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Biologics Effectiveness and Safety Initiative

A Structured Review of Electronic Coding Algorithms for Bell's Palsy Using Administrative Claims and Electronic Health Records

Final Report

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List of Acronyms

AFHSB	United States Armed Forces Health Surveillance Branch
AHRQ	Agency for Healthcare Research and Quality
BEST	Biologics Effectiveness and Safety
CBER	Center for Biologics Evaluation and Research
CMS	Centers for Medicare and Medicaid Services
CI	Confidence Interval
CPCSSN	Canadian Primary Care Sentinel Surveillance Network
CPT	Current Procedural Terminology
DX	Diagnosis
ED	Emergency Department
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GEM	General Equivalence Mapping
HBV	Hepatitis B Virus
HCPCS	Healthcare Common Procedure Coding System
H-ICDA	Hospital International Classification of Diseases Adapted
HSV-1	Herpes Simplex Virus Type 1
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-AM	International Classification of Disease, Tenth Revision, Australian Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
LOINC	Logical Observation Identifiers Names and Codes
MeSH	Medical Subject Headings
MIV	Monovalent Inactivated Vaccine
NDC	National Drug Code
NPV	Negative Predictive Value
PICO	Population, Intervention, Comparator, Outcome
PPV	Positive Predictive Value
SME	Subject Matter Expert
TIV	Trivalent Influenza Vaccine
VSD	Vaccine Safety Datalink

A Summary

The United States (U.S.) Food and Drug Administration (FDA) Biologics Effectiveness and Safety (BEST) Initiative conducted a structured literature review (through August 6, 2020) to identify validated coding algorithms for ascertaining cases of Bell's palsy in large administrative healthcare databases. The studies selected for this targeted review used billing codes in claims, electronic health record (EHR), or electronic medical record (EMR) databases, as well as paper-based medical records to derive Bell's palsy coding algorithms.

Several relevant studies were reviewed, with two U.S. studies (EHR and paper medical records-derived) and one Canadian study (EMR-derived) providing performance measures (i.e., positive predictive value [PPV], negative predictive value [NPV], sensitivity and/or specificity) based on medical chart review. The results from validation studies of Bell' palsy EHR- and EMR-based algorithms suggest that the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 351.0 and 351.x have a high PPV of 84 and 90%, respectively. Details of the three validation studies are provided below. No U.S. studies that utilized International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes to identify Bell's palsy cases were found in the literature search. However, four international studies applied ICD-10-CM G51.0 (Bell's palsy) and one international applied ICD-10-CM G51.x (facial nerve disorders) without validation.

A U.S. study identified Bell's palsy among children diagnosed with ICD-9-CM 351.0 from an integrated health care system (i.e., Kaiser Permanente Northern California), followed with medical chart review. This EHR-based validation study reported a PPV of 84% (95% confidence interval [CI] 82–86%). In a U.S. validation study that assessed the validity of ICD-9-CM 351.x (facial nerve disorders), 767.5 (facial nerve injury due to birth trauma), and 053.11 (geniculate herpes zoster), as well as Hospital International Classification of Diseases Adapted (H-ICDA) code 350 (for potential Bell's palsy cases encountered from 1974–1978) in paper-based medical records, the authors reported a PPV of 81% (95% CI 76–85%) among individuals with Bell's palsy based on a neurologist chart review of 272 medical records from rehabilitation centers, hospitals, and medical clinics. Finally, a Canadian study assessed the feasibility and validity of identifying Bell's palsy cases from EMR data among 33 Bell's palsy cases and 220 age- and sex-matched controls. The authors used ICD-9-CM 351.x and text searches to identify Bell's palsy cases. The reported PPV of the study was 90% (95% CI 75.7–98.1%), NPV was 100% (95% CI 98.3–100%), sensitivity was 100% (95% CI 88.4–100%), and specificity was 98.6% (95% CI 96.1–99.7%).

The results of this literature review were used as the basis for developing a draft administrative claims-based outcome definition — hereafter referred to as "algorithm" — for identifying cases of Bell's palsy. General codes for facial nerve palsy were also included to optimize algorithm sensitivity and inclusiveness. Codes were mapped from ICD-9-CM to ICD-10-CM via forward–backward mapping, using General Equivalence Mappings (GEMs) for reference.[i] The draft algorithm was then reviewed by clinical subject matter experts (SMEs) from IBM (TB, JB), FDA Center for Biologics Evaluation and Research (CBER) (JC, DT), and Acumen.

The proposed case definition combines ICD-9-CM 351.0, 351.8 (other facial nerve disorders), and 351.9 (facial nerve disorder, unspecified) with ICD-10-CM G51.0, G51.8 (other disorders of facial nerve), and G51.9 (disorders of facial nerve, unspecified). As an initial step in assessing the feasibility of using the algorithm to identify Bell's palsy, the algorithm was applied in the IBM MarketScan® Research Databases (Commercial and Medicare Supplemental), a collection of commercially insured individuals in the U.S. Statistics describing the frequency and proportions of Bell's palsy codes included in the algorithm were generated.

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

Facial nerve palsy, or facial paralysis, is a cranial nerve disease that leads to facial deformation. Facial nerve palsy is characterized by paralysis of the seventh cranial nerve, and most commonly classified as Bell's palsy, which accounts for 60–75% cases of unilateral facial paralysis worldwide.[1] As a lower motor neuron palsy of idiopathic origin, Bell's palsy is typically diagnosed by the exclusion of identifiable causes of facial nerve palsy, such as infection, trauma, tumors, and stroke.[2] Bell's palsy usually presents with acute onset of unilateral facial weakness resulting in incomplete eye closure, which progresses over a two- to five-day period to include speech interruption, taste disturbance, hypersensitivity to low-frequency sounds, and decreased lacrimation.[3]

Prior studies have reported that treatment of Bell's palsy with corticosteroids alone and in combination with antivirals was found to bring about a rapid recovery of facial nerve function [3]. Most cases resolve completely and spontaneously (without treatment) and the re-occurrence rate in the same individual is 8-12%.[2,4] However, approximately 33% of patients experience incomplete resolution of facial weakness 6 months after onset.[5]

Bell's palsy has an estimated incidence ranging from 11.5 to 53.3 per 100,000 person-years in different populations, with an incidence rate that is proposed to be highest among young and middle-aged adults but may also increase with age.[6] An estimated 40,000 new cases of Bell's palsy occur per year.[4] Similar incidence is reported in men and women[3], although other studies have also reported a higher incidence among females.[6] The specific etiology of Bell's palsy is unknown, but infection by a reactivated virus, such as herpes simplex virus type 1 (HSV-1) or a cell-mediated autoimmune inflammatory response are potentially responsible for inflammation and concomitant compression of the facial nerve.[7] Bell's palsy has also been reported as an adverse reaction following immunization with influenza and hepatitis B virus (HBV) vaccines[8], although a study investigating the association between immunization and Bell's palsy in children did not observe an increased risk of Bell's palsy following immunization with inactivated trivalent influenza vaccine (TIV), HBV vaccine, or any vaccine among children.[9]

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

A structured literature review of coding algorithms for identifying potential cases of Bell's palsy using standard administrative diagnosis codes was conducted, leveraging findings from U.S. and international studies to inform the development of an algorithm. The draft algorithm was subject to review by clinical SMEs and testing in the MarketScan Research Databases, a large collection of administrative claims data accessed via the Treatment Pathways online analytic platform. **Section C** summarizes the literature

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

review methodology and findings, **Section D** provides clinical case definitions for facial nerve palsy (including Bell's palsy), which could be of value in further assessing the performance of proposed algorithms via chart validation studies; **Sections E** and **F** present the algorithm and its associated assumptions and decisions, respectively; **Section G** presents the results of the initial application of the algorithm to characterize the population with a Bell's palsy diagnosis 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 upon a Population, Intervention, Comparator, Outcome (PICO) framework. The PICO framework for this review can be summarized as follows:

- **Population:** *any population group (human)*
- **Intervention:** *any intervention or no intervention*
- **Comparator:** *any comparator, placebo*
- **Outcome:** *Bell's palsy; facial nerve palsy*

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

The review process began with conducting comprehensive searches of existing publications available in the CBER[iii] and Center for Drug Evaluation and Research Sentinel[iv] databases. Next, a structured review of the academic literature was conducted, using PubMed and Google Scholar to identify relevant resources. Only English language publications were selected for review. No restriction was imposed on publication date for the PubMed search (inception to August 6, 2020). The Google Scholar search was limited to January 2000 through August 6, 2020. The PubMed search strategy (Search 1 to 4) and the Google Scholar search strategy (Search 5 to 7) is summarized below. Search terms are not case sensitive.

- ***Search 1***: ((((("bell palsy"[MeSH Terms] OR ("bell"[All Fields] AND "palsy"[All Fields])) OR "bell palsy"[All Fields]) OR ("bell's"[All Fields] AND "palsy"[All Fields])) OR "bell's palsy"[All Fields]) AND (((((((("identifiable"[All Fields] OR "identifiably"[All Fields]) OR "identifie"[All Fields]) OR "identified"[All Fields]) OR "identifier"[All Fields]) OR "identifiers"[All Fields]) OR "identifies"[All Fields]) OR "identify"[All Fields]) OR "identifying"[All Fields]) retrieved **259 articles**
- ***Search 2:*** ((bell's palsy) AND (identify)) AND (ICD): retrieved **5 articles**
- ***Search 3***: (((Bell's Palsy)) AND (ICD)) AND (PPV): retrieved **2 articles**
- ***Search 4***: ((bell's palsy) AND (identify)) AND (validation)): retrieved **11 articles**
- ***Search 5***: bell's palsy and identify and ICD: retrieved **2,270 articles**
- ***Search 6:*** bell's palsy and identify and vaccines and ICD: retrieved **2,410 articles**
- ***Search 7:*** bell's palsy and identify and vaccines and administrative claim data and validation: retrieved **3,400 articles.**

Targeted and *ad hoc* searches of the gray literature were conducted, including clinical guidelines and reports from organizations such as the U.S. Armed Forces Health Surveillance Branch (AFHSB) and the

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

Agency for Healthcare Research and Quality (AHRQ).[v] A snowballing technique was also applied, wherein the bibliographies of relevant studies were scanned for additional publications. Abstract review was subsequently conducted for these publications. Since this was not a systematic review, authors did not track the total number of abstracts and full text screened after de-duplication.

