of their given year of birth. Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e., those under one year old), this population group has been left out of the charts that depict the proportions of individuals with febrile seizure by age. Infants under one year of age were not excluded from queries of the absolute number of patients receiving an ARDS diagnosis Further, recognizing that infants are a population of interest for febrile seizure, additional absolute counts of patients receiving a febrile seizure diagnosis have been generated for those under one year old. The workgroup also conducted a post-hoc analysis (not shown), removing the continuous enrollment requirement to assess whether this meaningfully impacted the proportion of those 0–1 or 0–5 years of age who received a febrile seizure diagnosis.

Age- and gender-specific data on MarketScan Research Databases enrollment and counts of individuals receiving a diagnostic code for febrile seizure (Option 1) or fever and convulsions (Option 2) were extracted. Code-specific queries for Option 1 and Option 2 described in **Section E** are summarized in **Appendix B.**

In addition to the code-specific queries, the authors executed queries that aggregated all ICD-9-CM codes, all ICD-10-CM codes, and all codes (ICD-9-CM and ICD-10-CM) for febrile seizure (Option 1). Further, the authors executed queries that aggregated ICD-9-CM and ICD-10-CM codes for fever and convulsions (Option 2) to test the impact of the more inclusive algorithm on identifying additional cases of febrile seizure.

G2 Results

Table 4 provides a summary of aggregate counts for ICD-9-CM and ICD-10-CM codes, suggesting that approximately 0.3–0.4 individuals per 1,000 individuals included in the MarketScan Research Databases received a code associated with febrile seizure each year. Among a cohort of 46,153,898 patients that combined those continuously enrolled for at least one calendar year between January 1, 2014 and December 31, 2018, 36,858 individuals (0.08%) had at least one ICD-9-CM or ICD-10-CM diagnosis code for febrile seizure.

Table 4. Overall counts of patients with febrile seizure (Option 1) by code set and year.

Code/ Description	Year				
	2014	2015[a]	2016	2017	2018
ICD-9-CM	10,036	6,526			
ICD-10-CM		2,117	7,269	6,638	6,589
ICD-9-CM OR ICD-10-CM	10,036	8,130	7,269	6,638	6,589
MarketScan Research Databases Enrollment	28,407,959	22,117,235	21,616,291	19,563,847	19,371,891
Proportion of Patients with febrile seizure per 1,000 Enrolled Population[b]	0.4	0.4	0.3	0.3	0.3

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

[a] In 2015, queries combining ICD-9-CM and ICD-10-CM codes returned lower patient counts than when codes were queried individually. This is because of cases in which both ICD-9-CM and ICD-10-CM codes were reported for the same individual, in the January–September and October–December timeframe, respectively.

[b] These proportions were calculated using the counts in the "ICD-9-CM OR ICD-10-CM" row.

Similar proportions were calculated for those 0–5 years of age, reflective of the cohort that would be expected to experience febrile seizures. Out of the 36,858 individuals with a febrile seizure diagnosis code, 28,412 (77.1%) were 0–5 years of age. Among a cohort of 3,050,460 individuals 0–5 years of age that were enrolled in the MarketScan Research Databases for at least one calendar year between 2014 and 2018, 9.3 individuals per 1,000 received a febrile seizure diagnosis. The annual proportion of individuals 0–5 years of age receiving a febrile seizure diagnosis varied from 5.1 to 5.6 per 1,000 enrolled across the five years of study (**Table 5**).

Table 5. Overall counts of patients (0–5 years of age) with febrile seizure (Option 1) by code set and year.

Code/ Description	Year				
	2014	2015[a]	2016	2017	2018
ICD-9-CM	7,188	4,818			
ICD-10-CM		1,534	5,771	5,468	5,573
ICD-9-CM OR ICD-10-CM	7,188	5,955	5,771	5,468	5,573
MarketScan Research Databases Enrollment	1,418,365	1,092,572	1,076,262	1,002,769	998,983
Proportion of Patients with febrile seizure per 1,000 Enrolled Population[b]	5.1	5.5	5.4	5.5	5.6

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

[a] In 2015, queries combining ICD-9-CM and ICD-10-CM codes returned lower patient counts than when codes were queried individually. This is because of cases in which both ICD-9-CM and ICD-10-CM codes were reported for the same individual, in the January–September and October–December timeframe, respectively.

[b] These proportions were calculated using the counts in the "ICD-9-CM OR ICD-10-CM" row.

The workgroup assessed whether the 2015 transition to ICD-10-CM and any associated changes in coding practices resulted in notable shifts in the overall frequency of febrile seizure reporting. **Figure 1** illustrates the proportion of the enrolled population with a diagnosis related to febrile seizure and suggests that the transition did not result in a substantial change to the proportion of individuals receiving a febrile seizure diagnosis.

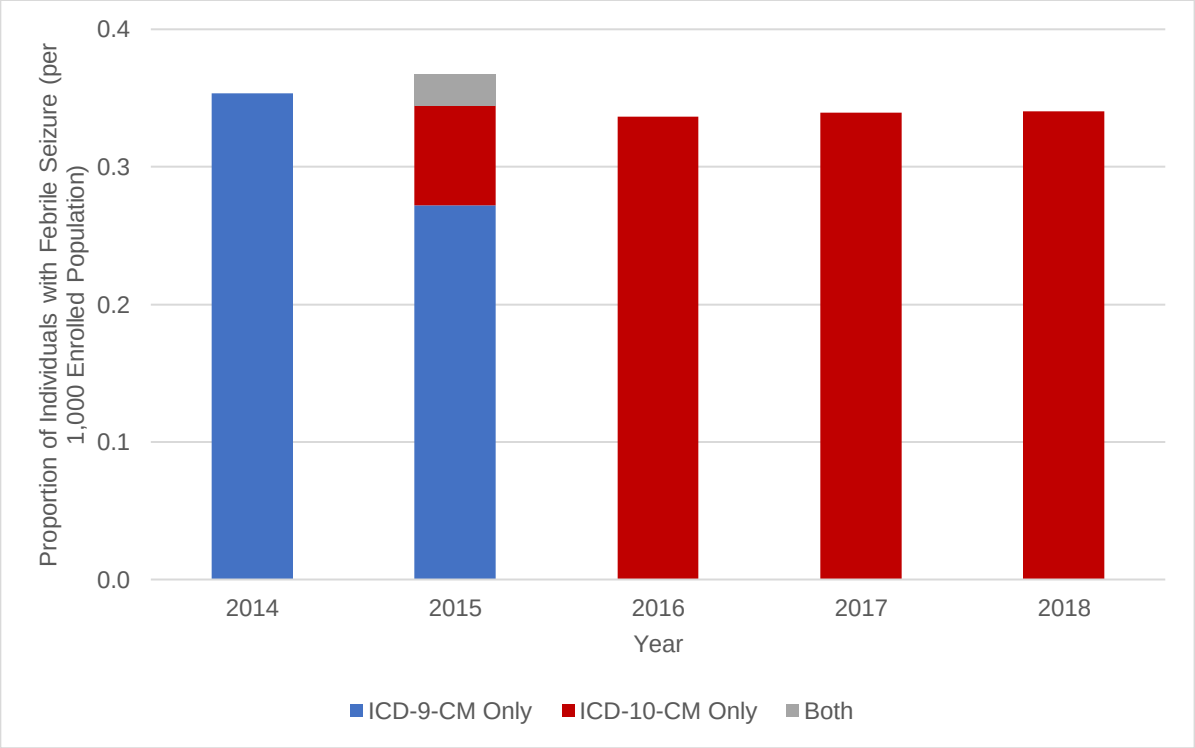

Figure 1. Proportion of patients with febrile seizure (Option 1), by year (2014–2018).

