# Table S-1. HL7 standard CVX code set to identify influenza vaccinations in the 2018–2019 influenza season, Vaccine Safety Datalink rapid cycle and end-of-season analyses

|  |  |  |
| --- | --- | --- |
| **CVX Code\*** | **CVX Full Vaccine Name** | **Classification** |
|
| 135 | Influenza, high dose seasonal, preservative-free | High-dose (IIV3-HD) |
| 140 | Influenza, seasonal, injectable, preservative free | Standard (split virus) (IIV3) |
| 141 | Influenza, seasonal, injectable | Standard (split virus) (IIV3) |
| 144 | Seasonal influenza, intradermal, preservative free | Standard (split virus) (IIV3) |
| 150 | Influenza, injectable, quadrivalent, preservative free | Standard (split virus) (IIV4) |
| 153 | Influenza, injectable, Madin Darby Canine Kidney, preservative free | Cell-cultured (ccIIV4) |
| 155 | Seasonal, trivalent, recombinant, injectable influenza vaccine, preservative free | Recombinant (RIV4) |
| 158 | influenza, injectable, quadrivalent, contains preservative | Standard (split virus) (IIV4) |
| 160 | Influenza A monovalent (H5N1), adjuvanted, National stockpile 2013 | Adjuvanted (aIIV3) |
| 161 | Influenza, injectable,quadrivalent, preservative free, pediatric | Standard (split virus) (IIV4) |
| 166 | influenza, intradermal, quadrivalent, preservative free, injectable | Standard (split virus) (IIV4) |
| 168 | Seasonal trivalent influenza vaccine, adjuvanted, preservative free | Adjuvanted (aIIV3) |
| 171 | Influenza, injectable, Madin Darby Canine Kidney, preservative free, quadrivalent | Standard (split virus) (IIV4) |
| 185 | Seasonal, quadrivalent, recombinant, injectable influenza vaccine, preservative free | Standard (split virus) (IIV4) |
| 186 | Influenza, injectable, Madin Darby Canine Kidney, quadrivalent with preservative | Standard (split virus) (IIV4) |

\* <https://www2a.cdc.gov/vaccines/iis/iisstandards/vaccines.asp?rpt=cvx>

# S-2. Full study protocol for Medicare self-controlled risk interval analyses in Medicare

Assessment of GBS risk following 2018–2019 influenza vaccinations in the Medicare population ages 65 and older

Protocol version 1.2 May 16, 2019

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ABBREVIATIONS

|  |  |
| --- | --- |
|  | |
| CDC | Centers for Disease Control and Prevention |
| CME | Common Medicare Enrollment |
| CMS | Centers for Medicare & Medicaid Services |
| CPT | Current Procedural Terminology |
| CWF | Common Working File |
| EDB | Enrollment Database |
| FDA | U.S. Food and Drug Administration |
| FFS | Fee-for-Service |
| GBS | Guillain-Barré syndrome |
| HCPCS | Healthcare Common Procedure Coding System |
| ICD-10 | International Classification of Diseases, Tenth Revision, Clinical modification |
| IP | Inpatient |
| OP | Outpatient |
| PB | Physician Billing/Supplier Part B Claims file /Carrier file |
| SCRI | Self-controlled risk interval |

Overview

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# EXECUTIVE SUMMARY

**Background**

The U.S. Food and Drug Administration and the Centers for Medicare & Medicaid Services have been actively monitoring the risk of Guillain-Barré syndrome (GBS) following influenza vaccination among Fee-for-Service (FFS) Medicare beneficiaries every season since 2008. The Vaccine Safety Datalink (VSD) is a collaborative project between the Centers for Disease Control and Prevention and eight health care organizations, which monitors rare and serious adverse events following immunization in nine million members total (3% of the U.S. population).[1](#_ENREF_1),[2](#_ENREF_2) In the 2018–2019 influenza season, VSD identified an increased risk of GBS among beneficiaries 65 years and older who received high-dose influenza vaccine. A total of 614,200 vaccinations with the high-dose influenza vaccine were observed as of December 12, 2018. Using the binomial maxSPRT procedure,[3](#_ENREF_3) six GBS cases were seen in the risk window (1-42 days post-vaccination), and zero cases were seen in the comparison window.

**Objective**

Assess the risk of GBS following 2018–2019 high-dose and seasonal influenza vaccinations among Medicare FFS beneficiaries ages 65 and older.

**Methods**

We will conduct self-controlled risk interval (SCRI) analyses to determine if the observed rates in the post-vaccination risk windows (days 8–21 and 1–42) are significantly higher than the GBS rates in the post-vaccination control windows (days 43–84). We will complete (1) an “early vaccination cut-off” SCRI analysis wherein we will use vaccination claims through November 9, 2018 (week 13) as the influenza vaccination cut-off; and (2) an end-of-season SCRI analysis using vaccination claims through June 29, 2019.