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 diagnostic accuracy (e.g., PPV and 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- or EHR-based coding algorithm but no independent validation OR a non-U.S. validation study
- ***Ranking 3***: Non-U.S. study that reported a claims- or EHR-based coding algorithm but no independent validation

Table 1. Data elements 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

Following title and abstract screening, full text review, and data extraction, 15 publications were identified as being particularly relevant (**Table A1**). Each publication reported measures of diagnostic accuracy associated with EHR-, EMR-, or paper-based algorithms (i.e., Bell's palsy codes derived from billing codes of admission or discharge medical records). No publication was identified that reported measures of diagnostic accuracy associated with claims-based coding algorithms (i.e., Bell's palsy codes derived

[v] U.S. Food and Drug Administration. National Drug Code Directory. November 9, 2017. https://www.fda.gov/drugs/informationondrugs/ucm142438.htm

from administrative insurance claims databases). Additional publications identified provided an ICD code-based approach for identifying cases of Bell's palsy using administrative claims or EHR/EMR data but did not validate their approaches. Across the selected studies, ICD diagnosis codes were the primary code sets used to identify cases.

Overall, medical record-based validation studies and several additional studies without validation identified in this literature review indicate that the approach of using ICD-9-CM 351.0 was consistently applied for identifying Bell's palsy cases.

2.a Medical Records-based Algorithms with Validation

A systematic review funded by FDA from Lee and colleagues (2013) was conducted to identify the diagnostic accuracy of billing, procedural, or diagnostic codes for Bell's palsy.[5] The authors used key terms to search the literature available in PubMed from January 1991 to September 2012. The study expanded the search further to incorporate gray literature and publications available in Google Scholar. The authors focused on studies from the U.S. and Canada that provided a clear claims- or EHR-based definition of Bell's palsy. In total, the authors identified and reviewed 124 publications, retaining six (with one study published in two papers). Of particular relevance, one U.S. study[6] by Rowhani-Rahbar and colleagues (2012a) reported measures of diagnostic accuracy performance (PPV) associated with EHR-based algorithms. The authors conducted an analysis in a Kaiser Permanente database and used ICD-9-CM 351.0 to identify all childhood cases of Bell's palsy and each medical record was reviewed by an otolaryngologist. The authors determined the occurrence of Bell's palsy in children and the association with three vaccine exposure groups: TIV, HBV vaccine, or any vaccines. The study reported a PPV of 84% (95% CI 82–86%)[vi] for definite[vii] or probable[viii] cases and found no correlation between Bell's palsy and any of the immunization exposure. In addition to the studies reviewed in Lee et al. (2013), five relevant studies[2,10-13] identified in this structured review were published after September 2012.

Another U.S. study cited in the Lee et al. (2013) systematic review reported performance measures in a paper medical record-based algorithm to identify Bell's palsy cases in Texas rehabilitation facilities, hospitals, and medical clinics.[14] The study classified the population with Bell's palsy using Hospital International Classification of Diseases Adapted (H-ICDA) 350 (for encounters from 1974–1978) and ICD-9-CM 351.x (facial nerve disorders), 767.5 (facial nerve injury due to birth trauma), and 053.11 (geniculate herpes zoster). The authors performed a validation analysis via neurologist chart review, reporting a PPV of 81% (95% CI 76–85%) for definite Bell's palsy.

In addition to this U.S. study, Bharathi and colleagues (2016) assessed the feasibility and validity of identifying Bell's palsy cases from EMR data in Canada.[10] The study was conducted using data from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) database and additional data from the provider's EMR system. The authors used ICD-9-CM 351.x and text searches to identify 33 Bell's palsy cases and 220 age- and sex-matched controls. The authors reported a PPV of 90% (95% CI 75.7–98.1%), NPV of 100% (95% CI 98.3–100%), sensitivity of 100% (95% CI 88.4–100%); and specificity of 98.6% (95% CI 96.1–99.7%).

2.b Algorithm Application without Validation

[vi] PPV and 95% CI for Rowhani-Rahbar et al (2012a) reported in Lee et al (2013)

[vii] Cases categorized as definite were required to meet all of the following criteria: 1) a definitive diagnosis of Bell's palsy in the chart, 2) unilateral weakness of all facial muscles (i.e., involvement of the forehead, eyelid, mouth, and cheek muscles), 3) acute onset within 72 hours between initial signs and maximum paresis, and 4) no report of head trauma or ipsilateral otologic disease within the 30 days prior to diagnosis, and no history of cerebrovascular incident, otologic surgery, brain tumor, sickle cell disease, Guillain-Barre´ syndrome, or other neurologic signs such as weakness of an extremity, coordination abnormalities, or other reflex or strength abnormalities or asymmetries.

[viii] Cases categorized as probable were children in whom unilateral weakness of all facial muscles was not documented (i.e., criteria 2 of definite cases) or the period of time between initial signs and maximum paresis was more than 72 hours (i.e., criteria 3 of definite cases).

Four studies[ix] [15-18] used electronic coding algorithms to identify Bell's palsy in U.S. claims and EHR data, three of which [16-18] investigated the association between vaccinations and Bell's palsy. All four studies utilized ICD-9-CM 351.0 to identify Bell's palsy cases. In addition, one study by McCarthy and colleagues[19] also used 350.x (trigeminal nerve disorders), 351.1 (geniculate ganglionitis), 351.8 (other facial nerve disorders), 351.9 (facial nerve disorder, unspecified), and 352.x (disorders of other cranial nerves) to identify other cranial nerve disorders. Among the three studies that evaluated vaccine safety and Bell's palsy, two EHR-based studies[17,18] obtained data from the Vaccine Safety Datalink Study (VSD) project to analyze adverse reactions, including Bell's Palsy, after patient receipt of the zoster vaccine[18] or H1N1 vaccine[17], respectively. Tseng and colleagues (2012) did not find any increased risk of Bell's palsy or facial nerve palsy 14 days after vaccination among the exposed group. However, when applying a risk window of 0–42 days in the other VSD-based study, Lee and colleagues (2011) reported that a statistical signal (i.e., greater than expected number of adverse events) was observed for Bell's palsy among adults 25 years of age and older exposed to the H1N1 monovalent inactivated vaccine (MIV). In contrast to this finding, a study applying a risk windows of 0 to 42 days for adverse events using administrative claims data did not find an association between Bell's palsy incidence and influenza vaccine (TIV and H1N1) exposure.[16] Finally, a U.S. study[15] using ICD-9-CM 351.0 to identify Bell's palsy cases in an administrative claims database reported a higher incidence of Bell's palsy among females, older age groups, Black and Hispanic populations, married people, and enlisted service members. The authors concluded that both arid climates and colder months were independent predictors of Bell's palsy risk.

In addition to these U.S. studies, we identified six international studies[11-13,20-22] that used diagnosis codes in claims and EHR data to identify Bell's palsy cases but did not report measures of diagnostic validity. A multi-country study estimating background rates of disease to assess vaccine safety during mass immunization with H1N1 influenza vaccine[20] analyzed hospital admissions EHR databases in the U.K., Finland, and the U.S. to identify Bell's palsy cases using ICD-9-CM 351 (U.S.), ICD-9 351 (Canada and the UK), and ICD-10 G51.0 (Bell's palsy) (Finland). We also identified a study of adverse events following H1N1 vaccinations in Taiwan that used ICD-9-CM 351.0 to identify cases of Bell's palsy in a claims database.[13] Additional studies from Scotland[11], Sweden[21], and Australia[12] described using ICD-10 G51.0 and ICD-10-Australian Modification (AM) G51.0 to identify cases of Bell's palsy in EHR databases (i.e., hospital admissions and discharges, outpatient visits) following receipt of vaccinations for human papillomavirus virus or influenza. Finally, a study from Germany[22] used ICD-10 G51.x (facial nerve disorders) to identify peripheral facial nerve palsy cases identified in an EMR database.

Overall, although these studies utilized claims- and EHR-based algorithms that were not validated, they consistently demonstrate the utilization of ICD-9-CM 351.0 for identifying Bell's palsy cases in claims and EHR databases, similar to the approach utilized in studies with validated algorithms[6,14] that is described in this report.