Note: In 2015, a patient could receive both an ICD-9-CM and an ICD-10-CM diagnosis, in the January–September and October–December timeframe, respectively.

Figure 2 presents counts of patients with an ICD-9-CM diagnosis for febrile seizure, stratified by age group. Counts were calculated for the timeframe of January 1, 2014 to September 30, 2015 among the cohort of 33,216,843 patients who were continuously enrolled for at least one calendar year between January 1, 2014 and December 31, 2015. There were 16,537 (0.05%) with at least one diagnosis for febrile seizure during this period, with a median age at first diagnosis of 2 years (range 0–99 years). Of this group, there were 1,613 (9.8%) and 10,358 (62.6%) in the 0–<1 and 1–5 years age groups, respectively.

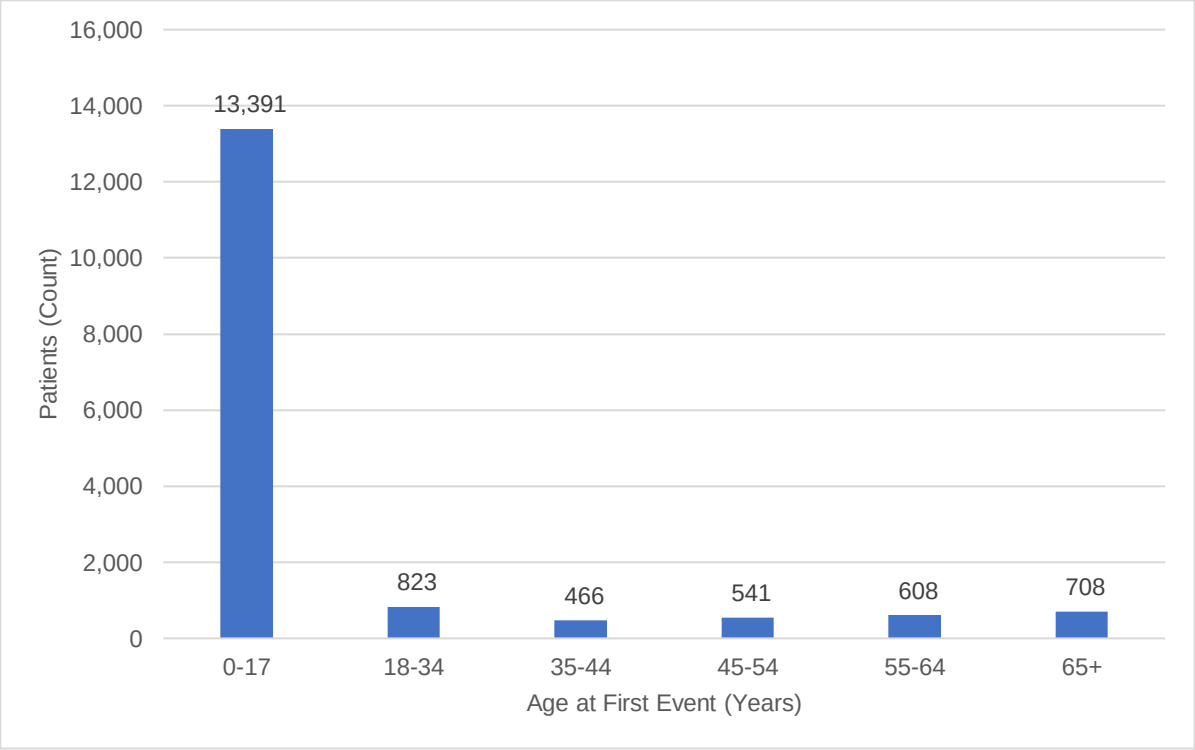

Figure 2. Patients with at least one ICD-9-CM diagnosis code for febrile seizure (Option 1), January 1, 2014–September 30, 2015, stratified by age group.

Figure 3 presents counts of patients with an ICD-10-CM diagnosis for febrile seizure, stratified by age group. Counts were drawn from a cohort of 35,337,738 patients who were continuously enrolled for at least one calendar year between October 1, 2015 and December 31, 2018. Among 21,784 individuals (0.06%) with at least one diagnosis for febrile seizure during this time period, the median age at first diagnosis was 2 years (range 0–102 years). Of this group, there were 2,118 (9.7%) and 15,494 (71.1%) in the 0–<1 and 1–5 years age groups, respectively, suggesting that the selection of febrile seizure codes among the target age group may have improved with the transition to ICD-10-CM.

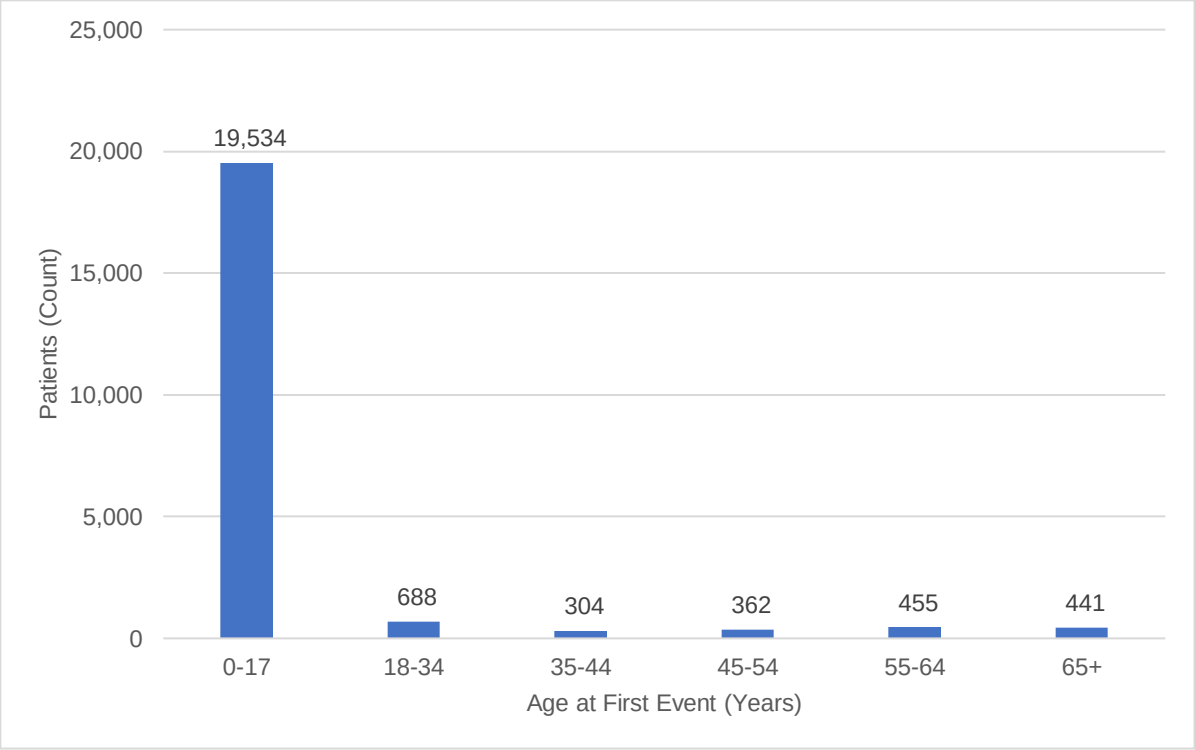

Figure 3. Patients with at least one ICD-10-CM diagnosis code for febrile seizure (Option 1), October 1, 2015–December 31, 2018, stratified by age group.