We will complete crude and seasonality-adjusted SCRI analyses for high-dose influenza vaccine and all seasonal influenza vaccines combined. The end-of-season analyses will additionally assess the GBS risk following other vaccine types and concurrent vaccinations based on power calculations (at least ≥80% power to detect an odds ratio of 3). We will use both claims-based and imputed GBS cases; the latter will use the positive predictive value (PPV) resulting from the medical record review process conducted during the 2015–2016 season. We will use conditional logistic regression models to calculate the odds ratios (ORs) with 95% CIs, offset by length of observation time. We will calculate attributable risk (AR) as the difference in the expected number of GBS cases observed in the risk and control windows, divided by the total number of vaccinated beneficiaries.

# BACKGROUND

Guillain-Barré syndrome (GBS) is an immune-mediated polyneuropathy that causes an individual’s immune system to damage nerve cells, causing muscle weakness and occasionally paralysis. GBS is a rare disorder that affects approximately 3,000–6,000 people each year in the United States (approximately one to two cases per 100,000 person-years).[[1]](#footnote-2) Approximately two-thirds of cases are triggered by a preceding respiratory or gastrointestinal infection, but GBS has also been associated with vaccinations.[4](#_ENREF_4)

During the 1976 influenza A pandemic threat, the risk of GBS during the six weeks following receipt of the A/New Jersey (swine) influenza vaccine was increased by nearly eight-fold.[5](#_ENREF_5) During the 2009–2010 pandemic, influenza A (H1N1) 2009 monovalent inactivated vaccines were associated in some studies with a small increased risk of GBS, which translated to approximately one to three excess cases of GBS per million people vaccinated.[6-10](#_ENREF_6) During epidemic seasons since 1976, several studies, including those performed by the U.S. Food and Drug Administration (FDA), have assessed the GBS risk following seasonal inactivated influenza vaccines and found either no risk or a small increased risk representing approximately one to two additional GBS cases per million people vaccinated.[11-17](#_ENREF_11) While it is difficult to determine the precise cause of GBS, the risk of GBS due to the influenza itself may be higher than the risk of GBS due to the influenza vaccine;[18](#_ENREF_18) regular surveillance ensures any increased GBS risk following influenza vaccination is identified.

FDA and the Centers for Medicare & Medicaid Services (CMS), in collaboration with Acumen LLC, have been actively monitoring the GBS risk following influenza vaccination among Medicare beneficiaries for every influenza season since 2008.[10](#_ENREF_10) For the 2017–2018 influenza season, we used a multilayered approach to active safety surveillance, which consisted of near real-time surveillance for early detection of a high GBS risk, regular monitoring of GBS rates post-vaccination, and an end-of-season analysis aimed at obtaining the least biased GBS risk estimate for the season. This multilayered approach is part of FDA’s broader vaccine safety surveillance system, which is part of the FDA’s pandemic preparedness activities. Surveillance is conducted annually mainly because (1) each seasons’ vaccine components change based on recommended influenza strains (Appendix A), (2) new vaccines that use diverse manufacturing techniques are entering the U.S. market, (3) vaccination is required annually because immunity is short-lived, (4) the elderly is a high-risk group for GBS as well as a recommended group for vaccination, and (5) monitoring promotes confidence in the influenza vaccine program and its safety. FDA did not conduct near real-time surveillance in the 2018–2019 season.

The Vaccine Safety Datalink (VSD) is a collaborative project between the Centers for Disease Control and Prevention (CDC) and eight health care organizations, which monitors rare and serious adverse events following immunization in nine million members total (3% of the U.S. population).[1](#_ENREF_1),[2](#_ENREF_2) VSD found an increased GBS risk among beneficiaries 65 years and older who received the 2018–2019 high-dose influenza vaccine. A total of 614,200 vaccinations with high-dose influenza vaccine were observed, and six GBS cases were seen in the risk window (1–42 days post-vaccination), and zero cases were seen in the comparison window using the binomial maxSPRT procedure.[3](#_ENREF_3)

# OBJECTIVES

The objectives are to (1) assess the GBS risk following 2018–2019 high-dose vaccination and all 2018–2019 seasonal influenza vaccinations combined among Medicare FFS beneficiaries ages 65 years and older receiving influenza vaccination from August 11, 2018 through November 9, 2018; and (2) assess the GBS risk following 2018–2019 influenza vaccinations among Medicare FFS beneficiaries ages 65 years and older receiving influenza vaccination from August 11, 2018 through June 29, 2019.

We will conduct this assessment by comparing GBS risk in days 8–21 and 1–42 post-vaccination (primary and secondary risk windows, respectively) to GBS risk in days 43–84 post-vaccination (control window) for the same season using a retrospective modified cohort design (self-controlled risk interval).