D Facial Nerve Palsy Clinical Case Definition

The Brighton Collaboration Bell's Palsy Working Group developed a case definition and guideline for peripheral facial nerve palsy and Bell's palsy.[2] The case definition is summarized in **Table 2**. The Working Group recommended implementing the case definition to support the meaningful collection of data and standardize the process of data collection, analysis, and presentation of information for Bell's palsy and peripheral facial nerve palsy. Peripheral facial nerve palsy, a disturbance of the facial nerve is due to idiopathic causes in 60-75% of cases. The acute-onset (i.e., minutes to days) idiopathic form of peripheral facial nerve palsy is Bell's palsy.[3]

The Brighton clinical case definitions and criteria for peripheral facial nerve palsy and idiopathic peripheral facial nerve palsy (i.e., Bell's palsy) are included in **Table 2**. The case definition is intended to be used in combination with the Working Group's clinical guidelines but may be useful for subsequent validation studies of the algorithm proposed in **Section E$**. As an initial step in the determination of Bell's palsy

[ix] Two of these studies were cited in the Lee (2013): Tseng, 2012 and Campbell, 2002

case status, the diagnosis of acute-onset peripheral facial nerve palsy should be confirmed. Following confirmation, the case can be evaluated to see if it meets the criteria for being idiopathic (i.e., Bell's palsy) as described in **Table 2**.

Table 2. Brighton Collaboration Bell's Palsy Working Group clinical case definitions for facial nerve palsy (including Bell's palsy)

Peripheral facial nerve palsy	Idiopathic peripheral facial nerve palsy (Bell's Palsy)
All levels of diagnostic certainty	**All levels of diagnostic certainty**
Weakness of the facial muscles innervated by cranial nerve VII, which is either complete (paralysis) OR incomplete paresis (includes facial muscle weakness and decreased facial muscles movement) and may manifest unilaterally OR bilaterally (bilateral peripheral facial nerve palsy is an unusual manifestation).	Has an unknown etiology, which has a sudden onset (occurs unexpectedly and without warning) **AND** shows initial rapid progression of symptoms and signs (worsening of disease over a short period of time) **AND** shows resolution (symptom and sign resolution with or without treatment)
Definite	**Definite**
Level 1 of diagnostic certainty Manifests with the acute onset decreased ability (paralysis OR paresis) to wrinkle the forehead **OR** to raise the eyebrows at the affected side.	**Level 1 of diagnostic certainty** Remains unexplained after excluding known causes (including diagnosis of an alternative illness) by review of clinical history **AND** physical examination **AND** laboratory investigations **AND** radiological studies
Probable	**Probable**
Level 2 of diagnostic certainty Not applicable	**Level 2 of diagnostic certainty** Remains unexplained after excluding known causes (including diagnosis of an alternative illness) by review of clinical history **AND** physical examination **AND** laboratory investigations
Possible	**Possible**
Level 3 of diagnostic certainty Not applicable	**Level 3 of diagnostic certainty** Remains unexplained after excluding known causes (including diagnosis of an alternative illness) by review of clinical history **AND** physical examination

Source: Rath and colleagues [2]

E Bell's Palsy Coding Algorithm

The aim of this review was to develop an algorithm to identify cases of Bell's palsy that could be of potential interest following exposure to a biologic product. To form a comprehensive list of Bell's palsy codes for clinical consideration, all ICD codes for Bell's palsy 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.[x] The resulting G51.x codes were consistent with ICD-10 approaches observed in the literature. The draft algorithm was then reviewed by clinical SMEs from IBM, FDA CBER, and Acumen. This approach supports alignment and comparability with past studies and reflects current coding practices.

The final algorithm is presented in **Table 3**. This algorithm may be subject to refinements as a result of specific research questions that arise in the future. For example, recognizing that most studies focused specifically on Bell's palsy used only ICD-9-CM 351.0, the workgroup decided on a more inclusive approach that also included other and unspecified facial nerve disorders. Users seeking a more specific algorithm may want to restrict analyses to ICD-9-CM 351.0 and ICD-10-CM G51.0. Annual counts of patients with specific diagnosis codes are provided in **Appendix B**.

Specific decisions and assumptions related to construction of the algorithm are summarized in **Section F**. Overall, the clinical SMEs recommended the inclusion of additional codes or exclusion of codes from the expanded draft code list based on clinical relevance and optimizing the balance between specificity and sensitivity. A list of excluded codes is provided in **Appendix C**. These codes were ultimately determined by the clinical SMEs to be too general and could potentially increase the risk of misclassification. As such, while they were not applied as exclusion criteria, the codes in **Appendix C** were left out of the algorithm options to identify cases of Bell's palsy.

The proposed algorithm may be summarized as follows:

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

Table 3. Facial nerve palsy algorithm.

Code	Description	Code Category	Code Type
351.0	Bell's palsy	DX	9
351.8	Other facial nerve disorders	DX	9
351.9	Facial nerve disorder, unspecified	DX	9
G51.0	Bell's palsy	DX	10
G51.8	Other disorders of facial nerve	DX	10
G51.9	Disorder of facial nerve, unspecified	DX	10

Abbreviations: DX, Diagnosis

F Assumptions and Decisions

The algorithm presented above was reviewed internally and with CBER stakeholders and partners. Decisions and assumptions relevant to the algorithm are listed below. Some of the decisions made may be modified depending on the study research question.

[x] 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.

- The algorithm is intended to identify Bell's palsy events likely following exposure to a biologic and has excluded codes which are unlikely to be related or are too general.
- To be inclusive, codes for other or unspecified facial nerve disorders were included: ICD-9-CM 351.8, and 351.9; ICD-10-CM G51.8, and G51.9. Users prioritizing specificity may want to exclude these codes, and only use those specific to Bell's palsy (ICD-9-CM 351.0; ICD-10-CM G51.0).
- Risk windows used to determine the association of Bell's palsy with a particular exposure should be determined on the basis of the particular research question and exposure of interest, though previous studies of vaccine safety have used risk windows of 1–14 days[6,13,17,18], 0–42 days[16] or 1–42 days.[6,13,17,18]
- To define an incident occurrence, a "washout period" should be considered in the future, wherein individuals would be excluded from the study if they had a Bell's palsy event within a certain time period (e.g., six months) prior to the exposure of interest.

G Algorithm Characterization

G1 Methods

To summarize the epidemiology of Bell's palsy among a commercially insured population in the U.S., the workgroup used the IBM MarketScan Research Databases (Commercial and Medicare Supplemental), accessed via the Treatment Pathways[xi] online analytic platform, to query and analyze the diagnostic codes included in the Bell's palsy algorithm (**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 or restrict the query cohort based on the diagnosis position. It is recommended that the proposed algorithm undergo a validation study prior to use, though future analytical studies should also tailor the algorithm specifications according to the study question of interest.

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

Counts of individual patients that had a diagnosis code related to Bell's palsy within a given calendar year, rather than counts of Bell's palsy codes, were presented. As such, counts relate to the first diagnosed Bell's palsy event for an individual during a given query period (e.g., January 1–December 31, 2014), and individuals could only be counted once per query period. Since we did not estimate the incidence of Bell's palsy 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 has been left out of two charts that depict the proportions of individuals with Bell's palsy by age. Infants under one year of age were not excluded from queries of the absolute number of patients receiving a Bell's palsy diagnosis.

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

Age- and gender-specific data on MarketScan Research Databases enrollment and counts of individuals receiving a diagnostic code for Bell's palsy were extracted. Code-specific queries and results described in **Section E** are summarized in **Appendix B**. In addition to the code-specific queries, the authors executed queries that aggregated all ICD-9-CM codes, all ICD-10-CM codes, and all codes (ICD-9-CM and ICD-10-CM) for Bell's palsy.

G2 Results

Of the codes included in the Bell's palsy algorithm, codes for Bell's palsy (ICD-9-CM 351.0 and ICD-10-CM G51.0) were the most frequently used during the study period (**Appendix B**). Of those receiving at least one Bell's palsy diagnosis between 2014 and 2018 (n=112,546), 35.2% (n=39,610) and 50.5% (n=56,879) had at least one ICD-9-CM 351 and ICD-10-CM G51.0 code, respectively.

Table 4 provides a summary of aggregate counts for ICD-9-CM and ICD-10-CM codes, suggesting that approximately 1.0–1.2 individuals per 1,000 individuals included in the MarketScan Research Databases received a code associated with Bell's palsy each year. Among a cohort of 46,153,898 patients that combined those continuously enrolled for at least one calendar year between January 1, 2014 and December 31, 2018, 112,546 individuals (0.24%) had at least one ICD-9-CM or ICD-10-CM diagnosis code for Bell's palsy.

Table 4. Counts of patients with Bell's palsy by code set and year.

Code/ Description	Year				
	2014	**2015[a]**	**2016**	**2017**	**2018**
ICD-9-CM	34,637	21,939			
ICD-10-CM		8,038	22,911	20,086	19,344
ICD-9-CM OR ICD-10-CM	34,637	27,007	22,911	20,086	19,344
MarketScan Research Databases Enrollment	28,407,959	22,117,235	21,616,291	19,563,847	19,371,891
Proportion of Patients with Bell's palsy per 1,000 Enrolled Population[b]	**1.2**	**1.2**	**1.1**	**1.0**	**1.0**

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

The workgroup assessed whether the 2015 transition to ICD-10-CM and any associated changes in coding practices resulted in notable shifts in the overall frequency of Bell's palsy reporting. **Figure 1** illustrates the proportion of the enrolled population with a diagnosis related to Bell's palsy and suggests that the transition did not result in a substantial change to the proportion of individuals receiving a Bell's palsy diagnosis. However, the proportion of patients receiving a Bell's palsy diagnosis gradually decreased between 2016 and 2018. This decrease may be attributable in part to changes in the coding process following the transition from ICD-9-CM to ICD-10-CM codes. Independent analyses also indicated a decrease in the proportion of patients receiving a diagnosis for acute bronchitis, COPD, acute respiratory distress syndrome, and pneumonia for the same period. Therefore, this decrease may also be due to incomplete data capture in the MarketScan Research Databases for the recent years (2016–2018).