Figure 4 presents counts of patients with either an ICD-9-CM or ICD-10-CM code for febrile seizure among a cohort of 46,153,898 individuals who were continuously enrolled for at least one calendar year between 2014 and 2018. Among 36,858 (0.08%) who received a diagnosis code for febrile seizure between January 1, 2014, and December 31, 2018, the median age at first diagnosis was 2 years (range 0–102 years). Of this group, there were 3,818 (10.4%) and 24,594 (66.7%) in the 0–<1 and 1–5 years age groups, respectively.

The possible inclusion of Option 2 was also assessed, and found an increase to 50,011 individuals, though the proportion of individuals 0–<1 and 1–5 years of age decreased to 8.5% (n=4,241) and 51.7% (n=25,869), respectively, suggesting that the application of Option 2 without proper age limits could introduce a source of misclassification. Overall, between 0.93% (Option 1) and 0.99% (Option 2) of children 0–5 years old who were enrolled for a least one calendar year between 2014 and 2018 received a febrile seizure diagnosis in this period. In other words, expanding to include the more sensitive algorithm (Option 2) only added incrementally to the results obtained from Option 1.

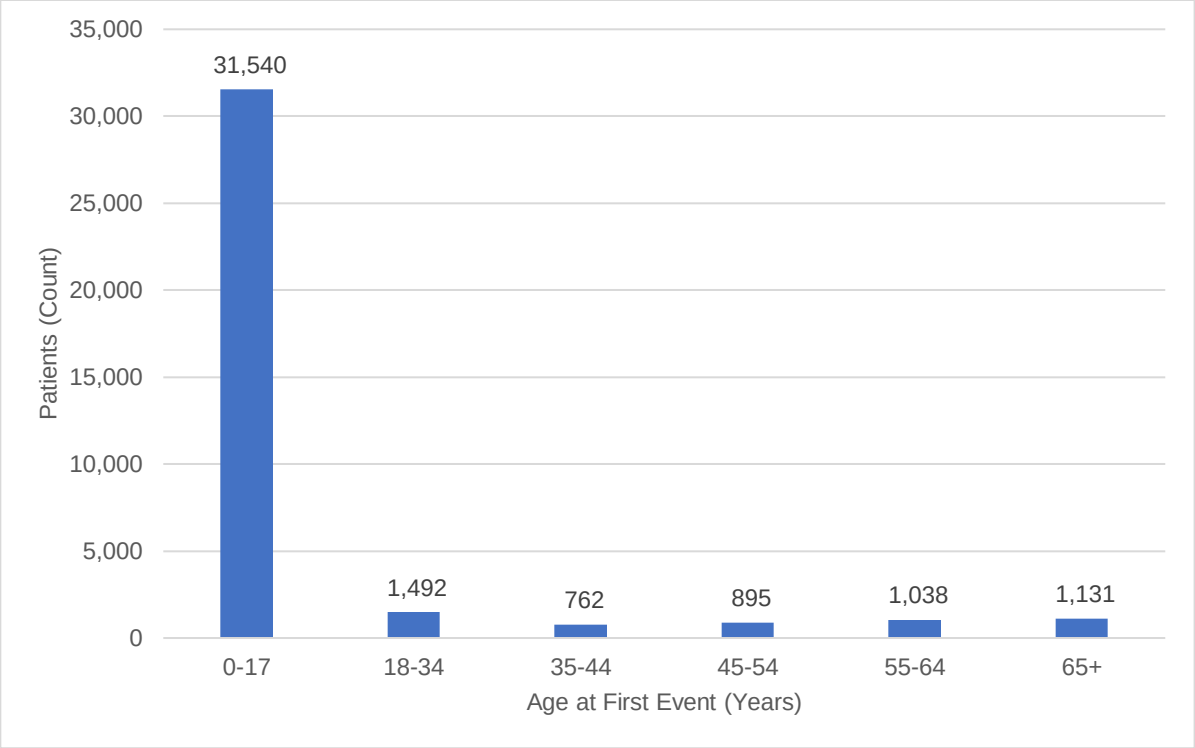

Figure 4. Patients with at least one ICD-9-CM or ICD-10-CM diagnosis code for febrile seizure (Option 1), January 1, 2014–December 31, 2018, stratified by age group.

Figure 5 summarizes the proportion of the population (top: 1–85+ years; bottom 1–5 years) with at least one ICD-9-CM or ICD-10-CM code for febrile seizure (per 1,000 population enrolled in the MarketScan Research Databases) between January 1, 2014, and December 31, 2018, by age and gender. Patients 85 years or older were grouped to minimize the effect of unstable estimates due to the smaller enrolled population sizes available in this age range in the commercially insured population. The 46 million-patient cohort was used for this analysis and individuals were required to be enrolled for at least one calendar year between 2014 and 2018 but were not required to be enrolled for the full five-year period to be included in the calculations. The results suggest that the proportion of patients with febrile seizure peaks among those 1–2 years of age and is higher among males.

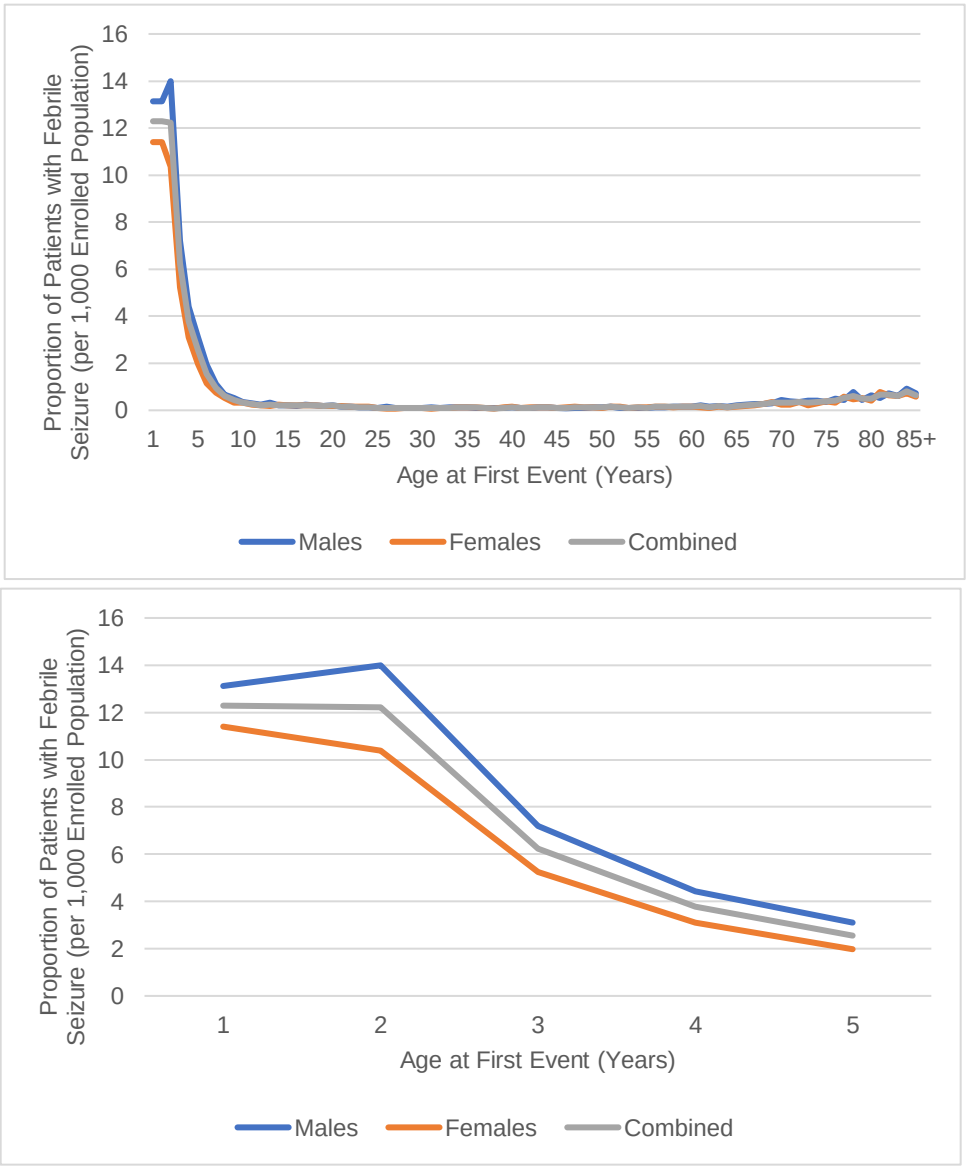

Figure 5. Proportion of patients with at least one ICD-9-CM or ICD-10-CM diagnosis code for febrile seizure (Option 1) per 1,000 population by age and gender, 1–85+ years (top) and 1–5 years (bottom) (January 1, 2014–December 31, 2018).*

*Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e., those under 1-year old), the proportion of those under 1-year old experiencing febrile seizure is excluded from the chart.

