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Biologics Effectiveness and Safety Initiative

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

Final Report

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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

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List of Acronyms

ADEM	Acute Disseminated Encephalitis, Myelitis and Encephalomyelitis
BEST	Biologics Effectiveness and Safety
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
EHR	Electronic Health 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-AM	International Classification of Diseases, Tenth Revision, Australian Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
LAIV	Live Attenuated Influenza Vaccine
LOINC	Logical Observation Identifiers Names and Codes
MeSH	Medical Subject Headings
NDC	National Drug Code
NPV	Negative Predictive Value
PICO	Population, Intervention, Comparator, Outcome
PPV	Positive Predictive Value
SMEs	Subject Matter Experts

A Summary

The United States (U.S). Food and Drug Administration (FDA) Biologics Effectiveness and Safety (BEST) Initiative conducted a literature review (through July 10, 2020) to identify validated coding algorithms for ascertaining cases of encephalitis in large administrative healthcare databases. The studies selected for this targeted review used billing codes in claims or electronic health record (EHR) databases to derive encephalitis coding algorithms. Five studies reported on the use of a claims- or EHR-based outcome definition (hereafter referred to as an "algorithm") and included performance measures (positive predictive value [PPV], sensitivity, or specificity).[1-5] Overall, previously published validated algorithms for encephalitis generally had poor performance with low PPV for identifying cases of encephalitis.[1-5] A summary of key findings from the structured literature review are described below.

A U.S. study used International Classification of Diseases, Ninth Revision, Clinical Modification (ICM-9-CM) hospitalization codes in the primary diagnostic position to identify patients with meningitis and encephalitis covered by the Tennessee Medicaid program.[5] Their claims-based algorithm resulted in a PPV of 50.0% (95% confidence interval [CI] 23.7–76.3%).[5] A U.S. EHR-based study reported on the accuracy of ICD-9-CM codes in identifying patients with encephalitis, finding that only 19.6% of patients with an encephalitis discharge code met the International Encephalitis Consortium definition.[4] An EHR-based study conducted in Australia used International Classification of Diseases, Tenth Revision, Australian Modification (ICD-10-AM) codes to identify encephalitis cases in children under the age of 14 years.[2] The resulting PPV was 14% with a sensitivity of 64% and specificity of 9%.[2] The study also alluded to a trade-off between sensitivity and both specificity and PPV, because excluding certain codes from the algorithm decreased sensitivity but increased specificity and PPV.[2] Another Australian, EHR-based validation study examined patients hospitalized with an encephalitis diagnosis in the primary position, reporting that fewer than 50% had clinical features or laboratory and neuroimaging results consistent with encephalitis.[3] Finally, an EHR-based validation study from Denmark aimed to identify autoimmune encephalitis in children under the age of 18 years; authors reported a PPV of 8% (95% CI 3-15%).[1] Additional algorithms from other studies were identified in the literature review but were not subject to validation. The complete lists of codes used in each study are provided in **Appendix A**.

Findings from this review were leveraged to develop a comprehensive algorithm, which was refined further via consultation with clinical subject matter experts (SMEs) from IBM (TB, JB), FDA Center for Biologics Evaluation and Research (CBER) (JC, DT), and Acumen. The algorithm developed and proposed below incorporated findings from all the publications identified to build a preliminary algorithm based on the best available evidence and refined after consultation with clinical SMEs. The proposed algorithm uses both ICD-9-CM and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes. Codes were mapped from ICD-9-CM to ICD-10-CM via forward–backward mapping, using General Equivalence Mappings (GEMs) for reference.[i] Encephalitis-related codes were included regardless of their specific etiology, and the algorithm includes encephalitis diagnoses related to biologic exposures and external agents such as viral, bacterial, fungal, and protozoan pathogens. The algorithm can be tailored based on specific research questions.

As an initial step in assessing the feasibility of using the algorithm to identify encephalitis, 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., to assess the feasibility of its use. Statistics describing the frequency and proportions of codes included in the algorithm were generated and the results are reported below.

[i] [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.

B Background

Among other responsibilities, FDA is mandated to protect the public health by ensuring the safety and efficacy of drugs, biologics, and medical devices.[ii] In support of this mandate, 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 while minimizing risks to the public for each biologic product. The BEST Initiative is a program initiated by CBER with the objective to assess the safety and effectiveness of biologic products using large datasets of administrative healthcare data.

Encephalitis is characterized as inflammation of the brain that can cause neurologic dysfunction, disability, and death.[6,7] Symptoms can be nonspecific and range from differing levels of consciousness, personality changes, seizures, fever, limbic and respiratory symptoms, movement disorder, and acute flaccid paralysis.[6,8] Recovery from encephalitis varies widely depending on the etiology of the illness, with some patients making a full (neurological) recovery while others may suffer from long-term learning disabilities, speech and hearing impairment, and neurological complications and deficits, with some cases resulting in death.[8] According to the International Encephalitis Consortium, encephalitis is associated with significant morbidity and mortality world-wide.[6] In the U.S., the overall rate of hospitalization for encephalitis was estimated to be 7.3 per 100,000 population, with an average length of stay of 11.2 days and a mortality of 5.6% among those hospitalized.[9]

Encephalitis has a complex etiology, with over 100 different identified pathogens — including viral, bacterial, fungal, and protozoan pathogens — and immune-mediated conditions (i.e., driven by immune response, including autoimmune diseases or in response to vaccination) acting as potential causes.[7,8] Unfortunately, the cause of the disease is found in fewer than 50% of cases, meaning that most encephalitis cases have an unknown or unspecified cause.[7,8] Vaccines have been created to prevent the illness from some known pathogens — such as yellow fever, rabies, and tick-borne encephalitis — which have led to a decrease in incidence.[8,10]

Studies have examined possible associations between vaccine exposure and encephalitis, including encephalitis as an adverse event following influenza and adenovirus vaccine exposure.[11,12] The objective of this review was to assess and understand the validity of electronic coding algorithms using billing codes for identifying cases of encephalitis from administrative claims and EHR using billing codes, enabling CBER and other researchers to assess encephalitis risk in the context of exposure to biologics. These methods draw on a variety of coding standards, including International Classification of Diseases (ICD), Healthcare Common Procedure Coding System (HCPCS), Current Procedural Terminology (CPT), National Drug Code (NDC), and Logical Observation Identifiers Names and Codes (LOINC). As the intent of this study was to develop an encephalitis algorithm that was exposure-agnostic, codes were included regardless of their specific etiology.[7]

A structured literature review of coding algorithms for identifying potential cases of encephalitis using administrative claims- and EHR-based codes was conducted, leveraging findings from U.S. and international studies to inform the development of an algorithm. The draft algorithm was then reviewed by clinical SMEs (TB, JB, JC, DT), and testing in the IBM MarketScan® Research Databases (Commercial and Medicare Supplemental), a large collection of U.S. administrative insurance claims data accessed via the Treatment Pathways online analytic platform.

Section C summarizes the literature review methodology and findings; **Section D** provides clinical case definitions for encephalitis, which could be of value in further assessing the performance of the proposed algorithms via chart review validation studies; **Sections E** and **F** present the algorithm and its associated assumptions and decisions, respectively; **Section G** presents the results of an initial application of the

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

algorithms to characterize the population with encephalitis in a claims database; and **Section H** provides discussion and concluding thoughts.

C Literature Review

C1 Methods

A literature review search strategy was developed for the BEST Initiative, based on the Population, Intervention, Comparator, Outcome (PICO) framework. The PICO framework used can be summarized as follows:

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

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

The literature review process started with a comprehensive search of existing publications available in the CBER[iii] and Center for Drug Evaluation and Research Sentinel[iv] databases (no studies were found). A review of the academic literature was then conducted using a structured search method. The search was conducted on July 10, 2020, and no publication date restrictions were applied. Only publications available in English were included for review. PubMed and Google Scholar were used to identify relevant resources. The search strategy, which is not case-sensitive, is summarized below:

- **Search 1** (PubMed): encephalitis "algorithm" – **retrieved 146 articles**
- **Search 2** (PubMed): (encephalitis[Title/Abstract]) AND (validation[Title/Abstract]) – **retrieved 123 results**
- **Search 3** (PubMed): (encephalitis[Title]) AND (icd[Title/Abstract]) – **retrieved 23 results**
- **Search 4** (PubMed): ((encephalitis[Title/Abstract]) AND (hospitalizations[Title/Abstract]) AND (diagnosis[Title/Abstract]) – **retrieved 21 results**
- **Search 5** (Google Scholar): encephalitis algorithm icd – **retrieved 1970 results**

Further searches were then conducted to focus on specific causes of encephalitis:

- **Search 6** (Google Scholar): encephalitis caused by "vaccine" icd – **retrieved 2710 results**
- **Search 7** (Google Scholar): encephalitis "vaccination" icd – **retrieved 2360 results**
- **Search 8** (PubMed): "autoimmune" encephalitis algorithm – **retrieved 35 results**

A snowballing technique was also used, wherein the reference lists of relevant studies were scanned for additional publications of potential relevance.

Publications that met the above search criteria were screened. In total,12 papers were reviewed in full text. 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 algorithm specifications ("Algorithm"), and the measures of validity and

[iii] U.S. Food and Drug Administration. Science & Research (Biologics). Last updated March 28, 2019. https://www.fda.gov/BiologicsBloodVaccines/ScienceResearch/default.htm
[iv] Sentinel. Publications and Presentations. https://www.sentinelinitiative.org/communications/publications

diagnostic accuracy (e.g., PPV and Negative Predictive Value [NPV]). Relevance rankings were assigned based on the following criteria:

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

Table 1. Data elements recorded 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, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; PPV, Positive predictive value; NPV, Negative predictive value; 95% CI, 95% confidence interval

C2 Results of Literature Review

Following title and abstract screening and full-text review, 11 publications were identified as being particularly relevant (additional details and complete lists of included codes are provided for each study in **Appendix A**).[1-5,9,11,13-16] Each publication reported either measures of diagnostic accuracy associated with claims-based algorithms (i.e., encephalitis codes derived from administrative insurance claims databases) or EHR-based algorithms (i.e., encephalitis codes derived from admission or discharge medical records). Additional publications identified cases of encephalitis using administrative claims or EHR data but did not validate their codes. Of the 11 publications, five studies were from the U.S., two studies were from Australia, and there was one study each from Canada, England, Norway, and Denmark. Publication dates for these studies ranged from 2003 to 2019. Across the selected studies, diagnosis codes were the primary code sets used to identify encephalitis.

Of the 11 papers, five included validation and measures of performance such as positive predictive value (PPV), sensitivity, and specificity (none included NPV).[1-5] Across these studies, diagnostic performance measures for encephalitis algorithms were consistently poor with low PPV. We summarized the literature below by the data source from which each coding algorithm was derived (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 a U.S. validation study, Wiese and colleagues sought to validate discharge codes related to serious infections — including meningitis and encephalitis — in patients covered by the Tennessee Medicaid program.[5] The study was restricted to those over 50 years old with at least 180 days of enrollment in the Medicaid program, no life-threatening conditions that could increase risk for infection, at least one pharmacy prescription filled, and at least one encounter with ICD-9-CM coding for meningitis or encephalitis. Using ICD-9-CM codes in the primary diagnosis position, a PPV of 50.0% (95% confidence interval [CI] 23.7–76.3%) was reported.[5] However, it is important to note that the algorithm and validation were for both meningitis and encephalitis, so the performance of the algorithm is likely to differ from one algorithm considering encephalitis alone.