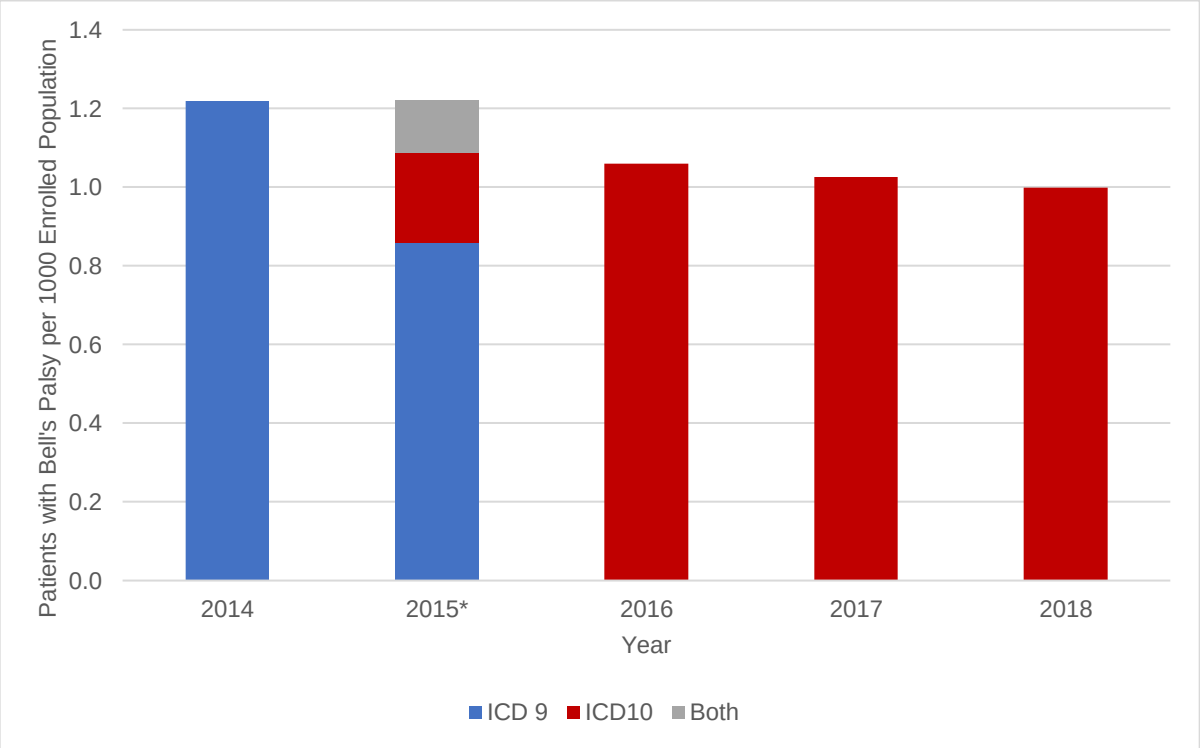

Figure 1. Proportion of patients with Bell's palsy, by year (2014–2018).

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 Bell's palsy diagnosis (defined inclusively using ICD-9-CM 351.0, 351.8 and 351.9), 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 54,311 (0.16%) with at least one diagnosis for Bell's palsy during this period, with an average age at first diagnosis of 49 years.

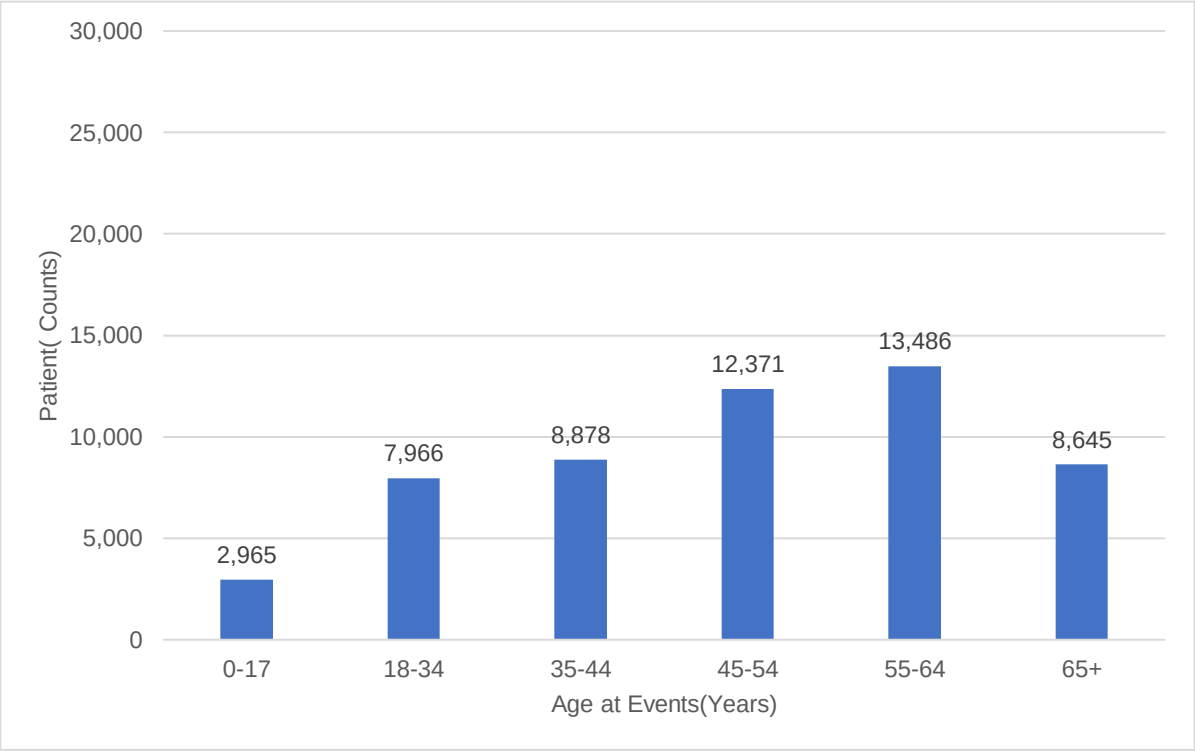

Figure 2. Patients with at least one diagnosis code for Bell's palsy (ICD-9-CM), January 1, 2014–September 30, 2015, stratified by age.

Figure 3 presents counts of patients with Bell's palsy (defined by ICD-10-CM codes listed in **Table 3)** stratified by age group. Counts were drawn from a cohort of 35,337,738 patients who were continuously enrolled for at least one calendar year between October 1, 2015 and December 31, 2018 (i.e., January 1–December 31 for at least one of 2015, 2016, 2017, or 2018). Among 64,911 individuals (0.18%) with at least one diagnosis for Bell's palsy during this time period, the average age at first diagnosis was 48 years.

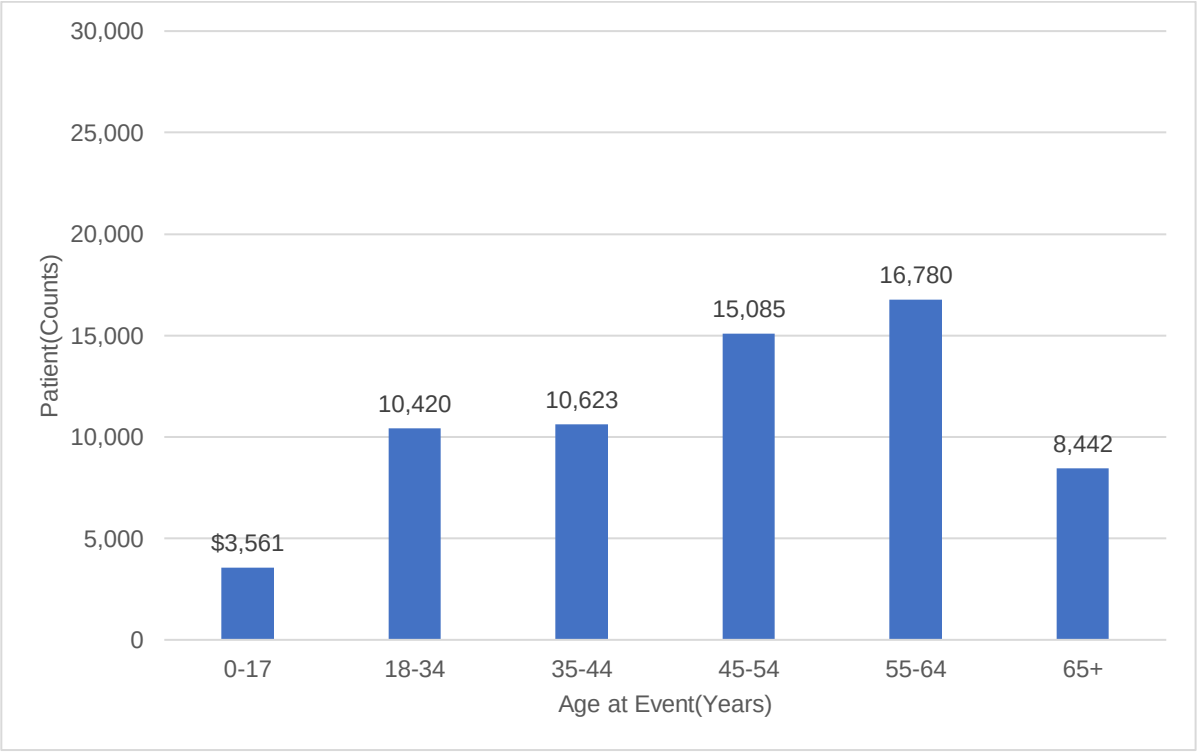

Figure 3. Patients with at least one diagnosis code for Bell's palsy (ICD-10-CM), October 1, 2015–December 31, 2018, stratified by age.