The workgroup also assessed whether there was notable variation in the proportion of patients with febrile seizure by calendar year of diagnosis. **Figure 6** presents the annual proportions of patients with a diagnosis code for febrile seizure for ages 1–85+ years (top) and 1–5 years (bottom). Results suggest that proportions were consistent across calendar years. It should be noted that the proportions presented in **Figure 6** are lower than those in **Figure 5**, where febrile seizure encounters were queried for the entire 2014–2018 period instead of for a single year.

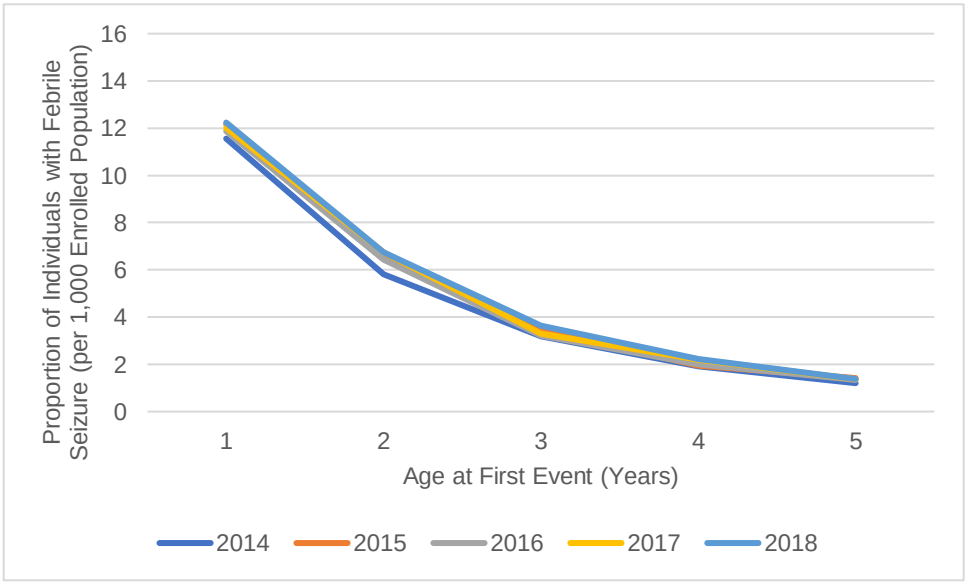

Figure 6. Proportion of patients with at least one ICD-9-CM or ICD-10-CM diagnosis code for febrile seizure (Option 1) per 1,000 population by age and calendar year, 1–85+ years (top) and 1–5 years (bottom) (January 1, 2014–December 31, 2018).*

*Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e., those under 1 year old), the proportion of those under 1-year old experiencing febrile seizure is excluded from the chart.

Analyses were also conducted to test whether there was a temporal association in the occurrence or reporting of febrile seizure according to the time of the year, possibly as a result of an association with weather patterns or vaccination schedules. To test this, enrollment and febrile seizure encounter data for January 1–June 30 and July 1–December 31 were queried for each year. As presented in **Table 6** and **Figure 7**, with the exception of 2016 — which demonstrated a marked decrease in the proportion of individuals experiencing febrile seizure in the second half of the year compared to all other periods — there did not appear to be a substantial difference in the proportion of patients experiencing febrile seizure during the first and second halves of the calendar year.

Table 6. Counts and proportions of patients with at least on ICD-9-CM or ICD-10-CM diagnosis for febrile seizure (Option 1),* stratified by time of year (2014–2018).

Description	Calendar Year				
	2014	2015	2016	2017	2018
January–June patient count	6,304	5,419	4,882	4,454	4,433
July–December patient count	5,974	4,473	2,747	3,694	3,689
January–June enrollment	31,110,014	24,094,695	23,531,649	21,406,675	21,225,754
July–December enrollment	30,867,380	23,759,879	23,243,348	20,866,148	20,866,232
January–June proportion (per 1,000 enrolled)	0.2	0.2	0.2	0.2	0.2
July–December proportion (per 1,000 enrolled)	0.2	0.2	0.1	0.2	0.2

* The sum of the proportions presented here exceeds those presented for full calendar years. This is because a patient can be counted in both time periods when queries are run separately, whereas they would only be counted once when the query spans the full year.

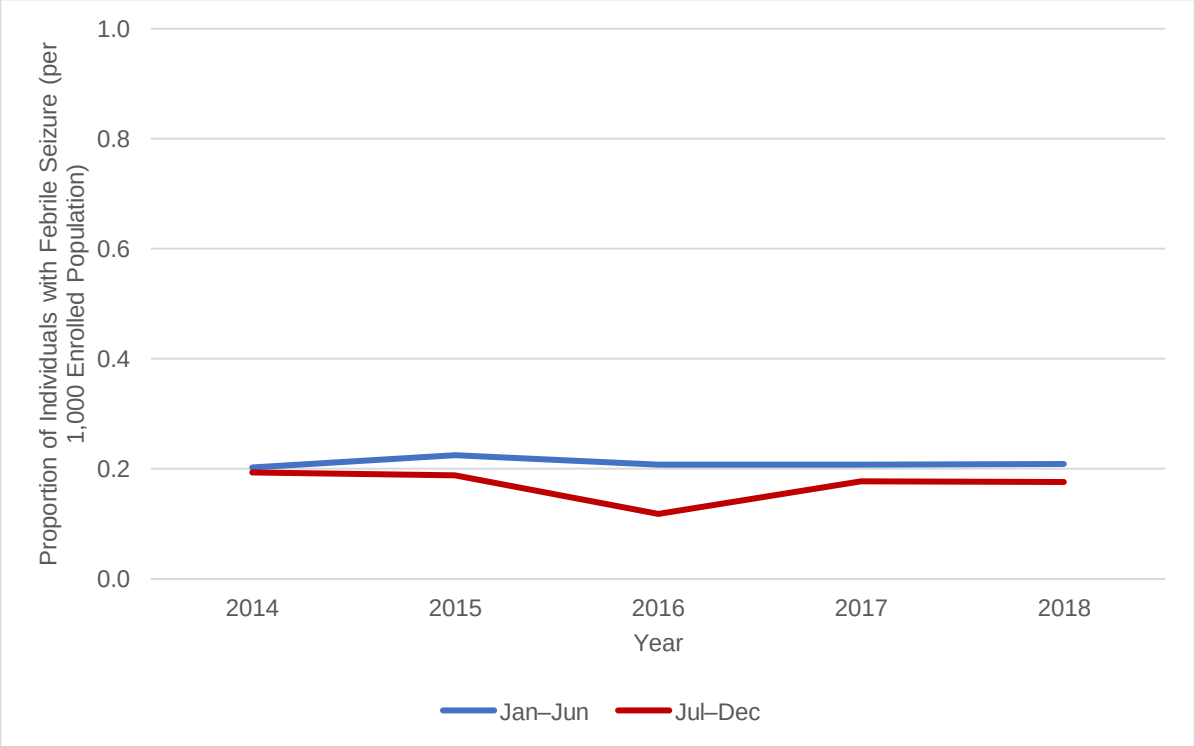

Figure 7. Proportion of patients with at least one ICD-9-CM or ICD-10-CM diagnosis code for febrile seizure (Option 1), stratified by time of year (2014–2018).