2.b Medical Records-based Algorithms with Validation

One U.S. study and three international studies that validated EHR-based algorithms for encephalitis were found.[1-4] A U.S. study by Samannodi and colleagues conducted a retrospective study to determine the accuracy of ICD-9-CM codes in identifying patients with encephalitis.[4] They identified all adults with a discharge code of encephalitis using code families 323 (encephalitis myelitis and encephalomyelitis), 062 (mosquito-borne viral encephalitis), 046 (slow virus infection and prion diseases of central nervous system), and 066 (other arthropod-borne viral diseases).[4] It was determined that only 19.6% of patients with an encephalitis discharge code met the International Encephalitis Consortium definition.[4]

In a validation study by Britton and colleagues, the authors sought to validate ICD-10-AM codes used for encephalitis surveillance in the pediatric population of Australia.[2] Their population of interest consisted of children under 14 years of age hospitalized due to encephalopathy with symptoms, neuroimaging results, or cerebrospinal fluid screening test evidence consistent with encephalitis.[2] A PPV of 14% with a sensitivity of 64% and specificity of 9% was reported (no 95% CI reported).[2] By excluding G93.4 (unspecified encephalopathy [including influenza]), B94.1 (sequelae of viral encephalitis) and B94.8 (sequelae of infectious and parasitic disease) from their proposed algorithm, the sensitivity was lowered to 12% but the specificity increased to 27% and PPV increased to 33% which points to a possible trade-off between sensitivity and both specificity and PPV.[2] Performance measures for encephalitis were not reported separately.

Another Australian study conducted by Huppatz and colleagues explored the diagnostic accuracy of an EHR-based encephalitis algorithm.[3] The population of interest was patients aged 18 years or over who were hospitalized and received a primary discharge code of encephalitis.[3] The following ICD-10-AM code families were used to identify patients: A32 (listeriosis), A85 (other viral encephalitis, not elsewhere classified), B00 (herpes viral [herpes simplex] infections), B01 (varicella [chickenpox]), B02 (zoster [herpes zoster]), G05 (encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere), G04 (encephalitis, myelitis and encephalomyelitis), and A86 (unspecified viral encephalitis).[3] The authors concluded that, of the cases identified, fewer than 50% had clinical features or laboratory and neuroimaging results consistent with encephalitis.[3]

A third EHR-based validation study, conducted in 2019 by Boesen and colleagues, sought to validate ICD-10 codes related to pediatric autoimmune encephalitis in Denmark.[1] Limiting their population to children under 18 years of age who received testing for autoimmune encephalitis, authors reported a PPV of 8% (95% CI 3-15%).[1]

2.c Algorithm Application without Validation

Searches identified six additional publications that applied encephalitis coding algorithms without validation. Although no diagnostic performance measures were reported, these studies supported efforts to create a comprehensive list of encephalitis codes and to identify specific codes to identify encephalitis cases potentially associated with exposure to biologics.

In a U.S. study, George and colleagues used ICD-9-CM codes to identify the hospitalization rates and inpatient mortality for patients admitted into acute inpatient care.[9] This study used several code families including 054 (herpes simplex), 048 (other enterovirus diseases of central nervous system), 052 (chickenpox), 058 (other human herpesvirus), 045 (acute poliomyelitis), 046 (slow virus infection and prion diseases of central nervous system), 049 (other non-arthropod-borne viral diseases of central nervous system), 056 (rubella), 062 (mosquito-borne viral encephalitis), 063 (tick-borne viral encephalitis), 071 (rabies), 072 (mumps), 323 (encephalitis myelitis and encephalomyelitis), 066 (other arthropod-borne viral diseases), 055 (measles), 130 (toxoplasmosis), 036 (meningococcal infection), 013 (tuberculosis of meninges and central nervous system), 090 (congenital syphilis), 094 (neurosyphilis), 136 (other and unspecified infectious and parasitic diseases), and 064 (viral encephalitis transmitted by other and unspecified arthropods).[9]

Davison and colleagues identified viral encephalitis cases in England to evaluate the accuracy of current surveillance systems for the disease.[13] Hospital admissions of interest for patients over the age of 18 years included diagnosis codes related to ICD-9 code families 062 (mosquito-borne viral encephalitis), 063 (tick-borne viral encephalitis), 064 (viral encephalitis transmitted by other and unspecified arthropods), 066 (other arthropod-borne viral diseases), 323 (encephalitis myelitis and encephalomyelitis), 054 (herpes simplex), 055 (measles), 072 (mumps), 056 (rubella), 049 (other non-arthropod-borne viral diseases of central nervous system), 312 (lymphocytic choriomeningitis virus), 049 (other non-arthropod-borne viral diseases of central nervous system) and ICD-10 code families A83 (mosquito-borne viral encephalitis), A84 (tick-borne viral encephalitis), A85 (other viral encephalitis, not elsewhere classified), B00 (herpes viral [herpes simplex] infections), B01 (varicella [chickenpox]), B02 (zoster [herpes zoster]), B05 (measles), B26 (mumps), B06 (rubella [German measles]), A87 (viral meningitis), A85 (other viral encephalitis, not elsewhere classified), A86 (unspecified viral encephalitis), and G05 (encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere).[13] Authors reported that, among both viral encephalitis cases and encephalitis-related deaths, data available from hospital episode statistics was underreported to the Office of National Statistics.[13]

Three studies focused on encephalitis following immunization. A Norwegian, EHR-based study conducted by Ghaderi and colleagues investigated encephalitis cases after influenza vaccination.[12] Hospitalizations related to encephalitis were identified among the Norwegian population registered in the Norwegian Patient Registry using ICD-10 codes related to hospitalization with the following code families: A86 (unspecified viral encephalitis), A87 (viral meningitis), A89 (unspecified viral infection of central nervous system), G03 (meningitis due to other and unspecified causes), and G04 (encephalitis, myelitis and encephalomyelitis).[12] Choudhry and colleagues evaluated the safety of type 4 and type 7 adenovirus vaccinations in military recruits in the U.S.[11] They compared military recruits between the age of 17 and 50 years who received the adenovirus vaccines with recruits that had the same other vaccine requirements as the exposed group, but did not receive the adenovirus vaccines, in the same training site.[11] Using the ICD-9-CM code group 323 (encephalitis myelitis and encephalomyelitis) in the primary diagnostic code position, encephalitis cases related to immunizations were identified. Authors found one case of encephalitis possibly related to vaccine exposure.[11] In another U.S. study, Millman and colleagues investigated hospitalizations related to exposure to live attenuated influenza vaccine (LAIV) in the pediatric population.[15] The population of interest included children 2–18 years of age who received the LAIV and had a subsequent hospitalization. Hospitalizations related to encephalitis were identified using ICD-9-CM code group 323 (encephalitis myelitis and encephalomyelitis) in the primary diagnostic code position.

Finally, in a Canadian study Parpia and colleagues categorized a comprehensive list of ICD-10 encephalitis codes into etiology groups.[7] Etiology groups included immune-mediated, other, unknown, viral, bacterial, amebic, fungal, and parasitic etiologies.[7] The etiology groups most relevant for the algorithm proposed in this report comprised immune-mediated, other, and unknown etiologies, which included ICD-10 code families G04 (encephalitis, myelitis and encephalomyelitis), G36 (other acute disseminated demyelination), M32 (systemic lupus erythematosus), G05 (encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere), G13 (systemic atrophies primarily affecting central nervous system in diseases classified elsewhere), and A86 (unspecified viral encephalitis).[7]

D Encephalitis Clinical Case Definition

Two clinical case definitions, the Brighton Collaboration Encephalitis Working Group and International Encephalitis Consortium were noted in the literature review.[6,17] These definitions demonstrated notable similarities but differed in their complexity. The optimal case definition may depend on the priorities of a particular research or validation study and available data.

The Brighton Collaboration Encephalitis Working Group's encephalitis case definition was the most commonly identified. The Working Group proposed a case definition that could be applied to identify cases of encephalitis as an adverse event following immunization, which could be of particular relevance to assessing the performance of the proposed algorithm within the context of a particular biologic exposure.[17] This encephalitis case definition is separated into three different levels of diagnostic certainty with Level 1 representing the highest level of diagnostic certainty and Level 3 representing the lowest.[17] Levels 2 and 3 are distinguished by the number of indicators of central nervous system inflammation required (≥2 vs 1, respectively). The case definition is summarized below[v]:[17]

- **Level 1**
  - Demonstration of acute inflammation of central nervous system parenchyma (± meninges) by histopathology.
- **Level 2**
  - Encephalopathy (e.g., depressed or altered level of consciousness, lethargy, or personality change lasting >24 h),

  AND INCLUDING ONE OR MORE of the following:
  - Decreased or lack of response to environment, as defined by responses to loud noise or painful stimuli,
  - Decreased or absent eye contact,
  - Inconsistent or absent response to external stimuli,
  - Decreased arousability,
  - Seizure associated with loss of consciousness.

  OR Focal or multifocal findings referable to the central nervous system, including **ONE OR MORE** of the following:
  - Focal cortical signs (including but not limited to aphasia, alexia, agraphia, cortical blindness),
  - Cranial nerve abnormalities,
  - Visual field defect(s),
  - Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex),
  - Motor weakness (either diffuse or focal; more often focal),
  - Sensory abnormalities (either positive of negative; sensory level),
  - Altered deep tendon reflexes (hypo- or hyperreflexia, reflex asymmetry),
  - Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus.

  AND (for both possibilities to reach Level 2) TWO OR MORE of the following indicators of inflammation of the central nervous system:
  - Fever (temperature ≥38°C),
  - Cerebrospinal fluid pleocytosis,
  - Electroencephalography findings consistent with encephalitis, or
  - Neuroimaging consistent with encephalitis.
- **Level 3**
  - Encephalopathy e.g., depressed or altered level of consciousness, lethargy, or personality change lasting >24 h,

  AND INCLUDING ONE OR MORE of the following:
  - Decreased or absent response to environment, as defined by response to loud noise or painful stimuli,
  - Decreased or absent eye contact,

[v] Definition is drawn verbatim from publication by Sejvar and colleagues.[17] It should be noted that these diagnostic criteria may not be applicable to children and infants who have not achieved the same level of development as older children and adults.

- Inconsistent or absent response to external stimuli,
- Decreased arousability,
- Seizure associated with loss of consciousness

OR Focal or multifocal findings referable to the central nervous system, including **ONE OR MORE** of the following:

- Focal cortical signs (including but not limited to aphasia, alexia, agraphia, cortical blindness),
- Cranial nerve abnormality/abnormalities
- Visual field defect(s),
- Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex),
- Motor weakness (either diffuse or focal; more often focal),
- Sensory abnormalities (either positive or negative; sensory level),
- Altered deep tendon reflexes (hypo- or hyperreflexia, reflex asymmetry), or
- Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus.

AND (for both possibilities to reach Level 3) ONE of the following indicators of inflammation of the central nervous system**:**

- Fever (temperature ≥38◦C),
- Cerebrospinal fluid pleocytosis,
- Electroencephalography findings consistent with encephalitis, or
- Neuroimaging consistent with encephalitis.

- **Level 3A**
  - Insufficient information available to distinguish case between acute encephalitis or ADEM; case unable to be definitively classified.
- **Exclusion criterion for Level 2 and 3**
  - Other diagnosis for illness present.

In 2012, the International Encephalitis Consortium released a consensus document that proposed a standardized case definition for encephalitis.[6] The Consortium suggested that the Brighton Collaboration Encephalitis Working Group definition may have limited applicability for infectious and autoimmune encephalitis, as well as unknown diagnostic accuracy for each level diagnostic certainty. In response, the Consortium sought to develop a more inclusive and simplified case definition.[6] The resulting case definition (**Table 2**) includes signs of encephalopathy as a major criterion with additional, "minor" criteria required to establish possible, probable, or confirmed encephalitis.

Table 2. International Encephalitis Consortium Case Definition[6]

Major Criteria (Required)	Minor Criteria (2 Criteria=Possible Case, 3 or More Criteria=Probable or Confirmed Case)
Altered mental status lasting 24 hours or more with no cause identified. Altered mental status includes the following: - Decreased or altered level of consciousness - Lethargy - Personality change	- Fever of 38° C or 100.4° F 72 hours before or after hospitalization - Generalized or partial seizures not caused by existing seizure disorder - New focal neurologic findings - Central nervous system white blood cell count equal to or more than 5/cubic mm - Neuroimaging suggesting new abnormality in brain parenchyma or of encephalitis - Electroencephalography abnormalities consistent for encephalitis

Identification of the specific cause of the encephalitis (e.g. identifying the pathogen that caused it) is not required for the diagnosis.[6] To be considered a confirmed case of encephalitis, at least one of the following criteria must also be met (in addition to the criteria specified in Table 2): [6]

- Pathologic evidence of brain inflammation suggestive of encephalitis **OR**

- Pathologic, microbiologic, or serologic evidence for an acute infection related to a microorganism associated with encephalitis from a clinical specimen **OR**
- Autoimmune condition that is closely associated with encephalitis with laboratory evidence

E Encephalitis Coding Algorithm

The aim of this review was to develop an algorithm to identify cases of encephalitis that could be of potential interest following exposure to a biologic product. To form a comprehensive list of encephalitis codes for clinical consideration, all ICD codes for encephalitis were extracted from the 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.[18-21] 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.