Figure 4 presents counts of patients with either an ICD-9-CM or ICD-10-CM code for Bell's palsy among a cohort of 46,153,898 individuals who were continuously enrolled for at least one calendar year between 2014 and 2018. Among 112,546 (0.24%) who received a diagnosis code for Bell's palsy between January 1, 2014, and December 31, 2018, the average age at first diagnosis was 48 years. Absolute patient counts were highest in the age group of 55-64 years, with the lowest absolute counts in the 0-17 age group. The absolute counts for age group 65+ are lower partly due to fewer enrollment into commercial insurance and incomplete claims ascertainment from Medicare supplemental among this group.

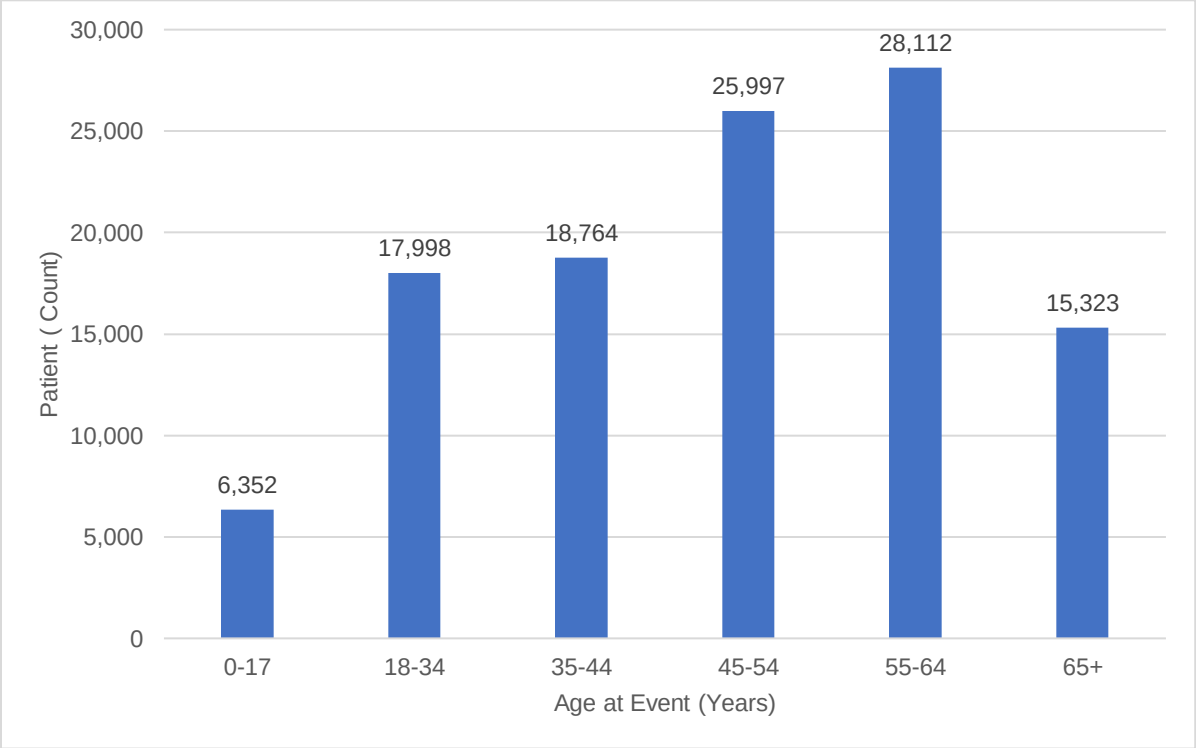

Figure 4. Patients with at least one diagnosis code for Bell's palsy (ICD-9-CM or ICD-10-CM), January 1, 2014–December 31, 2018, stratified by age.

Figure 5 summarizes the proportion of the population aged 1-85+ years with at least one ICD-9-CM or ICD-10-CM code for Bell's palsy (per 1,000 population enrolled in the MarketScan Research Databases) between January 1, 2014, and December 31, 2018, by age and gender. Patients 85 years or older were grouped to minimize the effect of unstable estimates due to the smaller enrolled population sizes available in this age range in the commercially insured population. The 46 million-patient cohort was used for this analysis and individuals were required to be enrolled for at least one calendar year between 2014 and 2018 but were not required to be enrolled for the full five-year period to be included in the calculations. The results suggest that the proportion of patients with Bell's palsy increases with age. At 65 years, the proportion of individuals experiencing Bell's palsy decreases sharply, though this may be due to shifts in enrollment as individuals move off from their commercial insurance plans, and proportions begin to increase again at 66 years of age. In addition, the results indicate that the proportion of patients with Bell's palsy is distributed evenly between boys and girls, though a consistently higher proportion was observed in adult women 20–60 years old relative to men of the same age.

Figure 5. Proportion of patients (1-85+)* with at least one diagnosis code for Bell's palsy (ICD-9-CM or ICD-10-CM) per 1,000 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 Bell's palsy is excluded from the chart.

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

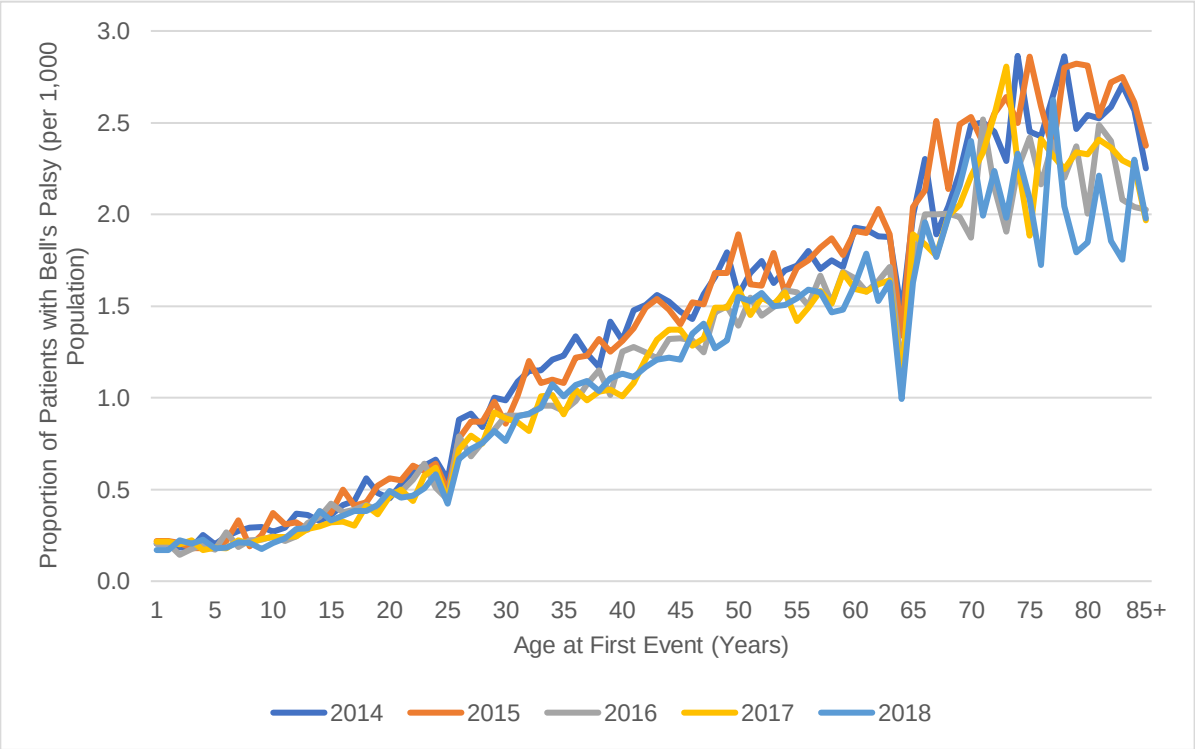

Figure 6. Proportion of patients (1-85+)* with at least one diagnosis code for Bell's palsy (ICD-9-CM or ICD-10-CM) per 1,000 population, by age and calendar year (January 1, 2014–December 31, 2018).

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 1-year old experiencing Bell's palsy is excluded from the chart.

Analyses were also conducted to test whether there was a temporal association in the occurrence or reporting of Bell's palsy according to the time of the year, possibly as a result of an association with weather patterns or vaccination schedules. To test this, enrollment and Bell's palsy 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**, except for 2016 — which demonstrated a higher proportion of Bell's palsy in the first half of the year compared to the second — there did not appear to be a substantial difference in the proportion of patients experiencing Bell's palsy during the first and second halves of the calendar year.