The same temporal analyses were also conducted among those 1–5 years of age to test whether the association changed when restricting analyses to the age cohort that would be expected to experience febrile seizures. Those under one year of age were excluded out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants. As presented in **Table 7** and **Figure 8**, the overall trend remained essentially unchanged from that observed in analyses of all age groups, although a slightly higher proportion of individuals receiving a febrile seizure diagnosis was observed in the second half of 2014.

Table 7. Counts and proportions of patients 1–5 years of age with at least on ICD-9-CM or ICD-10-CM diagnosis for febrile seizure (Option 1),* stratified by time of year (2014–2018).

Description	Calendar Year				
	2014	2015	2016	2017	2018
January–June patient count	3,717	3,419	3,224	3,126	3,147
July–December patient count	4,056	3,066	1,985	2,915	2,974
January–June enrollment	1,560,592	1,193,811	1,170,273	1,092,528	1,087,224
July–December enrollment	1,553,839	1,189,673	1,048,311	1,080,070	1,084,146
January–June proportion (per 1,000 enrolled)	2.4	2.9	2.8	2.9	2.9
July–December proportion (per 1,000 enrolled)	2.6	2.6	1.9	2.7	2.7

* The sum of the proportions presented here exceeds those presented for full calendar years. This is because a patient can be counted in both time periods when queries are run separately, whereas they would only be counted once when the query spans the full year.

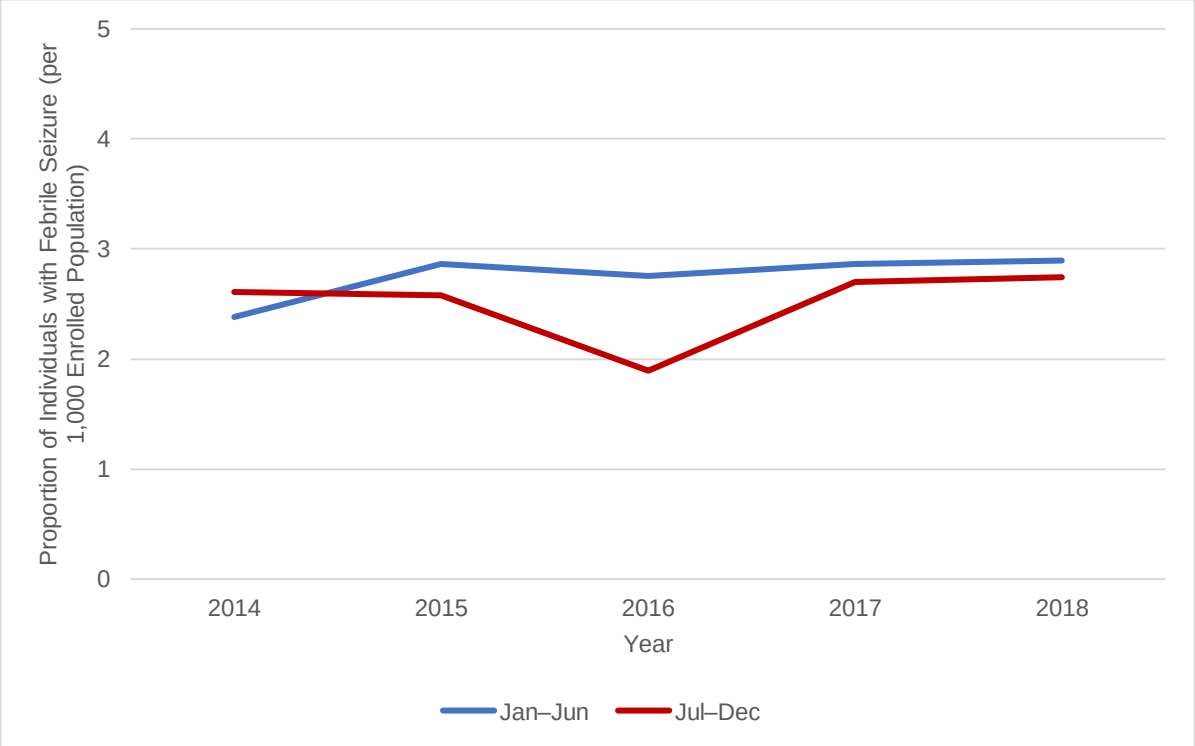

Figure 8. Proportion of patients 1–5 years of age with at least one ICD-9-CM or ICD-10-CM diagnosis code for febrile seizure (Option 1), stratified by time of year (2014–2018).

H Discussion and Conclusion

The objective of this structured review was to assess and understand the validity of an electronic coding algorithm for identifying febrile seizure from administrative claims and EHRs using billing codes. It is unclear how diagnostic code-based algorithms would perform differently in EHRs compared to claims databases. A structured review found seven studies judged to be of relevance. None reported using ICD-10-CM codes to identify potential cases of febrile seizure. One U.S. study validated an algorithm derived from insurance claims data and reported a strong PPV associated with specific ICD-9-CM febrile seizure codes (780.31 and 780.32), and a poorer performance using the combination of more general fever and convulsion codes.[1] Literature review findings were leveraged in conjunction with consultation with clinical SMEs to develop an algorithm that offered two levels of specificity, with Option 1 (more specific) being restricted to specific febrile seizure codes and Option 2 (more sensitive) expanding to include fever and convulsion codes reported on the same day.

The algorithm was then applied in the MarketScan Research Databases, accessed via the Treatment Pathways analytic tool, to test the feasibility of algorithm use and conduct some initial analyses describing the epidemiology of febrile seizure in a U.S. database of commercially insured patients. Option 1 was used for these queries. Findings suggest that approximately 0.3–0.4 individuals per 1,000 population experienced at least one febrile seizure event per year between 2014 and 2018. Out of 36,858 individuals with a febrile seizure diagnosis code, 28,412 (77.1%) were 0–5 years of age. As febrile seizure is believed to occur in those five years of age and younger, this finding suggests that nearly a quarter of febrile seizure codes reported could be due to other reasons, such as coding error. It will therefore be important to apply an age limit in future applications of the algorithm.

Meanwhile, among children 0–5 years old who were enrolled for a least one calendar year between 2014 and 2018 (n=3,050,460), between 0.93% (Option 1) and 0.99% (Option 2) received a febrile seizure diagnosis in this period, depending on the algorithm used. Option 1 identified an annual proportion of 5.1–5.6 individuals per 1,000 enrolled individuals 0–5 years of age receiving a febrile seizure diagnosis between 2014 and 2018. This is lower than estimates from the literature — which suggest that 2–5% of children will experience a febrile seizure by the age of 5 years — though this may be due to the fact that febrile seizure is often not medically attended. This lower estimate may also be due to the requirement for one calendar year of continuous enrollment, which may have excluded infants under 1 year of age.