The workgroup has sought an approach that is consistent with those reported in the published literature; this involved selecting the specific codes for encephalitis regardless of etiology, while excluding codes related to distinct conditions such as meningitis. This approach supports alignment and comparability with past studies and reflects current coding practices. However, this broad approach may impact the performance of the algorithm (i.e., potential decrease in specificity).

The proposed algorithm for identifying encephalitis using administrative claims codes is presented in **Table 3**. This algorithm takes a general approach to defining encephalitis and may be subject to refinements for specific research questions in the future. While not excluding codes based on etiology, the algorithm codes have been organized into Inclusion Categories in order to facilitate tailoring based on particular research questions or study priorities. These categories are organized as follows:

- Inclusion Category 1: Codes that could reasonable be associated with a biologic exposure
- Inclusion Category 1.5: Unspecified codes related to encephalitis
- Inclusion Category 2: Codes related to encephalitis due to other specified causes

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 B**. 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, they were left out of the algorithm options to identify cases of encephalitis. Meanwhile, annual counts of patients with individual diagnosis codes included in the algorithm are provided in **Appendix C**.

The proposed algorithm can be summarized as follows:

> **INCLUDE: ANY** (“either–or” logic) of the codes listed in Table 3**,** regardless of health care setting or coding position (only one code required).

Table 3. Encephalitis Algorithm

Code	Description	Code Category	Code Type	Inclusion Category
323.51	Encephalitis and encephalomyelitis following immunization procedures	DX	9	1
G04.02	Postimmunization acute disseminated encephalitis, myelitis and encephalomyelitis	DX	10	1
323.62	Other postinfectious encephalitis and encephalomyelitis	DX	9	1.5
323.81	Other causes of encephalitis and encephalomyelitis	DX	9	1.5

Code	Description	Code Category	Code Type	Inclusion Category
323.9	Unspecified causes of encephalitis, myelitis, and encephalomyelitis	DX	9	1.5
G04.00	Acute disseminated encephalitis and encephalomyelitis, unspecified	DX	10	1.5
G04.81	Other encephalitis and encephalomyelitis	DX	10	1.5
G04.90	Encephalitis and encephalomyelitis, unspecified	DX	10	1.5
G05.3	Encephalitis and encephalomyelitis in diseases classified elsewhere	DX	10	1.5
013.60	Tuberculous encephalitis or myelitis, unspecified	DX	9	2
013.61	Tuberculous encephalitis or myelitis, bacteriological or histological examination not done	DX	9	2
013.62	Tuberculous encephalitis or myelitis, bacteriological or histological examination unknown (at present)	DX	9	2
013.63	Tuberculous encephalitis or myelitis, tubercle bacilli found (in sputum) by microscopy	DX	9	2
013.64	Tuberculous encephalitis or myelitis, tubercle bacilli not found (in sputum) by microscopy, but found by bacterial culture	DX	9	2
013.65	Tuberculous encephalitis or myelitis, tubercle bacilli not found by bacteriological examination, but tuberculosis confirmed	DX	9	2
013.66	Tuberculous encephalitis or myelitis, tubercle bacilli not found by bacteriological or histological examination, but tuberculosis confirmed by other methods [inoculation of animals]	DX	9	2
036.1	Meningococcal encephalitis	DX	9	2
046.2	Subacute sclerosing panencephalitis	DX	9	2
052.0	Postvaricella encephalitis	DX	9	2
054.3	Herpetic meningoencephalitis	DX	9	2
055.0	Postmeasles encephalitis	DX	9	2
058.21	Human herpesvirus 6 encephalitis	DX	9	2
058.29	Other human herpesvirus encephalitis	DX	9	2
062.0	Japanese encephalitis	DX	9	2
062.1	Western equine encephalitis	DX	9	2
062.2	Eastern equine encephalitis	DX	9	2
062.3	St. Louis encephalitis	DX	9	2
062.4	Australian encephalitis	DX	9	2
062.5	California virus encephalitis	DX	9	2
062.8	Other specified mosquito-borne viral encephalitis	DX	9	2
062.9	Mosquito-borne viral encephalitis, unspecified	DX	9	2
063.0	Russian spring-summer [taiga] encephalitis	DX	9	2
063.1	Louping ill	DX	9	2
063.2	Central European encephalitis	DX	9	2
063.8	Other specified tick-borne viral encephalitis	DX	9	2
063.9	Tick-borne viral encephalitis, unspecified	DX	9	2
064	Viral encephalitis transmitted by other and unspecified arthropods	DX	9	2
066.41	West Nile Fever with encephalitis	DX	9	2
072.2	Mumps encephalitis	DX	9	2
090.41	Congenital syphilitic encephalitis	DX	9	2
094.81	Syphilitic encephalitis	DX	9	2
130.0	Meningoencephalitis due to toxoplasmosis	DX	9	2

Code	Description	Code Category	Code Type	Inclusion Category
139.0	Late effects of viral encephalitis	DX	9	2
323.01	Encephalitis and encephalomyelitis in viral diseases classified elsewhere	DX	9	2
323.1	Encephalitis, myelitis, and encephalomyelitis in rickettsial diseases classified elsewhere	DX	9	2
323.2	Encephalitis, myelitis, and encephalomyelitis in protozoal diseases classified elsewhere	DX	9	2
323.41	Other encephalitis and encephalomyelitis due to other infections classified elsewhere	DX	9	2
323.71	Toxic encephalitis and encephalomyelitis	DX	9	2
A17.82	Tuberculous meningoencephalitis	DX	10	2
A32.12	Listerial meningoencephalitis	DX	10	2
A39.81	Meningococcal encephalitis	DX	10	2
A50.42	Late congenital syphilitic encephalitis	DX	10	2
A52.14	Late syphilitic encephalitis	DX	10	2
A81.1	Subacute sclerosing panencephalitis	DX	10	2
A83.0	Japanese encephalitis	DX	10	2
A83.1	Western equine encephalitis	DX	10	2
A83.2	Eastern equine encephalitis	DX	10	2
A83.3	St Louis encephalitis	DX	10	2
A83.4	Australian encephalitis	DX	10	2
A83.5	California encephalitis	DX	10	2
A83.6	Rocio virus disease	DX	10	2
A83.8	Other mosquito-borne viral encephalitis	DX	10	2
A83.9	Mosquito-borne viral encephalitis, unspecified	DX	10	2
A84.0	Far Eastern tick-borne encephalitis [Russian spring-summer encephalitis]	DX	10	2
A84.1	Central European tick-borne encephalitis	DX	10	2
A84.81	Powassan virus disease	DX	10	2
A84.89	Other tick-borne viral encephalitis	DX	10	2
A84.9	Tick-borne viral encephalitis, unspecified	DX	10	2
A85.0	Enteroviral encephalitis	DX	10	2
A85.1	Adenoviral encephalitis	DX	10	2
A85.2	Arthropod-borne viral encephalitis, unspecified	DX	10	2
A85.8	Other specified viral encephalitis	DX	10	2
A86	Unspecified viral encephalitis	DX	10	2
A92.31	West Nile virus infection with encephalitis	DX	10	2
B00.4	Herpesviral encephalitis	DX	10	2
B01.11	Varicella encephalitis and encephalomyelitis	DX	10	2
B02.0	Zoster encephalitis	DX	10	2
B05.0	Measles complicated by encephalitis	DX	10	2
B06.01	Rubella encephalitis	DX	10	2
B10.01	Human herpesvirus 6 encephalitis	DX	10	2
B10.09	Other human herpesvirus encephalitis	DX	10	2
B26.2	Mumps encephalitis	DX	10	2
B58.2	Toxoplasma meningoencephalitis	DX	10	2
B94.1	Sequelae of viral encephalitis	DX	10	2
G04.01	Postinfectious acute disseminated encephalitis and encephalomyelitis (postinfectious ADEM)	DX	10	2
G04.2	Bacterial meningoencephalitis and meningomyelitis, not elsewhere classified	DX	10	2

Abbreviation: DX, ICD-CM diagnosis.

F Assumptions and Decisions

The algorithm presented above in **Section E** was reviewed internally and by CBER stakeholders and partners. The decisions and assumptions made related to algorithm construction are summarized below. Some of these decisions and assumptions may be modified for future research questions.

- The algorithm includes codes regardless of encephalitis etiology. Users may tailor the algorithm further based on their specific research question.
- Based on the judgement of clinical experts, codes for encephalopathy and myelitis were excluded from the proposed algorithm, as they were deemed to be distinct from encephalitis.
- As informed by published literature and agreement by clinical SMEs, a decision was made to exclude procedural (CPT) and prescription (NDC, HCPCS) code standards, as they were unlikely to improve algorithm performance. Thus, the proposed algorithm is restricted to ICD diagnosis codes only.
- The appropriate risk window for associating a biologic exposure with encephalitis is likely to depend on the research question and study priorities and should be specified at the study planning stage.
- The proposed algorithm allows for the codes to be in any diagnosis code position (primary, secondary, unspecified) to ensure that the algorithm does not improperly exclude encephalitis cases.
- Findings of algorithm application should be interpreted with caution given the poor measures of diagnostic performance reported in the literature.
- The possible exclusion of ICD-10-CM G04.01 (postinfectious acute disseminated encephalitis and encephalomyelitis [postinfectious ADEM]) and G04.02 (post-immunization acute disseminated encephalitis, myelitis and encephalomyelitis [ADEM]) in the proposed algorithm was discussed, as the Vaccine Compensation Program considers ADEM to be distinct from encephalitis. These codes were retained given the symptoms and synonyms associated with the codes.

G Algorithm Characterization

G1 Methods

To characterize the population with encephalitis among a commercially insured cohort in the U.S., the workgroup used the IBM MarketScan Research Databases (Commercial, Medicare Supplemental), accessed via the Treatment Pathways online analytic platform[vi], to query and analyze the ICD-CM codes for encephalitis (Inclusion Categories 1, 1.5, and 2 in **Table 3**). 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. It is recommended that the proposed algorithm undergo a validation study prior to use and future analytical studies should tailor the algorithm specifications according to the study question of interest.

The figures presented below have been drawn from the study period of January 1, 2014–December 31, 2018. For all analyses, 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. This was done due to the U.S. transition from ICD-9-CM to ICD-10-CM on October 1, 2015, and a desire to exclude codes that were reported in error.

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

Counts of individual patients that had a diagnosis code related to encephalitis within a given calendar year, rather than counts of cases, were presented. As such, counts relate to the first diagnosed encephalitis 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 encephalitis in the study population, no washout period was applied.

Individuals had to be continuously enrolled in any enrollment category 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 was not included in the two charts that depict the proportions of individuals with encephalitis by age. Infants under one year of age were not excluded from queries of the absolute number of patients receiving an encephalitis diagnosis.

Age- and gender-specific data on MarketScan Research Databases enrollment and counts of individuals receiving a diagnostic code for encephalitis were extracted. Code-specific queries and results described in **Section E** are summarized in **Appendix C**. 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 encephalitis.

G2 Results

Table 4 provides a summary of aggregate counts for ICD-9-CM and ICD-10-CM codes, suggesting that approximately 19.3–22.9 individuals per 100,000 individuals enrolled in the MarketScan Research Databases received a relevant diagnosis code for encephalitis each year. Among the cohort of 46,153,898 patients that were continuously enrolled for at least one calendar year between January 1, 2014, and December 31, 2018, 22,125 individuals (0.05% of the cohort) had at least one relevant ICD-9-CM or ICD-10-CM diagnosis code for encephalitis.

Table 4. Counts of patients with encephalitis by code set and year.