Table 5. Counts and proportions of patients experiencing Bell's palsy*, 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	20,889	17,017	14,075	12,266	11,865
July–December patient count	22,036	16,492	12,223	12,305	12,062
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 1,000 enrolled)	**0.67**	**0.71**	**0.60**	**0.57**	**0.56**
July–December proportion (per 1,000 enrolled)	**0.71**	**0.69**	**0.51**	**0.59**	**0.58**

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

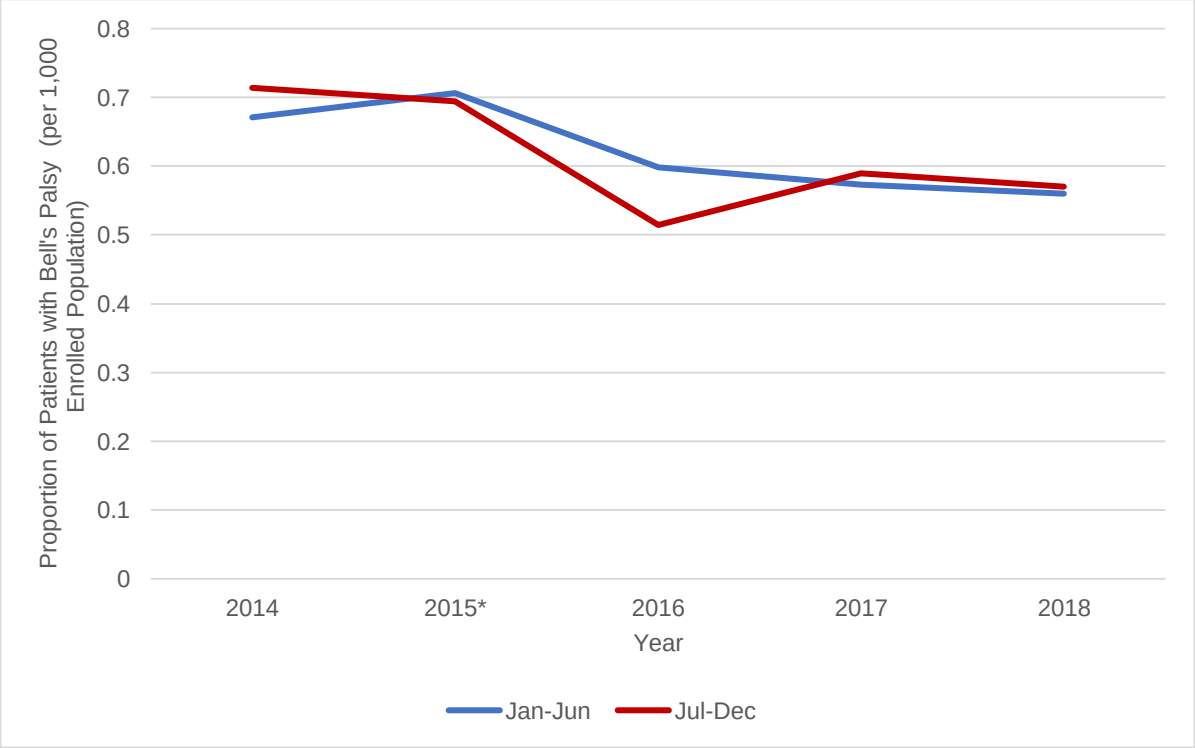

Figure 7. Proportion of patients with at least one diagnosis code for Bell's palsy (ICD-9-CM or ICD-10-CM), stratified by time of year (2014–2018).

H Discussion and Conclusion

The objective of this structured review was to understand and assess the validity of electronic coding algorithms for identifying Bell's palsy from administrative claims and EHRs using billing codes. Among the 15 publications identified, two U.S. studies[6,14] and one Canadian study[10] reported validation of Bell's palsy algorithms in medical records (EHR-, paper- and EMR-based) using an ICD-9-CM algorithm to identify cases of Bell's palsy. No studies were identified that reported on diagnostic accuracy associated with administrative claims-based algorithms for Bell's palsy in the U.S. population. Although a limited number of studies with performance measures for Bell's palsy algorithms identified in EHRs were reported in the literature, the results from validation studies suggest that the ICD-9-CM codes 351.0 and 351.x have a high PPV of 84 and 90%, respectively. In addition, four U.S. epidemiologic studies were identified that applied ICD-9-CM 351.0 to identify Bell's palsy cases in claims or medical records. These findings — in combination with ICD-10 codes identified from five international studies — were used to develop an updated algorithm that was refined through consultation with clinical SMEs.

The algorithm was then applied in the MarketScan Research Databases, accessed via the Treatment Pathways analytic tool, to test the feasibility of algorithm use and conduct some initial analyses describing the epidemiology of Bell's palsy in a U.S. database of commercially insured patients. Findings suggest that 1.0–1.2 individuals per 1,000 population had at least one Bell's palsy diagnosis code per year between 2014 and 2018. This result is much higher than the annual incidence of Bell's palsy reported in the literature, which ranges between 0.13 and 0.53 individuals per 1,000 population.[2,4,23] An older study population, which are at a greater risk of developing Bell's palsy, may have contributed to the higher proportion observed in the MarketScan Research Databases. The average age at first diagnosis during the query period was 48 years old, which is older than a median age at onset of 40 years reported in the literature.[23] In addition, unmeasured risk factors (e.g., diabetes, obesity, and hypertension) and differences in the methodology for the cited literature (e.g., non-U.S., small study population, older data, peripheral facial nerve palsy etiology) may have also contributed to the higher proportions observed.

The proportion of patients experiencing Bell's palsy was higher among adult women (20–60 years old) relative to their male counterparts, though the absolute difference was small (less than one patient per 1,000). Several studies[6,14,15,18,20] have also suggested that the incidence of Bell's palsy is higher in women and increases with age, consistent with findings presented in **Figure 5**. Except for 2016, the proportion of patients receiving a Bell's palsy diagnosis did not vary substantially between the first and second half of the year (**Figure 7**). The evidence for an association between season and Bell's palsy is inconsistent. Some studies have reported a higher incidence of Bell's palsy in colder months (November–March) compared to warmer months (May–September)[15,24] whereas, others have reported no difference in the seasonal distribution of Bell's palsy incidence.[25] Future analyses of the MarketScan Research databases could consider whether seasons and specific months are associated with peaks in Bell's palsy.

Strengths of this study are the development of a Bell's palsy algorithm for ICD-9-CM and ICD-10-CM codes based on a structured review of the literature and active engagement with clinical SMEs. To assess the plausibility of the algorithm, it was applied in a large administrative claims database to characterize Bell's palsy in the commercially insured U.S. population and generate descriptive statistics. The study also has limitations that should be considered when interpreting findings. First, a limited number of Bell's palsy validation studies were identified in the literature. The available studies did report strong performance measures in EHR/EMR databases. However, the external validity of these results is limited as algorithm performance is likely to vary in other systems due to differences in population characteristics and prevalence of Bell's palsy. As such, the performance of the Bell's palsy algorithm proposed herein remain unknown. The workgroup sought to optimize algorithm sensitivity by making the algorithm more inclusive, including ICD-9-CM and ICD-10-CM codes for facial nerve disorders (ICD-9-CM 351.8, 351.9; ICD-10-CM G51.8, G51.9) that could reasonably be associated with exposure to biologics. However, users seeking to prioritize specificity may want to exclude these codes and only use those specific to Bell's palsy (ICD-9-CM 351.0; ICD-10-CM G51.0). 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 a code list, health care settings, diagnosis positions, and/or a time window need be defined to identify potential cases in administrative databases.

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

J References

1. Newadkar UR, Chaudhari, L., Khalekar, Y. K. Facial Palsy, a Disorder Belonging to Influential Neurological Dynasty: Review of Literature. *N Am J Med Sci.* Jul 2016;8(7):263-267.
2. Rath B, Gidudu JF, Anyoti H, et al. Facial nerve palsy including Bell's palsy: Case definitions and guidelines for collection, analysis, and presentation of immunisation safety data. *Vaccine.* Apr 4 2017;35(15):1972-1983.
3. Heckmann JG, Urban, P. P., Pitz, S., Guntinas-Lichius, O., Gagyor, I. The Diagnosis and Treatment of Idiopathic Facial Paresis (Bell's Palsy). *Dtsch Arztebl Int.* Oct 11 2019;116(41):692-702.
4. Warner MJ, Hutchison, J., Varacallo, M. Bell Palsy. 2020; https://www.ncbi.nlm.nih.gov/books/NBK482290/. Accessed September 12, 2020.
5. Lee CD, Carnahan RM, McPheeters ML. A systematic review of validated methods for identifying Bell's palsy using administrative or claims data. *Vaccine.* Dec 30 2013;31 Suppl 10:K7-11.
6. Rowhani-Rahbar A, Baxter R, Rasgon B, et al. Epidemiologic and clinical features of Bell's palsy among children in Northern California. *Neuroepidemiology.* 2012a;38(4):252-258.
7. Zhang W, Xu, L., Luo, T., Wu, F., Zhao, B., Li, X. The etiology of Bell's palsy: a review. *J Neurol.* Jul 2020;267(7):1896-1905.
8. Rath B, Linder T, Cornblath D, et al. All that palsies is not Bell's -the need to define Bell's palsy as an adverse event following immunization. *Vaccine.* Dec 21 2007;26(1):1-14.
9. Rowhani-Rahbar A, Klein NP, Lewis N, et al. Immunization and Bell's palsy in children: a case-centered analysis. *Am J Epidemiol.* May 1 2012b;175(9):878-885.
10. Bharathi R, Sullivan, F., Aliarzadeh, B., Greiver, M. Validation of Identification of Bell's palsy Cases in Canadian Primary Care EMR Data-A Pilot Study. *Ann Otolaryngol Rhinol.* 2016;3(1082.).
11. Cameron R, Ahmed, S., Pollock, KG. Adverse event monitoring of the human papillomavirus vaccines in Scotland. *Intern Med J.* 2016 2015;46:452-457.
12. Clothier HJ, Lee, K. J., Sundararajan, V., Buttery, J. P., Crawford, N. W. Human papillomavirus vaccine in boys: background rates of potential adverse events. *Med J Aust.* Jun 3 2013;198(10):554-558.
13. Huang WT, Huang, W. I., Huang, Y. W., Hsu, C. W., Chuang, J. H. The reporting completeness of a passive safety surveillance system for pandemic (H1N1) 2009 vaccines: a capture-recapture analysis. *Vaccine.* Mar 9 2012;30(12):2168-2172.
14. Brandenburg NA, Annegers, J. F. Incidence and risk factors for Bell's palsy in Laredo, Texas: 1974-1982. *Neuroepidemiology.* 1993;12(6):313-325.
15. Campbell KE, Brundage JF. Effects of climate, latitude, and season on the incidence of Bell's palsy in the US Armed Forces, October 1997 to September 1999. *Am J Epidemiol.* Jul 1 2002;156(1):32-39.
16. McCarthy NL, Gee, J., Lin, N. D., Thyagarajan, V., Pan, Y., Su, S., Turnbull, B., Chan, K. A., Weintraub, E. Evaluating the safety of influenza vaccine using a claims-based health system. *Vaccine.* Dec 5 2013;31(50):5975-5982.
17. Lee GM, Greene SK, Weintraub ES, et al. H1N1 and seasonal influenza vaccine safety in the vaccine safety datalink project. *Am J Prev Med.* Aug 2011;41(2):121-128.
18. Tseng HF, Liu, A., Sy, L., Marcy, S. M., Fireman, B., Weintraub, E., Baggs, J., Weinmann, S., Baxter, R., Nordin, J., Daley, M. F., Jackson, L., Jacobsen, S. J. . Safety of zoster vaccine in adults from a large managed-care cohort: a Vaccine Safety Datalink study. *J Intern Med.* May 2012;271(5):510-520.
19. Drahos J, Vanwormer, J. J., Greenlee, R. T., Landgren, O., Koshiol, J. Accuracy of ICD-9-CM codes in identifying infections of pneumonia and herpes simplex virus in administrative data. *Annals of epidemiology.* May 2013;23(5):291-293.
20. Black S, Eskola J, Siegrist CA, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. *Lancet.* Dec 19 2009;374(9707):2115-2122.
21. Persson I, Granath, F., Askling, J., Ludvigsson, J. F., Olsson, T., Feltelius, N. Risks of neurological and immune-related diseases, including narcolepsy, after vaccination with