Analyses suggest that the proportions of those experiencing febrile seizure is higher in males than females, which is consistent with a recent study of children identified from the Danish Civil Registration System, which reported a 21% relative risk difference between males and females for febrile seizure.[11] The findings also suggest that the proportion of individuals receiving a febrile seizure diagnosis peaked in those 1–2 years of age; this is consistent with clinical expectations and prior publications reporting that the peak age of onset is around 18 months of age.[12] Results also suggested that the proportion of individuals receiving a febrile seizure diagnosis did not vary substantially within or across years of study, with the exception of a drop in the proportion of patients receiving a febrile seizure diagnosis in the second half of 2016, though the reasons for this decrease are unclear. A slightly higher proportion of individuals 0–5 years of age — the cohort that would be expected to receive these codes — captured by febrile seizure-specific ICD-10-CM coding compared to ICD-9-CM coding suggests that the application of febrile seizure codes did not deteriorate and may have improved with the transition to ICD-10-CM.

Strengths of this study are the development of a febrile seizure algorithm using ICD-9-CM and ICD-10-CM code standards, based on a structured review of code definitions and active engagement with clinical SMEs. To assess the plausibility of the algorithm, it was applied in a large administrative claims database to characterize febrile seizure in the U.S. population and generate descriptive statistics. The study also includes important limitations that should be considered in interpreting findings. First, the workgroup chose to query the more specific algorithm as the main descriptive analyses, out of concern that queries combining more general convulsion and fever codes could increase representation of older age groups and introduce the risk of misclassifying individuals as febrile seizure cases. Moreover, the results from analysis of Option 2, which combined codes for convulsions and fever, indicate an incremental number of

febrile seizure cases was added for the 0–5-year age group, compared to the more specific algorithm (Option 1). Second, the requirement for continuous enrollment may have excluded infants who experienced a febrile seizure event. However, a post-hoc analysis (not shown) that removed the continuous enrollment requirement did not demonstrate a substantial increase in the proportion of those 0–1 or 0–5 years old that received a febrile seizure diagnosis. The analyses conducted in the MarketScan Research Databases should be viewed as exploratory and generalizable to the U.S. population that is commercially insured, and additional studies among populations with different insurance coverage would be required to validate the results and observations stemming from these queries.

I Acknowledgements

Development of the febrile seizure algorithm and report benefitted from significant engagement with the FDA CBER team members and their partners. We thank them for their contributions and feedback. Additional feedback on the proposed algorithm and draft report was provided by IBM Watson Health, Acumen (Laurie Feinberg, Nirmal Choradia) and Epi Excellence LLC.

J References

1. Kawai AT, Martin D, Henrickson SE, et al. Validation of febrile seizures identified in the Sentinel Post-Licensure Rapid Immunization Safety Monitoring Program. *Vaccine.* 2019;37(30):4172-4176.
2. Mewasingh LD. Febrile seizures. *BMJ Clin Evid.* 2014;2014.
3. Jones T, Jacobsen SJ. Childhood febrile seizures: overview and implications. *Int J Med Sci.* 2007;4(2):110-114.
4. Chung S. Febrile seizures. *Korean J Pediatr.* 2014;57(9):384-395.
5. Klein NP, Fireman B, Yih WK, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics.* 2010;126(1):e1-8.
6. Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM. Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011. *Vaccine.* 2012;30(11):2024-2031.
7. Baker MA, Jankosky C, Yih WK, et al. The risk of febrile seizures following influenza and 13-valent pneumococcal conjugate vaccines. *Vaccine.* 2020;38(9):2166-2171.
8. Quantin C, Benzenine E, Velten M, Huet F, Farrington CP, Tubert-Bitter P. Self-controlled case series and misclassification bias induced by case selection from administrative hospital databases: application to febrile convulsions in pediatric vaccine pharmacoepidemiology. *Am J Epidemiol.* 2013;178(12):1731-1739.
9. Shui IM, Shi P, Dutta-Linn MM, et al. Predictive value of seizure ICD-9 codes for vaccine safety research. *Vaccine.* 2009;27(39):5307-5312.
10. Thyagarajan V, Su S, Gee J, et al. Identification of seizures among adults and children following influenza vaccination using health insurance claims data. *Vaccine.* 2013;31(50):5997-6002.
11. Dreier JW, Li J, Sun Y, Christensen J. Evaluation of Long-term Risk of Epilepsy, Psychiatric Disorders, and Mortality Among Children With Recurrent Febrile Seizures: A National Cohort Study in Denmark. *JAMA Pediatr.* 2019;173(12):1164-1170.
12. Laino D, Mencaroni E, Esposito S. Management of Pediatric Febrile Seizures. *Int J Environ Res Public Health.* 2018;15(10).

Appendix A. Literature Review Extracted Results

Table A1 below includes a summarized version of the data extraction table used to extract data from papers deemed of interest to febrile seizure algorithms. The seven papers summarized in the table informed the development of the proposed febrile seizure algorithm.

Table A1. Febrile Seizures Data Extraction Table

Author, Year	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims/EHR-Based Algorithm[ix]
Baker, 2020	The risk of febrile seizures following influenza and 13-valent pneumococcal conjugate vaccines.	U.S.	Identified cases of febrile seizures after inactivated influenza vaccine and 13-valent pneumococcal conjugate vaccine in 735,525 children between the ages of 6-23 months.	NR	2 algorithms using ICD-9-CM codes: Primary algorithm: 780.31 or 780.32 Secondary algorithm: 780.3, 780.31, 780.32, or 780.39	NA	Claims
Kawai, 2019	Validation of febrile seizures identified in the Sentinel Post-Licensure Rapid Immunization Safety Monitoring (PRISM) Program.	U.S.	Calculated PPV to validate four different algorithms to identify 216 potential cases of post-vaccination febrile seizures in children who have had vaccines.	Confirmed cases require medical records include description of a seizure and fever (i.e., measured temperature ≥ 38°C or fever reported within 24 hours before or after a seizure, or have a physician diagnosis of febrile seizure, or concomitant febrile illness plus seizure).	Four different algorithms using ICD-9-CM codes were proposed: Algorithm A: 780.3, 780.31, 780.32, or 780.39 Algorithm B: 780.31 or 780.32 Algorithm C: Exclude 780.31 and 780.32; include 780.3 with 780.6 or 780.61, 780.62, 780.63 on the same day; include 780.39 with 780.6 or 780.61, 780.62, or 780.63 on	PPV for four algorithms: Algorithm A: 70% (95% CI 64–76%) Algorithm B: 91% (95% CI 85–95%) Algorithm C: 20% (95% CI 1–72%) Algorithm D: 19% (95% CI 10–32%)	Claims

[ix] Each publication reported on a either a claims-based (i.e., febrile seizure codes derived from insurance claims) or EHR-based (i.e., febrile seizure codes derived from administrative medical records) algorithm.