Code/ Description	Year				
	2014	2015[a]	2016	2017	2018
ICD-9-CM	6,062	4,005			
ICD-10-CM		1,547	4,162	3,844	3,757
ICD-9-CM OR ICD-10-CM	6,062	5,073	4,162	3,844	3,757
MarketScan Research Databases Enrollment[b]	28,407,959	22,117,235	21,616,291	19,563,847	19,371,891
Proportion of Patients with Encephalitis per 100,000 Enrolled Population[c]	21.3	22.9	19.3	19.6	19.4

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] Individuals included in this row are those who were enrolled for the full calendar year (January 1–December 31) for 2014, 2015, 2016, 2017, and 2018, respectively.

[c] Proportions were calculated using the counts in the "ICD-9-CM OR ICD-10-CM" row.

Counts of patients with individual diagnosis codes associated with encephalitis were also queried and are presented in **Appendix C**. The resulting counts suggest that the majority of the aggregate counts are

represented by codes for unspecified or other encephalitis: ICD-9-CM code 323.9 (unspecified causes of encephalitis, myelitis, and encephalomyelitis) and ICD-10-CM codes G04.81 (other encephalitis and encephalomyelitis) and G04.90 (encephalitis and encephalomyelitis, unspecified), which were reported in 31.8%, 10.4%, and 28.3% of the population receiving any encephalitis diagnosis code between 2014 and 2018, respectively.

The workgroup assessed whether the 2015 transition to ICD-10-CM and any associated changes in coding practices resulted in notable shifts in the frequency of encephalitis cases of interest. **Figure 1** illustrates the proportion of the enrolled population with a relevant encephalitis diagnosis and suggests that the transition did not result in a substantial change to the proportion of individuals receiving an encephalitis diagnosis (a difference of 3.6 cases per 100,000 enrolled population was observed between years with the highest and lowest frequency). This may be due to the rarity of the condition masking changes associated with the transition, wherein the utilization of ICD-10-CM codes, which can account for specific etiologic factors, may have resulted in the identification of more relevant encephalitis cases. However, it is difficult to infer trends with confidence given the short time period and small absolute change across years.

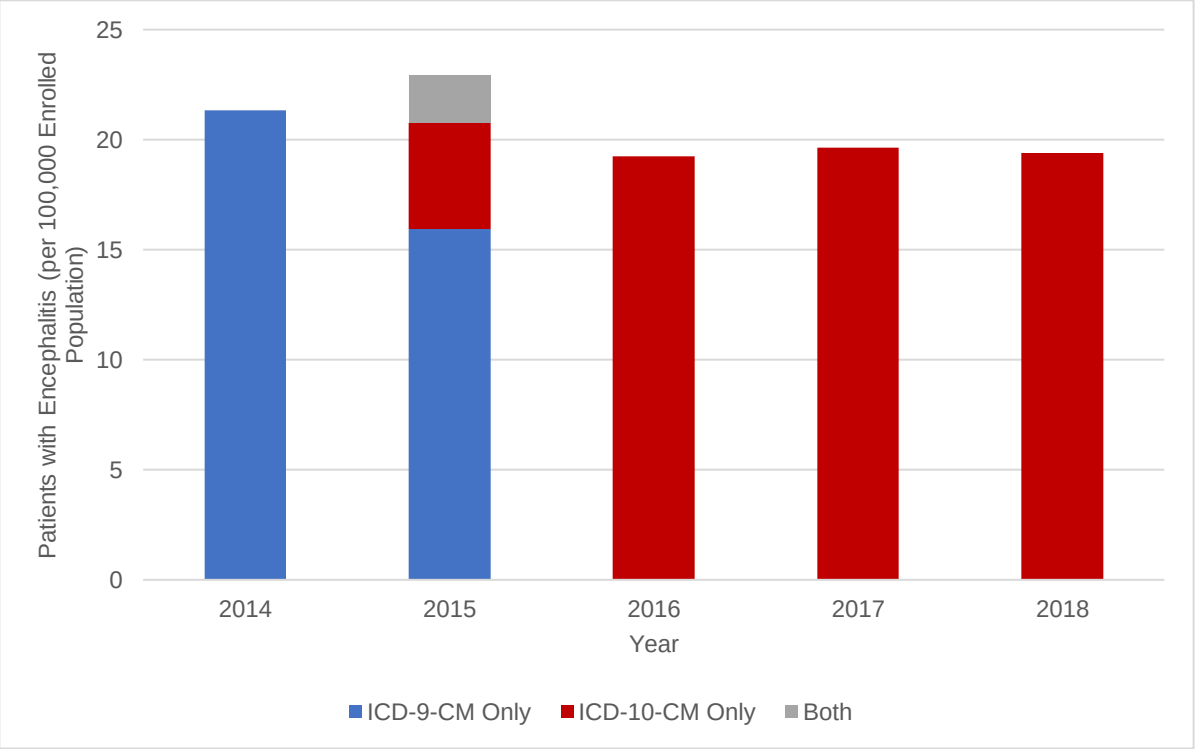

Figure 1. Proportion of patients with encephalitis code per 100,000 enrolled, by year (2014–2018).

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 a relevant ICD-9-CM encephalitis code listed in **Table 3** and 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 9,981 individuals (0.03%) with at least one ICD-9-CM code for encephalitis between January 1, 2014, and September 30, 2015, with an average age (calculated at the first event) of 46 years.

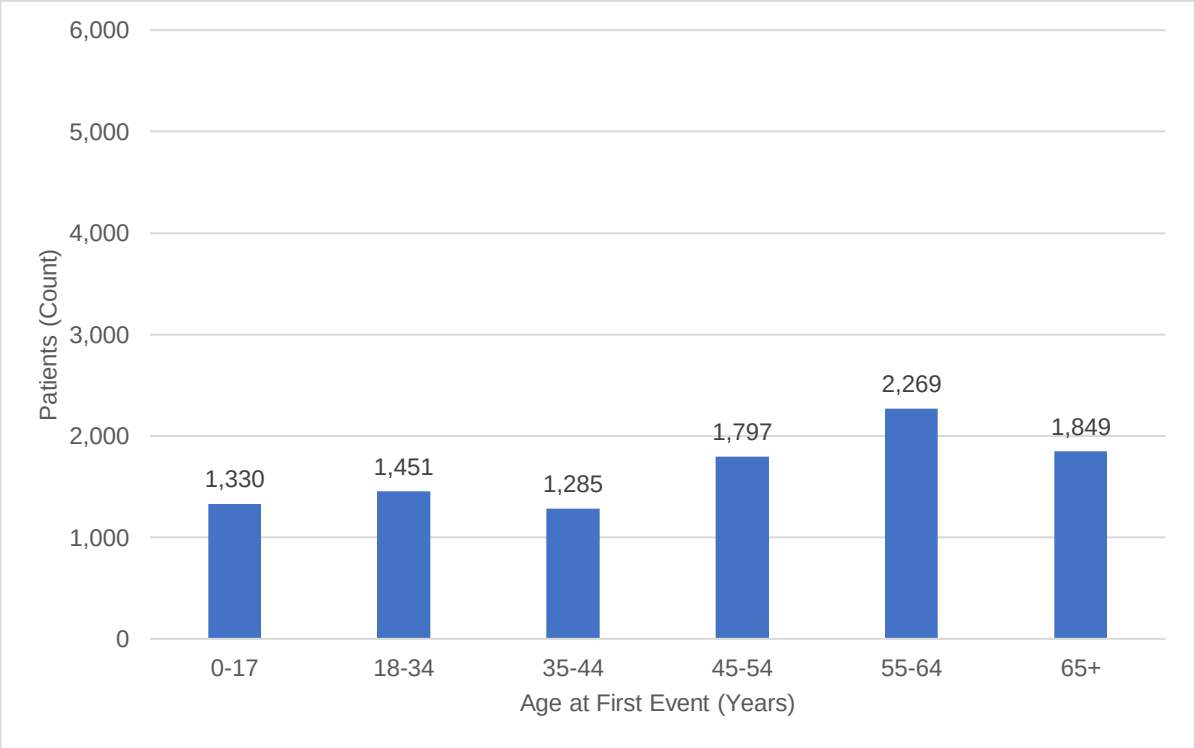

Figure 2. Patients with at least one diagnosis code for encephalitis defined by ICD-9-CM codes, January 1, 2014–September 30, 2015, stratified by age group.

Figure 3 presents counts of patients with a pertinent ICD-10-CM encephalitis code listed in **Table 3** and stratified by age group. Counts were based on a cohort of 35,337,738 individuals who were enrolled in a participating commercial insurance plan for at least one calendar year between 2015 and 2018 (i.e., January 1–December 31 for at least one of 2015, 2016, 2017, or 2018). Among 12,929 individuals (0.04%) with at least one ICD-10-CM code for encephalitis between October 1, 2015, and December 31, 2018, the average age at first event was 44 years. It should be noted that the higher absolute age-specific counts presented in **Figure 3** (relative to **Figure 2**) could be attributed to the longer time period included in this figure.

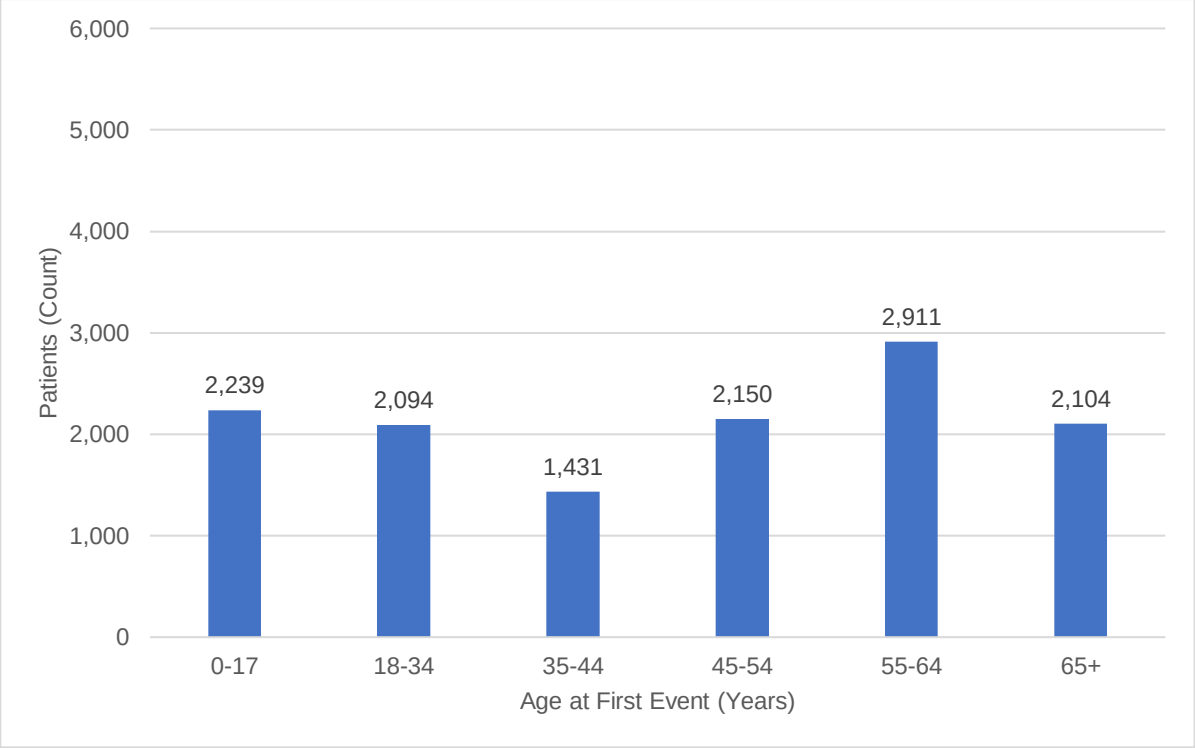

Figure 3. Patients with at least one diagnosis code for encephalitis defined by ICD-10-CM codes, October 1, 2015–December 31, 2018, stratified by age group.

Figure 4 presents counts of patients with either an ICD-9-CM or ICD-10-CM code for encephalitis among a cohort of 46,153,898 individuals who were continuously enrolled for at least one calendar year between 2014 and 2018. Among 22,125 individuals (0.05%) who received a diagnosis code for encephalitis between January 1, 2014, and December 31, 2018, the average age at the first event was 45 years.