Pandemrix: a population- and registry-based cohort study with over 2 years of follow-up. *J Intern Med.* Feb 2014;275(2):172-190.

22. Papan C, Kremp, L., Weiß, C., Petzold, A., Schroten, H., Tenenbaum, T. Infectious causes of peripheral facial nerve palsy in children-a retrospective cohort study with long-term follow-up. *Eur J Clin Microbiol Infect Dis.* Nov 2019;38(11):2177-2184.
23. Gilden DH. Bell's Palsy. In: Johnson RT, Griffin JW, McArthur JC, eds. *Current Therapy in Neurologic Disease (Seventh Edition)*. Philadelphia: Mosby; 2006:207-208.
24. De Diego JI, Prim, M. P., Madero, R., Gavilán, J. Seasonal patterns of idiopathic facial paralysis: a 16-year study. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Feb 1999;120(2):269-271.
25. Narcı H, Horasanlı, B., Uğur, M. Seasonal Effects on Bell's Palsy: Four-Year Study and Review of the Literature. *Iranian Red Crescent medical journal.* Aug 2012;14(8):505-506.

Appendix A. Literature Review Summary

Table A1, below, includes a summary of the data extraction table used to extract papers of relevance to Bell's palsy algorithms. The 14 papers[xii] summarized in this table informed the development of the proposed Bell's palsy algorithm.

Table A1. Literature review summary table

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims/EHR/EMR-based Algorithm[xiii]
Bharathi, 2016	Validation of Identification of Bell's palsy Cases in Canadian Primary Care EMR Data-A Pilot Study	Canada	Used ICD-9-CM 351.x to identify potential BP cases in Canada	Medical record review was used as the reference standard.	ICD-9-CM 351.x or Bell's Palsy as free text in the database	PPV: 90% (95% CI 75.7–98.1%) NPV: 100% (95% CI 98.3–100%) Sensitivity: 100% (95% CI 88.4–100%) Specificity: 98.6% (95% CI 96.1–99.7%)	EMR
Black, 2009	Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines	U.S.	Used ICD-9-CM 351 (U.S.), ICD-9 351 (UK, Canada), and ICD-10 G51.0 (Finland) to identify potential BP cases in the U.S.	NA (no validation)	ICD-9-CM 351 ICD-9 351 ICD-10 G51.0	NA (no validation)	EHR

[xii] A total of 15 papers were identified as being particularly relevant. Of these 15 articles, data from Lee (2013), a review article, is not included in **Table A1**. Results from Lee (2013) are reported on a study-specific basis (i.e., Black 2009; Campbell 2002; Rowhani-Rahbar 2012a; Tseng 2012; Brandenburg 1993) in **Table A1**.

[xiii] Each publication reported on a either a claims-based (i.e., Bell's palsy codes derived from insurance reimbursement claims) or EHR-/EMR-based (i.e., Bell's palsy codes derived from administrative medical records) algorithm.

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims/EHR/EMR-based Algorithm[xiii]
Brandenburg, 1993	Incidence and risk factors for Bell's palsy in Laredo, Texas: 1974-1982	U.S.	Used ICD-9-CM 351.x, 767.5, and 053.11 and H-ICDA 350 to identify potential BP cases in the U.S.	Medical record review was used as the reference standard.	ICD-9-CM 351.x, 767.5, 053.11 H-ICDA: 350	PPV: 81% (95% CI 76-85%) for facial paralysis	Medical records
Cameron, 2015	Adverse event monitoring of the human papillomavirus vaccines in Scotland	UK	Used ICD-10-CM code G51.0 to identify potential BP cases in the UK	NA (no validation)	ICD-10-CM G51.0	NA (no validation)	EHR
Campbell, 2002	Effects of Climate, Latitude, and Season on the Incidence of Bell's Palsy in the US Armed Forces, October 1997 to September 1999	U.S.	Used ICD-9-CM 351.0 to identify potential BP cases in the U.S.	NA (no validation)	ICD-9-CM 351.0	NA (no validation)	Claims
Clothier, 2013	Human papillomavirus vaccine in boys: background rates of potential adverse events	Australia	Used ICD-10-AM G51.0 to identify potential BP cases in Australia	NA (no validation)	ICD-10-AM G51.0	NA (no validation)	EHR
Huang, 2012	The reporting completeness of a passive safety surveillance system for pandemic (H1N1) 2009 vaccines: a capture-recapture analysis	Taiwan	Used ICD-9-CM 351.0 to identify potential BP cases in Taiwan	NA (no validation)	ICD-9-CM 351.0	NA (no validation)	Claims
Lee, 2011	H1N1 and seasonal influenza vaccine safety in the vaccine safety datalink project	U.S.	Used ICD-9-CM 351.0 to identify potential BP cases in the U.S.	NA (no validation)	ICD-9-CM 351.0	NA (no validation)	EHR

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims/EHR/EMR-based Algorithm[xiii]
McCarthy, 2013	Evaluating the safety of influenza vaccine using a claims-based health system	U.S.	Used ICD-9-CM 351.0 to identify potential BP cases and ICD-9-CM 350.x, 351.1, 351.8, 358.9, and 352.x to identify potential cases with other cranial nerve disorders in the U.S.	NA (no validation)	ICD-9-CM 351.0	NA (no validation)	Claims
Papan, 2019	Infectious causes of peripheral facial nerve palsy in children—a retrospective cohort study with long-term follow-up	Germany	Used ICD-10-CM G51.x to identify potential peripheral facial nerve palsy cases in Germany.	NA (no validation)	ICD-10-CM G51.x	NA (no validation)	EMR
Persson, 2016	Risks of neurological and immune-related diseases, including narcolepsy, after vaccination with Pandemrix: a population- and registry-based cohort study with over 2 years of follow-up	Sweden	Used ICD-10-CM G51.0 to identify potential Bell's palsy cases in Sweden.	NA (no validation)	ICD-10 G51.0	NA (no validation)	National Health Registry
Rowhani-Rahbar, 2012a	Epidemiologic and clinical features of Bell's palsy among children in Northern California	U.S.	Used ICD-9-CM 351.0 to identify potential BP cases in the U.S.	Medical record review was used as the reference standard, with the following diagnostic criteria:	ICD-9-CM 351.0	PPV[xiv] for definite or probable cases: 84% (95% CI 82-86%)	EHR

[xiv] PPV and 95% CI for Rowhani-Rahbar et al (2012a) reported in Lee et al (2013)

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims/EHR/EMR-based Algorithm[xiii]
				Definitive diagnosis (meeting all of the following criteria): 1) definitive Bell's palsy diagnosis in chart, 2) unilateral weakness of all facial muscles, 3) acute onset with 72 hours between initial signs and maximum partial paralysis, and 4) no report of head trauma or hearing disorder within 30 days prior to diagnosis, and no history of cerebrovascular event, otologic surgery, brain tumor, sickle cell disease, Guillain- Barre´ syndrome, or other neurologic signs. Probable diagnosis: children exhibited unilateral weakness of all facial muscles not recorded or the time between initial signs and maximum partial paralysis was >72 hours			
Rowhani-Rahbar, 2012b	Immunization and Bell's palsy in children: a case-centered analysis	U.S.	Used ICD-9-CM 351.0 to identify potential BP cases in the U.S. **Article uses same population as Rowhani-Rahbar, 2012a**	Medical record review was used as the reference standard, with the following diagnostic criteria: Definitive diagnosis (meeting all of the following criteria): 1) definitive Bell's palsy diagnosis in chart, 2)	ICD-9-CM 351.0	PPV[xv] for definite or probable cases: 84% (95% CI 82-86%)	EHR