Author, Year	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims/EHR-Based Algorithm[ix]
					the same day Algorithm D: Exclude 780.31 and 780.32; include 780.39 without 780.6 or 780.60, 780.61, 780.62, or 780.63 on the same day; include 780.3 without 780.6 or 780.60, 780.61, 780.62, or 780.63 on the same day		
Klein, 2010	Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures.	U.S.	Calculated PPV and validated algorithm identifying seizure events after measles-mumps-rubella-varicella vaccinations in 712,507 children between 12 to 23 months old.	First occurrence of seizure within a 0–42-day period post vaccination with chart-confirmed diagnosis of febrile seizure (with or without concurrent febrile illness).	In ED or inpatient setting: ICD-9-CM code 345* or 780.3* In outpatient setting: ICD-9-CM 780.6	Overall PPV: 87% PPV within 7-10 days after vaccination: 90% (95% CI 87-94%) PPV outside days 7-10 (days 0-6 and 11-42): 83% (95% CI 78 – 88%)	EHR
Quantin, 2013	Self-controlled case series and misclassification bias induced by case selection from administrative hospital databases: application to febrile convulsions in pediatric vaccine pharmacoepidemiology.	France	Calculated PPV and sensitivity for four different algorithms that identify febrile convulsions in 695 children 1 month to 3 years old who have been hospitalized for febrile convulsions.	Febrile seizure hospitalizations identified in Dijon University Hospital registry of convulsion cases and administrative database or identified in medical record and the administrative database	Four algorithms were proposed using ICD-10 codes: Algorithm 1: R56.0 or R56.8 in any diagnosis position Algorithm 2: R56.0 as principal diagnosis Algorithm 3: R56.0 as principal diagnosis and admission to ED Algorithm 4: R56.0 as principal diagnosis and admission to ED and neurological investigation	PPV: Algorithm 1: 80.7% (95% CI 77.8–83.7%) Algorithm 2: 95.0% (95% CI 93.1–96.9%) Algorithm 3: 96.3% (95% CI 94.7–98.0%) Algorithm 4: 98.3% (95% CI 96.6–	EHR

Author, Year	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims/EHR-Based Algorithm[ix]
						100.0%) Sensitivity: Algorithm 1: 98.5% (95% CI 96.5–99.99%) Algorithm 2: 89.1% (95% CI 83.8–94.3%) Algorithm 3: 86.9% (95% CI 81.2–92.5%) Algorithm 4: 47.5% (95% CI 39.1–55.8%)	
Shui, 2009	Predictive value of seizure ICD-9 codes for vaccine safety research	U.S.	Calculated predictive value of seizure events identified in the 30 days following pneumococcal vaccination in children 6 weeks to 23 months of age with 859 medical charts available for review.	Brighton Collaboration definition for generalized convulsive seizure.	ICD-9-CM codes 333.2, 345.xx, 780.3x, and 779.90	PPV (emergency department): 96.6% (95% CI 93.1–98.6%) PPV (inpatient): 64.0% (95% CI 57.3–70.7) PPV (outpatient days 1-30): 16.4% (95% CI 12.4-21.2%) PPV (outpatient day 0): 1.8% (0.4–5.3%)	EHR

Author, Year	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims/EHR-Based Algorithm[ix]
Thyagarajan, 2013	Identification of seizures among adults and children following influenza vaccination using health insurance claims data.	U.S.	A U.S. study sought to validate an algorithm for potential seizures in 224 children and adults who received an influenza vaccine using data from a large administrative claims database	Insufficient information for application of Brighton Collaboration definition, classified by abstractors. Definite cases had medical record documentation of a clinical diagnosis. Possible cases had medical record documentation by the treating clinician noting a possible seizure with further documentation unavailable to confirm.	ICD-9-CM 345.xx (epilepsy and recurrent seizures) or 780.3x (convulsions) reported within 29 days of vaccine receipt, with no codes reported in the 42 days prior to the potential seizure.	PPV (emergency department): 93.9% (95% CI 86.3–98.0) PPV (inpatient): 38.3 (95% CI 28.5–48.9%)	Claims
Tse, 2012	Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011.	U.S.	Calculated PPV and validated algorithm identifying seizures in 206,174 children between the age of 6-59 months who received a trivalent inactivated influenza vaccine.	Vaccine Safety Datalink (VSD) criteria or Brighton Criteria for seizure met in addition to medical record including fever (i.e., ≥ 38°C within 24 hours before seizure, a parent report of a fever, or clinician diagnosis of febrile seizure)	ICD-9-CM 730.3, 780.31, 780.32, and 780.39	PPV in risk interval (0-1 days): 83% PPV in control interval (14-20 days): 71%	EHR

Abbreviations: EHR, electronic health record; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; NA, not applicable; NR, not reported; PPV, positive predictive value; PRISM, Post-Licensure Rapid Immunization Safety Monitoring.VSD, Vaccine Safety Datalink

Appendix B. Counts of Patients with Specific Codes Proposed for the Algorithm

As an initial test of the proposed algorithm, the workgroup ran code-specific queries in a large U.S. administrative claims dataset. Researchers used the MarketScan Research Databases (Commercial, Medicare Supplemental), accessed via the Treatment Pathways online analytic platform, querying the past five full years of available data. Because the transition between International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9-CM to ICD-10-CM) occurred on October 1, 2015, ICD-9-CM codes were queried for January 1, 2014–September 30, 2015, and ICD-10-CM codes were queried for October 1, 2015–December 31, 2018.

For Option 1, ICD-CM codes queried for febrile convulsions are presented in **Table B1**. For Option 2, ICD-CM codes for fever were queried among those with a convulsion code included in the algorithm, from one day before to one day following the convulsion code. Option 2 results are presented in **Table B2**. Subtotal rows and "Total" columns may be smaller than the sum of individual cells, because patients with multiple codes in a single year and with more than one of the same diagnosis codes in different years will only be counted once in these rows and columns. As a result, the sum of all "% of Total" cells in a single column may exceed 100%. However, the "Total" column could also be larger than the sum of individual years, as a result of situations where an individual is only enrolled for part of the year that they experience a febrile seizure event but is then continuously enrolled for a separate year. For example, an individual could be continuously enrolled for a few days, weeks, or months in 2016 and experience a febrile seizure event, then be continuously enrolled for all of 2017. This event would not be captured in the column for the 2016 (as the individual would be excluded from that cohort) but would be captured in the "Total" column.

Of the codes included in the febrile seizure algorithm (Option 1), codes for febrile convulsions (simple) (ICD-9-CM 780.31; ICD-10-CM R56.00) were the most frequently used compared to codes for complex febrile convulsion. Of those receiving at least one febrile seizure diagnosis code between 2014 and 2018 (n=36,858), 42.8% (n=15,757) and 55.1% (n=20,310) had at least one ICD-9-CM 780.31 or ICD-10-CM R56.00 code, respectively.

Of the codes included in the fever/convulsions algorithm (Option 2), codes for fever, unspecified (ICD-9-CM 780.60; ICD-10-CM R50.9) were the most frequently used among patients with a convulsion-related diagnosis (ICD-9-CM 780.39, ICD-10-CM G40.89, or ICD-10 CM R56.9). Of those receiving a convulsion diagnosis and at least one fever-related diagnosis between 2014 and 2018 (n=21,174), 40.1% (n=8,489) and 58.4% (n=12,371) had at least one the fever-related diagnosis code (ICD-9-CM 780.60 or ICD-10-CM R50.9 code), respectively.

Table B1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in febrile seizure algorithm Option 1 (January 1, 2014–December 31, 2018).

Code	Code Description	Year										Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)	2018 (Count)	2018 (% of Total)		
ICD-9-CM													
780.31	Febrile convulsions (simple), unspecified	9,356	93.2	6,032	74.2							15,757	42.8
780.32	Complex febrile convulsions	1,375	13.7	982	12.1							2,490	6.8
ICD-9-CM Subtotal		10,036	100.0	6,526	80.3							16,952	46.0
ICD-10-CM													
R56.00	Simple febrile convulsions			1,875	23.1	6,696	92.1	6,123	92.2	6,071	92.1	20,310	55.1
R56.01	Complex febrile convulsions			364	4.5	1,305	18.0	1,185	17.9	1,229	18.7	3,957	10.7
ICD-10-CM Subtotal				2,117	26.0	7,269	100.0	6,638	100.0	6,589	100.0	21,825	59.2
Total		**10,036**	**100.0**	**8,130**	**100.0**	**7,269**	**100.0**	**6,638**	**100.0**	**6,589**	**100.0**	**36,858**	**100.0**

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

Table B2. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in febrile seizure algorithm Option 2 (January 1, 2014–December 31, 2018).