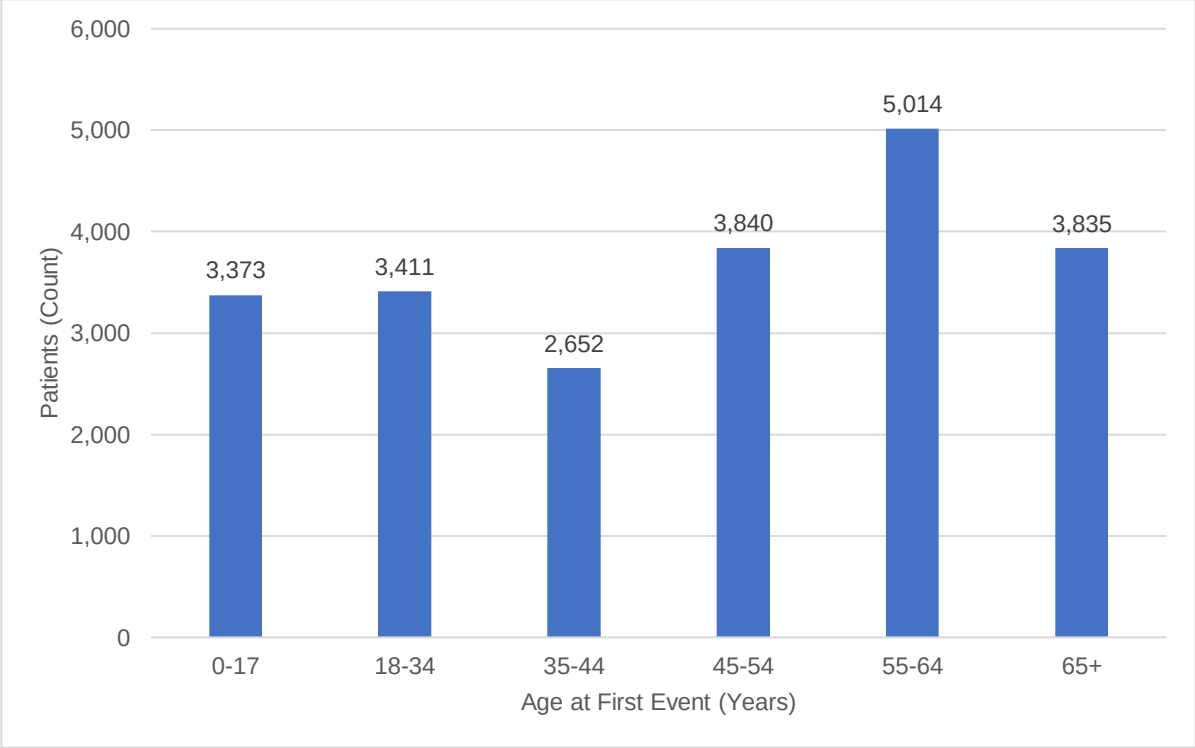

Figure 4. Patients with at least one diagnosis code for encephalitis (ICD-9-CM or ICD-10-CM), January 1, 2014–December 31, 2018, stratified by age group.

Figure 5 depicts the proportion of the population aged 1–85+ years old with at least one ICD-9-CM or ICD-10-CM code for encephalitis (per 100,000 population with continuous enrollment in the MarketScan Research Databases) between January 1, 2014, and December 31, 2018, by age and gender. Patients 85 years of age and older were grouped together in order 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. Results suggest that the proportion of patients with encephalitis increases with age and is distributed fairly evenly between males and females. There is a peak in children between 5–10 years of age where the proportion of cases is higher among males. This is followed by a slow increase to about 65 years of age. After this, there is a larger increase in the proportion of individuals experiencing encephalitis, especially among elderly men.

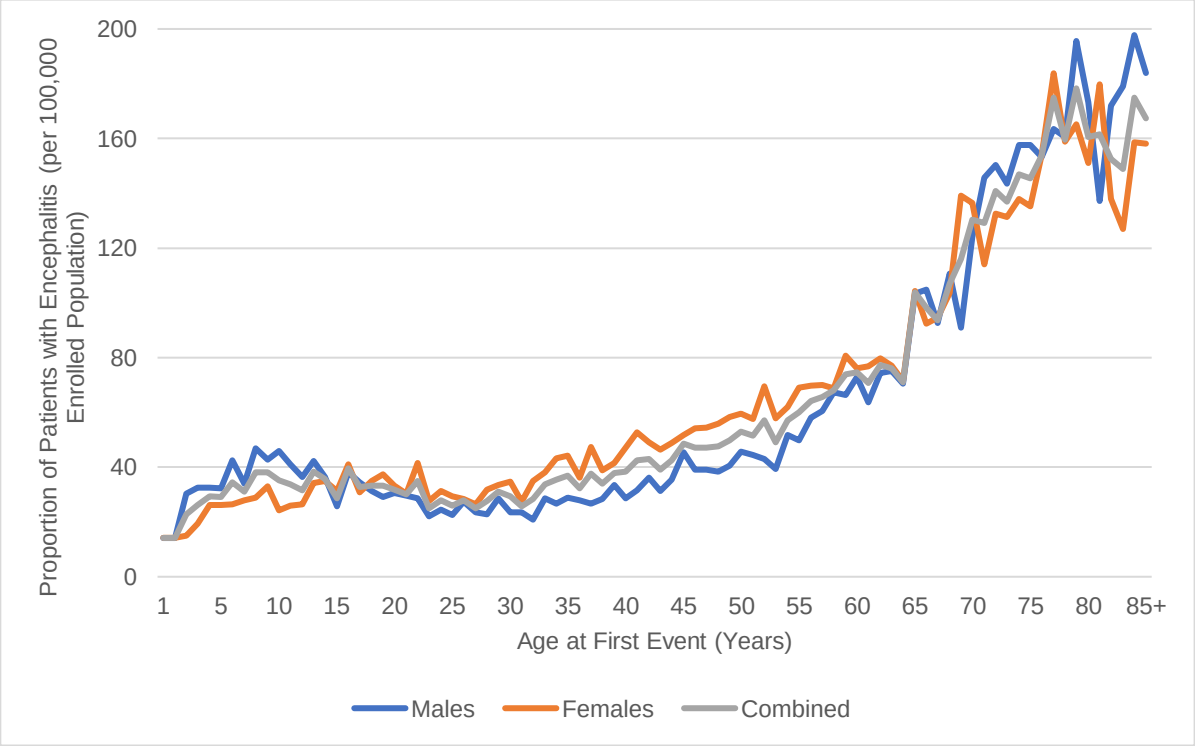

Figure 5. Proportion of patients (1–85+)* with at least one diagnosis code for encephalitis (ICD-9-CM or ICD-10-CM) per 100,000 enrolled population, by age and gender (January 1, 2014–December 31, 2018).

* 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 encephalitis is excluded from the chart.

The workgroup also assessed whether there was notable variation in the proportion of patients with encephalitis by calendar year of diagnosis. **Figure 6** presents the annual proportions of patients with encephalitis for ages 1–85+ years old and suggests that observed rates did not vary substantially across years, except for 2018 where the proportion of individuals between the ages of 5-15 years with encephalitis was higher than other years. It should be noted that the proportions presented in **Figure 6** are lower than those in **Figure 5**, where encephalitis encounters were queried for the entire 2014–2018 period instead of for a single year.

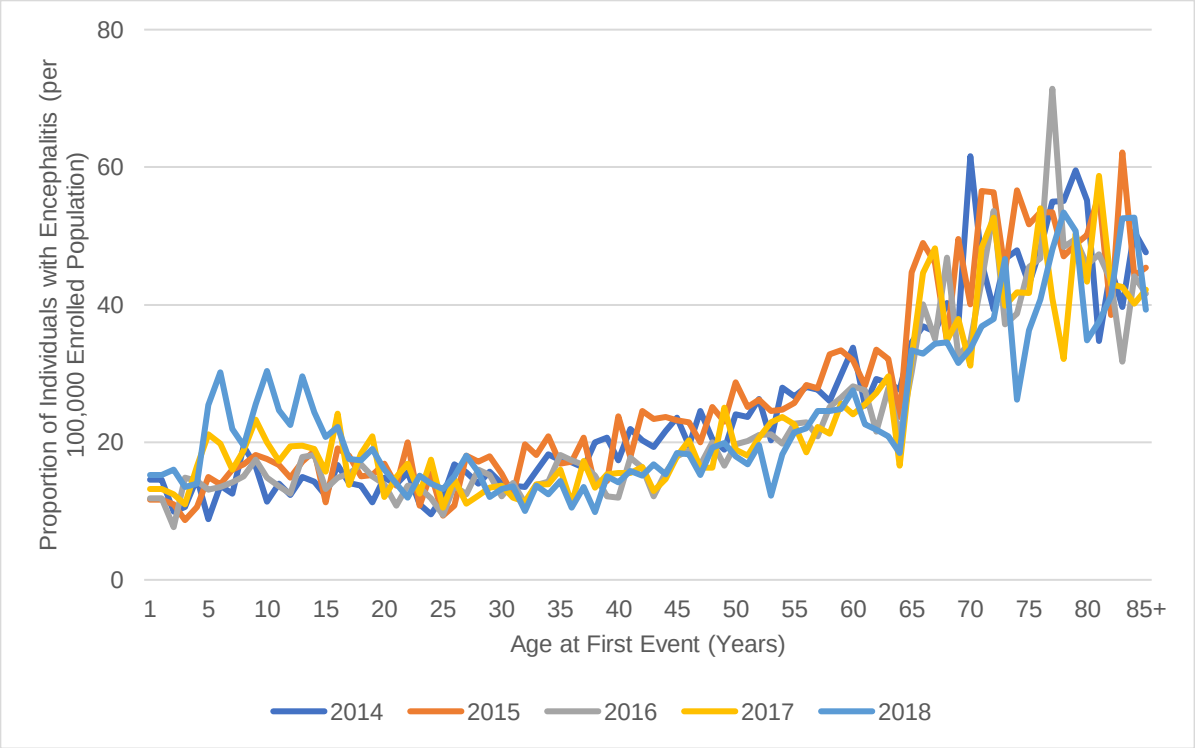

Figure 6. Proportion of patients (1–85+)* with at least one diagnosis for encephalitis (ICD-9-CM or ICD-10-CM) per 100,000 enrolled population, by age and year (January 1, 2014–December 31, 2018).

* 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 one year old experiencing encephalitis is excluded from the chart.

Analyses were also conducted to test whether a temporal association in the occurrence or reporting of encephalitis according to the time of the year. This analysis was inspired by a recent study that reported the U.S. incidence of childhood encephalitis increased in the summer and fall months, driven by the circulation of arboviruses and echoviruses.[22] To test this, enrollment and encephalitis encounter data for January 1–June 30 and July 1–December 31 were queried for each year. As presented in **Table 5** and **Figure 7**, there did not appear to be a substantial difference in the proportion of patients experiencing encephalitis during the first and second halves of the calendar year.

Table 5. Counts and proportions of patients experiencing encephalitis,[a] defined by ICD-9-CM and ICD-10-CM codes, stratified by time of year (2014–2018).

Description	Calendar Year				
	2014	**2015**	**2016**	**2017**	**2018**
January–June patient count	3,625	3,167	2,518	2,403	2,416
July–December patient count	3,932	3,094	2,420	2,449	2,468
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	23,759,879	20,866,148	20,866,232
January–June proportion (per 100,000 enrolled)	11.7	13.1	10.7	11.2	11.4
July–December proportion (per 100,000 enrolled)	12.7	13.0	10.2	11.7	11.8

[a] A patient can be counted in both time periods when queries are run separately, whereas they would be counted only once when the query spans the full year. Therefore, the sum of the proportions presented here will exceed those presented for full calendar years.