[xv] PPV and 95% CI for Rowhani-Rahbar et al (2012b) reported in Lee et al (2013)

Citation	Title	Country	Summary	Disease Definition	Algorithm/Criteria	Validity	Claims/EHR/EMR-based Algorithm[xiii]
				unilateral weakness of all facial muscles, 3) acute onset with 72 hours between initial signs and maximum partial paralysis, and 4) no report of head trauma or hearing disorder within 30 days prior to diagnosis, and no history of cerebrovascular event, otologic surgery, brain tumor, sickle cell disease, Guillain- Barre´ syndrome, or other neurologic signs. Probable: children exhibited unilateral weakness of all facial muscles not recorded or the time between initial signs and maximum partial paralysis was >72 hours			
Tseng, 2012	Safety of zoster vaccine in adults from a large managed-care cohort: a Vaccine Safety Datalink study	U.S.	Used ICD-9-CM 351.0 to identify potential BP cases in the U.S.	NA (no validation)	ICD-9-CM 351.0	NA (no validation)	EHR

Abbreviations: AE: Adverse Event; BP: Bell's palsy; CI: confidence interval; EHR: Electronic Health Record; EMR: Electronic Medical Record; H-ICDA: Hospital International Classification of Diseases Adapted; 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; NA: not applicable

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

As an initial test of the proposed algorithm, the workgroup ran code-specific queries in the MarketScan Research Databases (Commercial, Medicare Supplemental) using data during January 1, 2014 to December 31, 2018. Results are presented in **Table B1**. Because the transition between International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9-CM to ICD-10-CM) occurred on October 1, 2015, ICD-9-CM codes were queried for January 1, 2014–September 30, 2015, and ICD-10-CM codes were queried for October 1, 2015–December 31, 2018.

Subtotal rows and "Total" columns may be smaller than the sum of individual cells, because patients with multiple codes in a single year and with more than one of the same diagnosis codes in different years will only be counted once in these rows and columns. As a result, the sum of all "% of Total" cells in a single column may exceed 100%. However, the "Total" column could also be larger than the sum of individual years, as a result of situations where an individual is only enrolled for part of the year that they experience a Bell's palsy event but is then continuously enrolled for a separate year. For example, an individual could be continuously enrolled for a few days, weeks, or months in 2016 and have a diagnosis code for Bell's palsy, then be continuously enrolled for all of 2017. This event would not be captured in the column for the 2015 (as the individual would be excluded from that cohort) but would be captured in the "Total" column.

Of the codes included in the Bell's palsy algorithm, codes for Bell's palsy (ICD-9-CM 351.0 and ICD-10-CM G51.0) were the most frequently used during the study period. Of those receiving at least one Bell's palsy diagnosis between 2014 and 2018 (n=112,546), 35.2% (n=39,610) and 50.5% (n=56,879) had at least one ICD-9-CM 351.0 and ICD-10-CM G51.0 code, respectively. In addition, 13.0% (n=14,662) and 6.2% (n=6,973) received a code for other facial nerve disorders (ICD-9-CM 351.8) and other disorders of facial nerve (ICD-10-CM G51.8), respectively.

Table B1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in the Bell's palsy algorithm (January 1, 2014–December 31, 2018).

Code	Code Description	Year										Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)	2018 (Count)	2018 (% of Total)		
ICD-9-CM													
351.0	Bell's palsy	24,481	70.6	15,331	56.8							39,610	35.2
351.8	Other facial nerve disorders	9,403	27.1	6,214	23.0							14,662	13.0
351.9	Facial nerve disorder, unspecified	2,870	8.3	1,716	6.4							4,592	4.1
ICD-9-CM Subtotal		**34,637**	**100.0**	**21,939**	**81.2**							**55,234**	**49.1**
ICD-10-CM													
G51.0	Bell's palsy			6,454	23.9	19,683	85.9	17,670	88.0	17,004	87.9	56,879	50.5
G51.8	Other disorders of facial nerve			1,317	4.9	2,777	12.1	1,971	9.8	1,826	9.4	6,973	6.2
G51.9	Disorder of facial nerve, unspecified			583	2.2	1,550	6.8	1,261	6.3	1,373	7.1	4,565	4.1
ICD-10-CM Subtotal				**8,038**	**29.8**	**22,911**	**100.0**	**20,086**	**100.0**	**19,344**	**100.0**	**65,112**	**57.9**
Total		**34,637**	**100**	**27,007**	**100.0**	**22,911**	**100.0**	**20,086**	**100.0**	**19,344**	**100.0**	**112,546**	**100.0**

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

Appendix C. Counts of Patients with Specific Codes Excluded from the Algorithm

The diagnosis codes listed in **Table** were considered based on literature review and consultation with clinical SMEs (JB, TB, JC, DT), but were ultimately excluded from the algorithm due to the justification provided (e.g., too general, not related to exposure to biologics). The intent of this table is to provide an explanation for the omission of some closely related codes. These codes were not used to identify patients with a relevant Bell's palsy diagnosis.

Table C1. Excluded codes potentially relevant to facial nerve palsy identified from the literature or GEMs mapping.

Code	Description	Code Category	Code Type	Justification
351.1	Geniculate ganglionitis	DX	9	Severe paroxysmal neuralgic pain deep in the ear
767.5	Facial nerve injury due to birth trauma	DX	9	Excluded due to focus on biologics as exposure of interest.
G51.1	Geniculate ganglionitis	DX	10	Severe paroxysmal neuralgic pain deep in the ear
G51.2	Melkersson's syndrome	DX	10	Recurrent facial nerve palsy is a component, but once the diagnosis is known this is not idiopathic Bell's palsy
G51.31	Clonic hemifacial spasm, right	DX	10	Too general – can sometimes accompany Bell's palsy, but various other causes
G51.32	Clonic hemifacial spasm, left	DX	10	Too general – can sometimes accompany Bell's palsy, but many other causes
G51.33	Clonic hemifacial spasm, bilateral	DX	10	Too general - can sometimes accompany Bell's palsy, but many other causes
G51.39	Clonic hemifacial spasm, unspecified	DX	10	Too general - can sometimes accompany Bell's palsy, but many other causes
G51.4	Facial myokymia	DX	10	Hemifacial spasms
P11.2	Birth injury to facial nerve	DX	10	Excluded due to focus on biologics as exposure of interest

Abbreviations: DX, Diagnosis

Authors ran code-specific queries in the MarketScan Research Databases (Commercial and Medicare Supplemental) during January 1, 2014–December 31, 2018, to assess the number of patients with diagnosis codes in **Table** that were considered but ultimately excluded. This has been done to gain an understanding of how many patients will be excluded as a result of each code being omitted from the algorithm; however, patients with excluded codes may be included in the analysis if they *also* have a code that was in the algorithm. Results are presented in **Table C2**.

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 prior to 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 experience a Bell's palsy event but is then continuously enrolled for a separate year. For example, an individual could be continuously enrolled for a few days, weeks, or months in 2016 and have a diagnosis code for facial myokymia, then be continuously enrolled for all of 2017. This event would not be captured in the column for the 2016 (as the individual would be excluded from that cohort) but would be captured in the "Total" column.

Of those receiving an excluded code listed in **Table** between 2014 and 2018 (n=11,310), the code for facial myokymia (ICD-10-CM G51.4) was the most frequently used during the study period. Specifically, 80.5% (n=9,109) had at least one ICD-10-CM 51.4 code.

Table C2. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for exclusion from the Bell's palsy algorithm (January 1, 2014–December 31, 2018).

Code	Code Description	Year										Total (Count)	Total (% of Total)
		2014 (Count)	2014 (% of Total)	2015 (Count)	2015 (% of Total)	2016 (Count)	2016 (% of Total)	2017 (Count)	2017 (% of Total)	2018 (Count)	2018 (% of Total		
ICD-9-CM													
351.1	Geniculate ganglionitis	150	73.9	78	8.0							234	2.1
767.5	Facial nerve injury due to birth trauma	53	26.1	33	3.4							135	1.2
ICD-9-CM Subtotal		**203**	**100.0**	**110**	**11.3**							**368**	**3.3**
ICD-10-CM													
G51.1	Geniculate ganglionitis			30	3.1	83	2.9	80	2.9	103	2.3	294	2.6
G51.2	Melkersson's syndrome			48	4.9	78	2.7	55	2.0	64	1.5	198	1.8
G51.31	Clonic hemifacial spasm, right			0	0.0	0	0.0	0	0.0	351	8.0	359	3.2
G51.32	Clonic hemifacial spasm, left			0	0.0	0	0.0	0	0.0	369	8.4	377	3.3
G51.33	Clonic hemifacial spasm, bilateral			0	0.0	0	0.0	0	0.0	85	1.9	88	0.8
G51.39	Clonic hemifacial spasm, unspecified			0	0.0	0	0.0	0	0.0	792	18.0	816	7.2
G51.4	Facial myokymia			788	81.2	2,714	94.1	2,569	94.5	2,881	65.5	9,109	80.5
P11.2	Birth injury to facial nerve			3	0.3	12	0.4	15	0.6	12	0.3	40	0.4
ICD-10-CM Subtotal				**864**	**89.1**	**2,884**	**100.0**	**2,718**	**100.0**	**4,396**	**100.0**	**10,952**	**96.8**
Total		**203**	**100.0**	**970**	**100.0**	**2,884**	**100.0**	**2,718**	**100.0**	**4,396**	**100.0**	**11,310**	**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.