Code	Code Description	Total (Count)	Total (% of Total)
ICD-9-CM (780.39 [Other convulsions] AND)			
780.60	Fever, unspecified	8,489	40.1
780.61	Fever presenting with conditions classified elsewhere	379	1.8
780.62	Postprocedural fever	45	0.2
780.63	Postvaccination fever	4	0.0
ICD-9-CM Subtotal		8,654	40.9
ICD-10-CM (G40.89 [Other seizures] OR R56.9 [Unspecified convulsions] AND)			
R50.81	Fever presenting with conditions classified elsewhere	732	3.5
R50.82	Postprocedural fever	87	0.4
R50.83	Postvaccination fever	10	0.0
R50.84	Fever presenting with conditions classified elsewhere	10	0.0
R50.9	Fever, unspecified	12,371	58.4
ICD-10-CM Subtotal		12,697	60.0
Total		**21,174**	**100.0**

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

Appendix C. Codes Excluded from Proposed Algorithm

The diagnosis codes listed in **Table C1** are proposed for exclusion from the algorithm. These codes were initially considered for based on a literature review and their potential relation to febrile seizures. In consultation with clinical SMEs (TB, JB, JC, DT) these codes – which were not specific to febrile seizures - were ultimately determined to be too general and could potentially increase the risk of misclassification. Further, these codes were not used to identify patients with a relevant febrile seizure diagnosis.

Table C1. Excluded codes potentially relevant to febrile seizure identified from the literature or GEMs mapping.

Code	Description	Code Category	Code Type
333.2	Myoclonus	DX	9
345.00	Generalized nonconvulsive epilepsy, without mention of intractable epilepsy	DX	9
345.01	Generalized nonconvulsive epilepsy, with intractable epilepsy	DX	9
345.10	Generalized convulsive epilepsy, without mention of intractable epilepsy	DX	9
345.11	Generalized convulsive epilepsy, with intractable epilepsy	DX	9
345.2	Petit mal status	DX	9
345.3	Grand mal status	DX	9
345.40	Localization-related (focal) (partial) epilepsy and epileptic syndromes with complex partial seizures, without mention of intractable epilepsy	DX	9
345.41	Localization-related (focal) (partial) epilepsy and epileptic syndromes with complex partial seizures, with intractable epilepsy	DX	9
345.50	Localization-related (focal) (partial) epilepsy and epileptic syndromes with simple partial seizures, without mention of intractable epilepsy	DX	9
345.51	Localization-related (focal) (partial) epilepsy and epileptic syndromes with simple partial seizures, with intractable epilepsy	DX	9
345.60	Infantile spasms, without mention of intractable epilepsy	DX	9
345.61	Infantile spasms, with intractable epilepsy	DX	9
345.70	Epilepsia partialis continua, without mention of intractable epilepsy	DX	9
345.71	Epilepsia partialis continua, with intractable epilepsy	DX	9
345.80	Other forms of epilepsy and recurrent seizures, without mention of intractable epilepsy	DX	9
345.81	Other forms of epilepsy and recurrent seizures, with intractable epilepsy	DX	9
345.90	Epilepsy, unspecified, without mention of intractable epilepsy	DX	9
345.91	Epilepsy, unspecified, with intractable epilepsy	DX	9
779.0	Convulsions in newborn	DX	9
780.33	Post traumatic seizures	DX	9
780.64	Chills (without fever)	DX	9
780.65	Hypothermia not associated with low environmental temperature	DX	9
780.66	Febrile nonhemolytic transfusion reaction	DX	9
G25.3	Myoclonus	DX	10
G40.001	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, not intractable, with status epilepticus	DX	10

Code	Description	Code Category	Code Type
G40.009	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, not intractable, without status epilepticus	DX	10
G40.011	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, intractable, with status epilepticus	DX	10
G40.019	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, intractable, without status epilepticus	DX	10
G40.101	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, not intractable, with status epilepticus	DX	10
G40.109	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, not intractable, without status epilepticus	DX	10
G40.111	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable, with status epilepticus	DX	10
G40.119	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable, without status epilepticus	DX	10
G40.201	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, not intractable, with status epilepticus	DX	10
G40.209	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, not intractable, without status epilepticus	DX	10
G40.211	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable, with status epilepticus	DX	10
G40.219	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable, without status epilepticus	DX	10
G40.301	Generalized idiopathic epilepsy and epileptic syndromes, not intractable, with status epilepticus	DX	10
G40.309	Generalized idiopathic epilepsy and epileptic syndromes, not intractable, without status epilepticus	DX	10
G40.311	Generalized idiopathic epilepsy and epileptic syndromes, intractable, with status epilepticus	DX	10
G40.319	Generalized idiopathic epilepsy and epileptic syndromes, intractable, with status epilepticus, without status epilepticus	DX	10
G40.401	Other generalized epilepsy and epileptic syndromes, not intractable, with status epilepticus	DX	10
G40.409	Other generalized epilepsy and epileptic syndromes, not intractable, without status epilepticus	DX	10
G40.411	Other generalized epilepsy and epileptic syndromes, intractable, with status epilepticus	DX	10
G40.419	Other generalized epilepsy and epileptic syndromes, intractable, without status epilepticus	DX	10
G40.501	Epileptic seizures related to external causes, not intractable, with status epilepticus	DX	10
G40.509	Epileptic seizures related to external causes, not intractable, without status epilepticus	DX	10

Code	Description	Code Category	Code Type
G40.801	Other epilepsy, not intractable, with status epilepticus	DX	10
G40.802	Other epilepsy, not intractable, without status epilepticus	DX	10
G40.803	Other epilepsy, intractable, with status epilepticus	DX	10
G40.804	Other epilepsy, intractable, without status epilepticus	DX	10
G40.811	Lennox-Gastaut syndrome, not intractable, with status epilepticus	DX	10
G40.812	Lennox-Gastaut syndrome, not intractable, without status epilepticus	DX	10
G40.813	Lennox-Gastaut syndrome, intractable, with status epilepticus	DX	10
G40.814	Lennox-Gastaut syndrome, intractable, without status epilepticus	DX	10
G40.821	Epileptic spasms, not intractable, with status epilepticus	DX	10
G40.822	Epileptic spasms, not intractable, without status epilepticus	DX	10
G40.823	Epileptic spasms, intractable, with status epilepticus	DX	10
G40.824	Epileptic spasms, intractable, without status epilepticus	DX	10
G40.901	Epilepsy, unspecified, not intractable, with status epilepticus	DX	10
G40.909	Epilepsy, unspecified, not intractable, without status epilepticus	DX	10
G40.911	Epilepsy, unspecified, intractable, with status epilepticus	DX	10
G40.919	Epilepsy, unspecified, intractable, without status epilepticus	DX	10
G40.A01	Absence epileptic syndrome, not intractable, with status epilepticus	DX	10
G40.A09	Absence epileptic syndrome, not intractable, without status epilepticus	DX	10
G40.A11	Absence epileptic syndrome, intractable, with status epilepticus	DX	10
G40.A19	Absence epileptic syndrome, intractable, without status epilepticus	DX	10
G40.B01	Juvenile myoclonic epilepsy, not intractable, with status epilepticus	DX	10
G40.B09	Juvenile myoclonic epilepsy, not intractable, without status epilepticus	DX	10
G40.B11	Juvenile myoclonic epilepsy, intractable, with status epilepticus	DX	10
G40.B19	Juvenile myoclonic epilepsy, intractable, without status epilepticus	DX	10
P90	Convulsions of newborn	DX	10
R50.2	Drug induced fever	DX	10
R56.1	Post traumatic seizures	DX	10
R68.0	Hypothermia not associated with low environmental temperature	DX	10
R68.83	Chills (without fever)	DX	10

Abbreviation: DX, ICD-CM diagnosis.