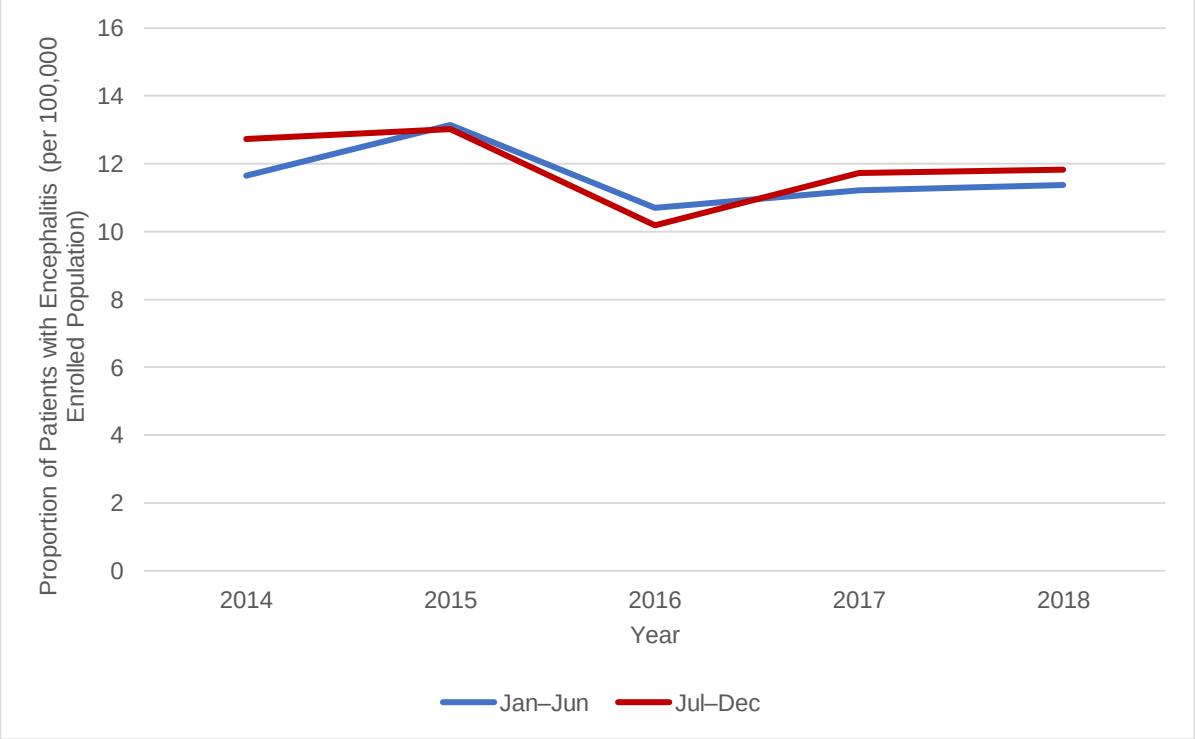

Figure 7. Proportion of patients with at least one diagnosis for encephalitis (ICD-9-CM or ICD-10-CM), stratified by time of year (2014–2018).

H Discussion and Conclusion

The objective of this structured review was to assess and understand the validity of electronic coding algorithms for identifying cases of encephalitis from administrative claims and EHRs using billing codes. It is unclear how diagnostic code-based algorithms would perform differently in EHR compared to claims databases, beyond the differences that already occur within different databases of either EHR or claims. The encephalitis diagnostic code-based algorithms validated in EHR were assessed as supplemental data to support the completeness of the code lists in this report. A structured literature review identified 11 publications of interest, with five reporting relevant measures of validity and diagnostic accuracy.[1-5] Across these studies, the diagnostic performance of encephalitis algorithms was poor. Using the data extracted from publications of interest, a proposed algorithm was drafted and was subsequently refined through consultation with clinical SMEs.

The final algorithm was applied in the MarketScan Research Databases (Commercial, Medicare Supplemental), to assess the feasibility of algorithm use and generate descriptive statistics for encephalitis in a U.S. database of commercially insured patients. Code-specific queries found that the majority of aggregate counts are represented by other and unspecified encephalitis codes, consistent with a report of encephalitis-related hospitalizations in the U.S. between 2000 and 2010, which found that about 50% had an unknown etiology.[9] This suggests that the application of the proposed algorithm for the purposes of assessing a specific form of encephalitis may be associated with risk of misclassification. Users seeking to identify specific encephalitis cases may consider restricting the algorithm to etiologically focused codes.

Additional analyses were performed to further characterize patients identified by the proposed algorithm in a commercially insured population. The findings suggest that approximately 19.3–22.9 individuals per 100,000 individuals received a diagnosis code related to encephalitis every year. This is higher than reported in two studies focusing on encephalitis-related hospitalizations in the U.S., which reported 7.3 hospitalizations per 100,000 population in 1988–1997 and 7.3 hospitalizations per 100,000 person-years in 2000–2010.[9,23] Other studies reported 1.5 viral encephalitis hospitalizations per 100,000 in the United Kingdom between 1989 and 1998, 5.2 encephalitis hospitalizations per 100,000 in Canada between 1994 and 2008, and 5.9 encephalitis hospitalizations per 100,000 in Italy between 1999 and 2005.[13,24,25] Proportions may have been higher in the present study as hospitalization was not required and some diagnosis codes may have been assigned as part of the diagnostic process to rule out encephalitis. This suggests that there is potential for misclassification based on the proposed approach, resulting in an overestimation of the observed rate.

The average age at the time of first diagnosis was 45 years, with the age distribution of cases being fairly even between males and females. These findings are consistent with a recent study of a U.S. patient population, which reported that the average age of patients hospitalized with encephalitis was 44.8 years, with the highest rates in infants (<1 year old) and seniors (≥65 years old).[9]

The proportion of individuals with encephalitis seems to demonstrate a small crest at the age of 5–10 years of age, then increase into older age. Findings are similar to another study from the U.S., which found that there were peaks in the proportion of hospitalized encephalitis cases among those under the age of 1 year and in those 65 years and over.[9] However, due to the minimum continuous enrollment requirement for this analysis, those under the age of 1 year old were excluded from calculations of proportions. Meanwhile, it has been suggested that encephalitis rates are lowest in those 10–14 years of age, so the small crest observed in those 5–10 years of age may be the result of comparison to the least-affected age cohort.[9]

The proportion of individuals receiving an encephalitis diagnosis was distributed fairly evenly between males and females, with a slight skew towards females, who represented 55.4% of the cohort receiving any encephalitis-related diagnosis code between 2014 and 2018 (compared to 51.8% of the enrolled population). This is consistent with the finding from a previous study that women accounted for 53% of encephalitis-related hospitalizations in the U.S. between 2000 and 2010.[9] Another U.S. study conducted

between 1988 and 1997 found that rates of hospitalization for encephalitis were significantly higher in males, however this difference was due to the predominance of toxoplasmic encephalitis and HIV infections among the males in the cohort.[23] Once hospitalizations due to HIV and toxoplasmic encephalitis were removed, there were no significant differences between males and females.[23]

There was little variation in the proportion of patients receiving a diagnosis for encephalitis across the years of study. A prior study found that encephalitis hospitalization rates increased from 6.6 to 7.6 per 100,000 between 2000 and 2010, possibly due to increases in diagnostic sensitivity (via improved brain imaging) and use of immunosuppressive therapies.[22] It is possible that this trend had stabilized by 2014. A small increase in the proportion of individuals 5–15 years of age was noted in 2018, though this may be an outlier. Similarly, there was little difference between the proportions of individuals receiving an encephalitis diagnosis in January-June and July-December during the years of study. This is consistent with a previous study that found a lack of seasonality among encephalitis hospitalizations in the U.S.[23] Previous studies had suggested that rates of viral encephalitis hospital admission were higher in the second half of the year (particularly July–September).[22,25] It was proposed that this increase mirrored the circulation of arboviruses and echoviruses, though an expansion to all-cause encephalitis in the present study may have masked this relationship.

An important strength of this study is the development of an encephalitis algorithm for ICD-9-CM and ICD-10-CM codes based on a structured review of coding definitions available in the literature and active engagement with clinical SMEs. The study also includes important limitations to be considered when interpreting findings. First, a limited number of validation studies were available, and all reported low measures of diagnostic accuracy. Second, few publications focused on encephalitis in the context of biologic exposure. Third, efforts were made to take an inclusive approach to optimize the sensitivity of the algorithm, which may introduce risk of misclassification given the frequency of use of other and unspecified encephalitis codes. Users seeking a more specific algorithm may wish to exclude these codes. 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.

Besides utilizing a pre-defined algorithm consisting of a code list sometimes in combination with health care settings, diagnosis positions, and/or a time window to identify potential cases in administrative databases, predictive modelling or machine learning is another potential tool to identify the health outcome of interest when it cannot be reliably identified using the traditional code-based approach. In the case of encephalitis where a poor PPV was reported in the literature using pre-defined coding algorithms, predictive modelling or machine learning approach may be considered.

I Acknowledgements

Development of the encephalitis algorithm and review report benefited from significant engagement with the FDA CBER team 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.

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Appendix A. Literature Review Extracted Results

Table A1 below includes a summary of the table used to extract data from papers deemed of interest. The 11 papers summarized were used to build the proposed encephalitis algorithm.

Table A1. Encephalitis Data Extraction Table

Author, Year	Title	Country	Summary	Disease Definition	Algorithm/ Criteria	Validity	Claims/EHR-based Algorithm[vii]
Boesen et al., 2019	Pediatric autoimmune encephalitis in Denmark during 2011-17: a nationwide multicenter population-based cohort study.	Denmark	Calculated PPV for pediatric autoimmune encephalitis ICD-10 coding in Denmark	Medical record-validated anti-NMDAR encephalitis	ICD-10 codes: G04.9, G05.1, G05.2, G05.8, A86	The positive predictive value of anti-NMDAR encephalitis ICD-10 codes was 8% (95% CI 0.03-0.15)	EHR
Britton et al., 2016	Pilot surveillance for childhood encephalitis in Australia using the Paediatric Active Enhanced Disease Surveillance (PAEDS) network.	Australia	Calculated PPV, sensitivity, and specificity for encephalitis ICD-10-AM codes in Australia in childhood population	Brighton and International Encephalitis Consortium (IEC) encephalitis case definitions, expert panel diagnosis as gold standard	Admission ICD-10-AM coding: A17.8 , A50.4, A52.1 , A81.1, A81.9, A82.x, A83.x, A84.x, A85.x, A86, A88.8, A89, A92.3, B00.4, B01.1, B02.0, B10.0, B05.0, B06.0, B20.x, B26.2, B45.1, B57.4, B56.x, B58.2, B60.2, G04.0, G04.2, G04.8, G04.9, G05.x, G93.4, B94.1, B94.8	PPV: 14%, Sensitivity: 64%, Specificity: 9%	EHR
Choudhry et al., 2016	Safety evaluation of adenovirus type 4 and type 7 vaccine live, oral in military recruits.	U.S.	Study explored the safety of adenovirus type 4 and type 4 vaccines by using ICD-9-CM codes to identify safety events related to the vaccination.	NR	Code in the primary diagnostic code position (ICD-9-CM): 323.5, 323.51	323.5 resulted in one abstraction which was then validated as a case of encephalitis, deemed to be possibly related to vaccination, none were found for 323.51	Claims

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

Author, Year	Title	Country	Summary	Disease Definition	Algorithm/ Criteria	Validity	Claims/EHR-based Algorithm[vii]
Davison et al., 2003	Viral encephalitis in England, 1989-1998: what did we miss?	England	Study used ICD-9 and ICD-10 codes to identify viral encephalitis cases to evaluate current surveillance systems for the disease.	No case definition is available for viral encephalitis, but diagnosis is generally based upon clinical evidence of viral encephalitis and available confirmatory laboratory data as recorded in the patient's medical record at the time of discharge.	Admission ICD-9 codes: 0620-0629, 0630-0638, 064, 0661, 0622, 3233, 0543, 0550, 0722, 0560, 0567, 0490, 3126, 0498, 3234, 0499, 3239 and ICD-10 codes: A830-A839, A840-A849, A852, B004, B011, B020, B050, B262, B060, A872, A851, A858, A86, G051	Number of viral encephalitis cases- Estimate of underreporting in laboratory reports %: herpes 73, VZV 62, measles 39, mumps 28, rubella 96, LCMV 100, adenoviruses 79, total 70. Number of viral encephalitis deaths- Estimate of underreporting in laboratory reports %: herpes 22, VZV 42, measles 100, mumps 0, rubella -, LCMV -, adenoviruses 0, total 24.	EHR

Author, Year	Title	Country	Summary	Disease Definition	Algorithm/ Criteria	Validity	Claims/EHR-based Algorithm[vii]
George et al., 2014	Encephalitis hospitalization rates and inpatient mortality in the United States, 2000-2010.	U.S.	Study used ICD-9 codes in order to identify encephalitis hospitalization and inpatient mortality in the U.S.	ICD-9 coding	Patients admitted to inpatient care with encephalitis were identified using International Classification of Disease, Ninth Revision (ICD-9-CM) diagnosis codes: 054.3, 048, 052, 058.2, 045, 046.2, 049.8, 056.01, 062.4, 063, 063.1, 063.2, 063.8, 071, 072.2, 323, 066.41, 062, 062.1, 062.2, 062.3, 062.5, 062.8, 066.2, 055, 323.6, 130, 036.1, 013.6, 090.41, 094.81, 136.29, 323.1, 323.2, 323.4, 323.5, 323.7, 323.8, 323.9, 062.9, 063.9, 049.9, 064	NR	EHR
Ghaderi et al., 2017	Encephalitis after influenza and vaccination: a nationwide population-based registry study from Norway.	Norway	Study used ICD-10 codes in order to identify encephalitis cases after influenza of influenza vaccinations.	Any hospitalization with any listed diagnosis code for diagnosis who had influenza or influenza vaccination. Only the dates of hospitalizations with acute encephalitis (obtained from the NPR) were considered, and all follow-up visits were disregarded.	Any of the following ICD-10 codes related to a 32hospitalization: A86, A87.9, A89, G03.9, G04.0, G04.8 and G04.9: A86, A87.9, A89, G03.9, G04.0, G04.8 and G04.9	NR	EHR

Author, Year	Title	Country	Summary	Disease Definition	Algorithm/ Criteria	Validity	Claims/EHR-based Algorithm[vii]
Huppatz et al., 2010	Should there be a standardised approach to the diagnostic workup of suspected adult encephalitis? A case series from Australia.	Australia	Study used ICD-10 codes in the primary diagnosis position in order to review the diagnostic assessment of encephalitis cases.	Clinician decision using a specially designed audit tool	ICD-10-AM code as primary discharge code: A321, A858, B004, B011, B020, G052, G040, G048, G049, A86	Clinical features and laboratory/neuroimaging were used to identify aspects of the patient record that were consistent with encephalitis 1) Signs and symptoms (headache, fever, and altered conscious state) in 26/74 (35.1% of cases) 2) Neuroimaging: 2/68 (2.9%) CT scans, 8/35 (22.8%) MRI scans consistent with encephalitis 3) EEG: 4/36 (11.1%) conducted showed activity consistent with Herpes Simplex encephalitis 4) Lab results: 29/67 (43.3%) had lab results consistent with viral encephalitis 5) Outcome using Glasgow Outcome Scale): 25/74 (33.8%) were disabled, 40/74 (54.1%) were normal at time of discharge, 4/74 (5.4%) died during stay	EHR

Author, Year	Title	Country	Summary	Disease Definition	Algorithm/ Criteria	Validity	Claims/EHR-based Algorithm[vii]
Millman et al., 2017	Hospitalizations within 14 days of vaccination among pediatric recipients of the live attenuated influenza vaccine, United States 2010-2012.	U.S.	Study used ICD-9-CM codes	Medically attended events were defined as an event associated with a known service date and an ICD-9 code.	Code in primary discharge diagnosis position: 323.5x	NR	Claims
Parpia et al., 2016	Encephalitis, Ontario, Canada, 2002-2013.	Canada	This study breaks down a comprehensive list of encephalitis codes into etiology categories including immune-mediated, mixed other, and unknown etiology.	NR	ICD-10 A811*, A812*, A83*, A840*, A841*, A848*, A849*, A850*, A851*, A852* A86*, A922*, B004*, B050*, B262*, B011*, B020*, B262*, B582*, G040*, G048*, G049*, G050*, G051*, G052*, G058*, G131*, G361*, M321*	NR	EHR
Samannodi et al., 2019	Lack of accuracy of the International Classification of Disease, ninth (ICD-9) codes in identifying patients with encephalitis.	U.S.	Study used ICD-9 codes to conduct a retrospective study to explore the accuracy of encephalitis diagnoses in the U.S.	International Encephalitis Consortium	Discharge ICD-9-CM coding: 323, 062, 046.2, 066	244/1241 patients (19.6%) met definition of encephalitis	EHR
Wiese et al., 2018	Validation of discharge diagnosis codes to identify serious infections among middle age and older adults.	U.S.	Calculated PPV for encephalitis ICD-9-CM codes in elderly population 50 and over in the U.S..	Disease definition created for study from previous validation studies and expert clinical knowledge. Definition included laboratory findings, treatment details, clinical symptoms, and other suggestive findings.	ICD-9-CM based primary diagnoses only: 003.21, 036.0, 047.x, 049.x, 053.0, 054.72, 072.1, 091.81, 094.2, 098.82, 100.81, 320.x, 036.1, 054.3, 056.01, 058.21, 058.29, 062.x, 063.x, 064.x, 066.41, 072.2, 094.81, 130.0, 323.x	Meningitis/encephalitis n=10 PPV 50.0 (95% CI 23.7-76.3)	Claims

Abbreviations: EHR, electronic health record; ICD-9, International Classification of Diseases, Ninth Revision; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10, International Classification of Diseases, Tenth Revision; ICD-10-AM, International Classification of Diseases, Tenth Revision, Australian Modification; NR, not reported; PPV, positive predictive value; U.S., United States; VZV, varicella zoster virus

Appendix B. Codes excluded from Proposed Algorithm

The diagnosis codes listed in **Table B1** are proposed for exclusion from the algorithm. These codes were initially considered for inclusion due to their potential relation to encephalitis, either as an etiologically relevant pathogen (e.g., herpes simplex, adenovirus, rabies) or as a condition that that come sometimes accompany encephalitis (e.g., rubella, fever). In consultation with clinical SMEs (TB, JB, JC, DT) these codes were ultimately determined to be too general or distinct from encephalitis and could potentially increase the risk of misclassification. Further, they were not used as exclusion criteria to identify patients with a relevant encephalitis diagnosis.

Table B1: Excluded codes potentially relevant to encephalitis identified from the literature or GEMs mapping

Code	Description	Code Category	Code Type
003.21	Salmonella meningitis	DX	9
036.0	Meningococcal meningitis	DX	9
046.9	Unspecified slow virus infection of central nervous system	DX	9
047.0	Meningitis due to coxsackie virus	DX	9
047.1	Meningitis due to echo virus	DX	9
047.8	Other specified viral meningitis	DX	9
047.9	Unspecified viral meningitis	DX	9
048	Other enterovirus diseases of central nervous system	DX	9
049.0	Lymphocytic choriomeningitis	DX	9
049.1	Meningitis due to adenovirus	DX	9
049.8	Other specified non-arthropod-borne viral diseases of central nervous system	DX	9
049.9	Unspecified non-arthropod-borne viral diseases of central nervous system	DX	9
053.0	Herpes zoster with meningitis	DX	9
053.19	Herpes zoster with other nervous system complications	DX	9
054.72	Herpes simplex meningitis	DX	9
056.01	Encephalomyelitis due to rubella	DX	9
056.9	Rubella with other neurological complications	DX	9
071	Rabies	DX	9
072.1	Mumps meningitis	DX	9
091.81	Acute syphilitic meningitis (secondary)	DX	9
094.2	Syphilitic meningitis	DX	9
098.82	Gonococcal meningitis	DX	9
100.81	Leptospiral meningitis (aseptic)	DX	9
136.29	Other specific infections by free-living amebae	DX	9
320.0	Hemophilus meningitis	DX	9
320.1	Pneumococcal meningitis	DX	9
320.2	Streptococcal meningitis	DX	9
320.3	Staphylococcal meningitis	DX	9
320.7	Meningitis in other bacterial diseases classified elsewhere	DX	9
320.81	Anaerobic meningitis	DX	9
320.82	Meningitis due to gram-negative bacteria, not elsewhere classified	DX	9
320.89	Meningitis due to other specified bacteria	DX	9
320.9	Meningitis due to unspecified bacterium	DX	9
321.0	Cryptococcal meningitis	DX	9
323.02	Myelitis in viral diseases classified elsewhere	DX	9
323.42	Other myelitis due to other infections classified elsewhere	DX	9
323.52	Myelitis following immunization procedures	DX	9
323.61	Infectious acute disseminated encephalomyelitis (ADEM)	DX	9
323.63	Postinfectious myelitis	DX	9
323.72	Toxic myelitis	DX	9
323.82	Other causes of myelitis	DX	9
341.8	Other demyelinating diseases of central nervous system	DX	9
348.30	Encephalopathy, unspecified	DX	9

Code	Description	Code Category	Code Type
348.31	Metabolic encephalopathy	DX	9
348.39	Other encephalopathy	DX	9
710.0	Systemic lupus erythematosus (SLE)	DX	9
066.xx	Other arthropod-borne viral diseases	DX	9
322.x	Meningitis of unspecified cause	DX	9
A02.21	Salmonella meningitis	DX	10
A27.81	Aseptic meningitis in leptospirosis	DX	10
A39.0	Meningococcal meningitis	DX	10
A51.41	Secondary syphilitic meningitis	DX	10
A52.13	Late syphilitic meningitis	DX	10
A54.81	Gonococcal meningitis	DX	10
A81.9	Atypical virus infection of central nervous system, unspecified	DX	10
A82.x	Rabies	DX	10
A87.0	Enteroviral meningitis	DX	10
A87.1	Adenoviral meningitis	DX	10
A87.2	Lymphocytic choriomeningitis	DX	10
A87.8	Other viral meningitis	DX	10
A87.9	Viral meningitis, unspecified	DX	10
A88.8	Other specified viral infections of central nervous system	DX	10
A89	Unspecified viral infection of central nervous system	DX	10
A92.xx	Other mosquito-borne viral fevers	DX	10
A93.x	Other arthropod-borne viral fevers, not elsewhere classified	DX	10
B00.3	Herpesviral meningitis	DX	10
B02.1	Zoster meningitis	DX	10
B06.9	Other neurological complications of rubella	DX	10
B26.1	Mumps meningitis	DX	10
B45.1	Cerebral cryptococcosis	DX	10
B60.19	Other acanthamebic disease	DX	10
B60.2	Naegleriasis	DX	10
G00.0	Hemophilus meningitis	DX	10
G00.1	Pneumococcal meningitis	DX	10
G00.2	Streptococcal meningitis	DX	10
G00.3	Staphylococcal meningitis	DX	10
G00.8	Other bacterial meningitis	DX	10
G00.9	Bacterial meningitis, unspecified	DX	10
G01	Meningitis in bacterial diseases classified elsewhere	DX	10
G03.x	Meningitis due to other and unspecified causes	DX	10
G04.1	Tropical spastic paraplegia	DX	10
G04.30	Acute necrotizing hemorrhagic encephalopathy, unspecified	DX	10
G04.31	Postinfectious acute necrotizing hemorrhagic encephalopathy	DX	10
G04.32	Postimmunization acute necrotizing hemorrhagic encephalopathy	DX	10
G04.39	Other acute necrotizing hemorrhagic encephalopathy	DX	10
G04.89	Other myelitis	DX	10
G04.91	Myelitis, unspecified	DX	10
G05.4	Myelitis in diseases classified elsewhere	DX	10
G36.1	Acute and subacute hemorrhagic leukoencephalitis [Hurst]	DX	10
G92	Toxic encephalopathy	DX	10
G93.40	Encephalopathy, unspecified	DX	10
G93.41	Metabolic encephalopathy	DX	10
G93.49	Other encephalopathy	DX	10
M32.xx	Systemic lupus erythematosus (SLE)	DX	10

Abbreviations: DX, ICD-CM diagnosis

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

Individual codes included in the encephalitis algorithm were queried in the MarketScan Research Databases (Commercial, Medicare Supplemental), accessed via the Treatment Pathways online platform to assess the number of patients with each diagnosis code proposed for inclusion and identify what specific codes were likely to account for the majority of the results being returned. Researchers queried the past five years of available data (January 1, 2014–December 31, 2018). In 2014, there were 28,407,959 patients enrolled for the entire year; 22,117,235 in 2015; 21,616,291 in 2016; 19,563,847 in 2017; 19,371,891 in 2018. A total of 46,153,898 patients were enrolled for at least one calendar year between 2014 and 2018. Results are presented in **Table C1**.

The transition from ICD-9-CM to ICD-10-CM occurred October 1, 2015; no ICD-9-CM codes were queried after this date and no ICD-10-CM codes were queried before this date. The coding standard-specific subtotal rows were calculated by querying all codes for a particular coding standard together. The “Total (Count)” column was calculated by querying the individual code in a cohort of patients who were enrolled for at least one calendar year between 2014 and 2018.

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 are diagnosed with encephalitis 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 be diagnosed with encephalitis, then be continuously enrolled for all of 2017. This event would not be captured in the column for 2016 (as the individual would be excluded from that cohort) but would be captured in the “Total” column.

ICD-9-CM codes 323.9 (unspecified causes of encephalitis, myelitis, and encephalomyelitis) and ICD-10-CM codes G04.81 (other encephalitis and encephalomyelitis) and G04.90 (encephalitis and encephalomyelitis, unspecified) are the most frequently reported codes, which were reported in 31.8%, 10.4%, and 28.3% of the population receiving any encephalitis diagnosis code between 2014 and 2018, respectively.

Table C1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in the encephalitis algorithm (2014–2018).

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													
013.60	Tuberculous encephalitis or myelitis, unspecified	10	0.2	3	0.1							12	0.1
013.61	Tuberculous encephalitis or myelitis, bacteriological or histological examination not done	2	0.0	0	0.0							2	0.0
013.62	Tuberculous encephalitis or myelitis, bacteriological or histological examination unknown (at present)	1	0.0	0	0.0							1	0.0
013.63	Tuberculous encephalitis or myelitis, tubercle bacilli found (in sputum) by microscopy	0	0.0	1	0.0							1	0.0
013.64	Tuberculous encephalitis or myelitis, tubercle bacilli not found (in sputum) by microscopy, but found by bacterial culture	0	0.0	0	0.0							0	0.0
013.65	Tuberculous encephalitis or myelitis, tubercle bacilli not found by bacteriological examination, but tuberculosis confirmed	0	0.0	0	0.0							0	0.0
013.66	Tuberculous encephalitis or myelitis, tubercle bacilli not found by bacteriological or histological examination, but tuberculosis confirmed by other methods [inoculation of animals]	0	0.0	0	0.0							0	0.0
036.1	Meningococcal encephalitis	59	1.0	36	0.7							99	0.4
046.2	Subacute sclerosing panencephalitis	29	0.5	24	0.5							59	0.3
052.0	Postvaricella encephalitis	62	1.0	48	0.9							123	0.6
054.3	Herpetic meningoencephalitis	401	6.6	247	4.9							659	3.0
055.0	Postmeasles encephalitis	8	0.1	8	0.2							15	0.1
058.21	Human herpesvirus 6 encephalitis	45	0.7	20	0.4							61	0.3
058.29	Other human herpesvirus encephalitis	60	1.0	33	0.7							103	0.5
062.0	Japanese encephalitis	22	0.4	16	0.3							41	0.2
062.1	Western equine encephalitis	7	0.1	12	0.2							19	0.1
062.2	Eastern equine encephalitis	10	0.2	9	0.2							19	0.1
062.3	St. Louis encephalitis	89	1.5	54	1.1							146	0.7
062.4	Australian encephalitis	1	0.0	0	0.0							2	0.0
062.5	California virus encephalitis	12	0.2	7	0.1							18	0.1
062.8	Other specified mosquito-borne viral encephalitis	36	0.6	16	0.3							52	0.2
062.9	Mosquito-borne viral encephalitis, unspecified	40	0.7	13	0.3							59	0.3
063.0	Russian spring-summer [taiga] encephalitis	4	0.1	1	0.0							9	0.0
063.1	Louping ill	8	0.1	5	0.1							16	0.1
063.2	Central European encephalitis	13	0.2	9	0.2							20	0.1
063.8	Other specified tick-borne viral encephalitis	26	0.4	15	0.3							41	0.2
063.9	Tick-borne viral encephalitis, unspecified	78	1.3	46	0.9							128	0.6
064	Viral encephalitis transmitted by other and unspecified arthropods	103	1.7	54	1.1							155	0.7
066.41	West Nile Fever with encephalitis	115	1.9	81	1.6							191	0.9

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)		
072.2	Mumps encephalitis	42	0.7	19	0.4							64	0.3
090.41	Congenital syphilitic encephalitis	4	0.1	0	0.0							4	0.0
094.81	Syphilitic encephalitis	5	0.1	2	0.0							7	0.0
130.0	Meningoencephalitis due to toxoplasmosis	105	1.7	43	0.8							147	0.7
139.0	Late effects of viral encephalitis	132	2.2	83	1.6							217	1.0
323.01	Encephalitis and encephalomyelitis in viral diseases classified elsewhere	211	3.5	134	2.6							356	1.6
323.1	Encephalitis, myelitis, and encephalomyelitis in rickettsial diseases classified elsewhere	41	0.7	16	0.3							63	0.3
323.2	Encephalitis, myelitis, and encephalomyelitis in protozoal diseases classified elsewhere	16	0.3	13	0.3							31	0.1
323.41	Other encephalitis and encephalomyelitis due to other infections classified elsewhere	76	1.3	39	0.8							120	0.5
323.51	Encephalitis and encephalomyelitis following immunization procedures	40	0.7	25	0.5							66	0.3
323.62	Other postinfectious encephalitis and encephalomyelitis	93	1.5	72	1.4							170	0.8
323.71	Toxic encephalitis and encephalomyelitis	24	0.4	26	0.5							58	0.3
323.81	Other causes of encephalitis and encephalomyelitis	699	11.5	530	10.4							1,193	5.4
323.9	Unspecified causes of encephalitis, myelitis, and encephalomyelitis	4,156	68.6	2,766	54.5							7,042	31.8
ICD-9-CM Subtotal		**6,062**	**100.0**	**4,005**	**78.9**							**10,136**	**45.8**
ICD-10-CM													
A17.82	Tuberculous meningoencephalitis			4	0.1	4	0.1	5	0.1	10	0.3	21	0.1
A32.12	Listerial meningoencephalitis			1	0.0	8	0.2	3	0.1	4	0.1	15	0.1
A39.81	Meningococcal encephalitis			17	0.3	26	0.6	17	0.4	21	0.6	91	0.4
A50.42	Late congenital syphilitic encephalitis			0	0.0	0	0.0	2	0.1	2	0.1	4	0.0
A52.14	Late syphilitic encephalitis			2	0.0	2	0.0	3	0.1	2	0.1	10	0.0
A81.1	Subacute sclerosing panencephalitis			5	0.1	20	0.5	14	0.4	5	0.1	42	0.2
A83.0	Japanese encephalitis			2	0.0	15	0.4	10	0.3	12	0.3	43	0.2
A83.1	Western equine encephalitis			3	0.1	6	0.1	10	0.3	6	0.2	23	0.1
A83.2	Eastern equine encephalitis			4	0.1	6	0.1	5	0.1	6	0.2	19	0.1
A83.3	St Louis encephalitis			25	0.5	79	1.9	83	2.2	74	2.0	273	1.2
A83.4	Australian encephalitis			0	0.0	3	0.1	0	0.0	0	0.0	3	0.0
A83.5	California encephalitis			3	0.1	7	0.2	7	0.2	6	0.2	24	0.1
A83.6	Rocio virus disease			1	0.0	2	0.0	2	0.1	0	0.0	5	0.0
A83.8	Other mosquito-borne viral encephalitis			2	0.0	10	0.2	3	0.1	2	0.1	18	0.1
A83.9	Mosquito-borne viral encephalitis, unspecified			5	0.1	23	0.6	20	0.5	16	0.4	67	0.3
A84.0	Far Eastern tick-borne encephalitis [Russian spring-summer encephalitis]			4	0.1	12	0.3	9	0.2	13	0.3	39	0.2
A84.1	Central European tick-borne encephalitis			1	0.0	1	0.0	1	0.0	3	0.1	6	0.0
A84.8	Other tick-borne viral encephalitis			16	0.3	45	1.1	43	1.1	44	1.2	145	0.7
A84.9	Tick-borne viral encephalitis, unspecified			25	0.5	99	2.4	90	2.3	94	2.5	327	1.5
A85.0	Enteroviral encephalitis			3	0.1	14	0.3	11	0.3	12	0.3	51	0.2
A85.1	Adenoviral encephalitis			2	0.0	5	0.1	4	0.1	3	0.1	17	0.1

Encephalitis Case Algorithm
May 2021

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)		
A85.2	Arthropod-borne viral encephalitis, unspecified			3	0.1	18	0.4	12	0.3	15	0.4	50	0.2
A85.8	Other specified viral encephalitis			21	0.4	96	2.3	78	2.0	52	1.4	276	1.2
A86	Unspecified viral encephalitis			113	2.2	475	11.4	408	10.6	313	8.3	1,410	6.4
A92.31	West Nile virus infection with encephalitis			52	1.0	82	2.0	95	2.5	73	1.9	276	1.2
B00.4	Herpesviral encephalitis			133	2.6	325	7.8	253	6.6	260	6.9	950	4.3
B01.11	Varicella encephalitis and encephalomyelitis			5	0.1	31	0.7	37	1.0	35	0.9	115	0.5
B02.0	Zoster encephalitis			171	3.4	494	11.9	376	9.8	212	5.6	1,361	6.2
B05.0	Measles complicated by encephalitis			6	0.1	11	0.3	16	0.4	25	0.7	59	0.3
B06.01	Rubella encephalitis			0	0.0	5	0.1	6	0.2	3	0.1	17	0.1
B10.01	Human herpesvirus 6 encephalitis			15	0.3	36	0.9	34	0.9	21	0.6	115	0.5
B10.09	Other human herpesvirus encephalitis			12	0.2	41	1.0	26	0.7	25	0.7	108	0.5
B26.2	Mumps encephalitis			13	0.3	19	0.5	8	0.2	5	0.1	51	0.2
B58.2	Toxoplasma meningoencephalitis			19	0.4	44	1.1	43	1.1	47	1.3	130	0.6
B94.1	Sequelae of viral encephalitis			46	0.9	107	2.6	60	1.6	47	1.3	243	1.1
G04.00	Acute disseminated encephalitis and encephalomyelitis, unspecified			105	2.1	272	6.5	226	5.9	232	6.2	720	3.3
G04.01	Postinfectious acute disseminated encephalitis and encephalomyelitis (postinfectious ADEM)			35	0.7	133	3.2	132	3.4	145	3.9	414	1.9
G04.02	Postimmunization acute disseminated encephalitis, myelitis and encephalomyelitis			13	0.3	23	0.6	27	0.7	24	0.6	88	0.4
G04.2	Bacterial meningoencephalitis and meningomyelitis, not elsewhere classified			21	0.4	61	1.5	75	2.0	65	1.7	250	1.1
G04.81	Other encephalitis and encephalomyelitis			226	4.5	650	15.6	727	18.9	962	25.6	2,303	10.4
G04.90	Encephalitis and encephalomyelitis, unspecified			707	13.9	1,863	44.8	1,769	46.0	1,782	47.4	6,272	28.3
G05.3	Encephalitis and encephalomyelitis in diseases classified elsewhere			43	0.8	130	3.1	97	2.5	97	2.6	360	1.6
ICD-10-CM Subtotal				**1,547**	**30.5**	**4,162**	**100.0**	**3,844**	**100.0**	**3,757**	**100.0**	**12,997**	**58.7**
Total		**6,062**	**100.0**	**5,073**	**100.0**	**4,162**	**100.0**	**3,844**	**100.0**	**3,757**	**100.0**	**22,125**	**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.
Note: Codes highlighted in yellow represent those that accounted for at least 10% of the overall count among the 2014-2018 cohort.