# METHODS

## Data Sources

This study will rely primarily on two types of data: Medicare enrollment data and claims data. The monthly Enrollment Database provides information about Medicare enrollment eligibility and consists of data from the Medicare Enrollment Database (EDB) and Common Medicare Enrollment (CME). Medicare claims data undergo three stages of processing: enumeration, adjudication, and final payment. We will use one source of claims data: the weekly Common Working File (CWF), which contains available information about patient services and diagnoses after adjudication. We will use the latest enrollment and claims data available by March 27, 2019, which is anticipated to be updated through March 15, 2019.

### Common Working File (CWF) Data

To identify influenza vaccinations and GBS diagnoses, we will use CWF to gather information on influenza vaccinations and GBS diagnoses. We will extract claims from the Outpatient (OP), Carrier (PB), and Inpatient (IP) files for the population enrolled in Medicare fee-for-service (FFS), wherein beneficiaries are enrolled in Medicare Parts A and B. We then will use OP and PB claims to identify influenza vaccinations , IP claims to detect hospitalized GBS cases, and OP and PB claims to exclude non-incident cases and estimate the case onset date.

The OP file contains claims submitted by institutional outpatient providers, such as hospital outpatient departments and rural health clinics; these claims include ICD, Current Procedual Terminology (CPT) codes, and Healthcare Common Procedure Coding System (HCPCS) codes. The PB file primarily consists of claims from non-institutional providers, such as physicians, physician assistants, and nurse practitioners; these claims include CPT/HCPCS codes. These files will be used to identify vaccination codes. The IP file contains claims submitted by inpatient hospital providers for reimbursement of facility costs. These claims include International Classification of Diseases, 10th revision, (ICD-10) diagnosis codes (October 1, 2015 onwards), which we use to detect GBS claims following an influenza vaccination.

## Study Population

Our early vaccination cut-off SCRI analyses will include Medicare FFS beneficiaries ages 65 and older who received an influenza vaccine during the 2018–2019 influenza season through November 9, 2018. This vaccination cut-off will allow for an estimated 96% of GBS cases in the control window to be observed (Appendix B). Beneficiaries with unknown sex will be excluded from all analyses. Beneficiares will be required to have continuous enrollment in Medicare FFS from 183 days prior to vaccination, to facilitate identifying and excluding beneficiaries with prior GBS, until 84 days post vaccination or until death.

We will additionally conduct an exploratory SCRI analysis adjusting for claims delay of GBS cases. The specifications of this analysis will be the same as in the early vaccination cut-off analysis, except that all eligible vaccinations up to March 15, 2019 will be included.

We will also conduct an end-of-season analysis including Medicare FFS beneficiaries ages 65 and older who receive an influenza vaccine during the 2018–2019 influenza season through June 29, 2019.

## Study Period (Influenza Season)

We define weeks as starting on a Saturday and ending on a Friday. The start date for the 2018–2019 season will be August 11, 2018, and the end date will be June 29, 2019. The early vaccination cut-off SCRI analyses will only include influenza vaccinees through November 9, 2018 and claims observed through March 15, 2019.

The end-of-season analyses will include influenza vaccinees through June 29, 2019 and claims observed through approximately September 27, 2019.

## Outcome (GBS)

We will define an incident GBS case as the first occurrence of a primary discharge diagnosis of GBS in the IP setting occurring during days 1–84 post-vaccination. We will exclude beneficiaries with: (1) a GBS diagnosis in any position and any setting during the 183 days pre-vaccination or on the influenza vaccination date or (2) a prior GBS claim in any setting more than seven days prior to the primary-coded GBS hospitalization. We assign each case’s “earliest onset date” as either the hospitalization date or as the date of an earlier GBS claim in any position in the inpatient or outpatient settings in the seven days prior; thus, if a primary-coded GBS hospitalization occurs in the 85–91 days post-vaccination but the earliest onset date is determined to be 84 days post-vaccination or less, the case will be included in the analyses. If a beneficiary died prior to the end of the observation period, we still include the entire planned person-time of the individual in the risk and control windows.

GBS claims are identified through the ICD-10 code G61.0 as principal discharge diagnosis.

The primary and secondary risk windows for GBS are days 8–21 and 1–42 post-vaccination, respectively. The control window will be days 43–84 post-vaccination. We will use days 8–21 post-vaccination as primary risk window because findings from prior studies, including those from the 1976 swine influenza vaccine, showed higher GBS risk in this window than in the 1–42 days post-vaccination window.[5](#_ENREF_5),[7](#_ENREF_7),[19](#_ENREF_19),[20](#_ENREF_20)

## Exposure (Influenza Vaccination)

Influenza vaccination is defined as an individual’s first administration of an influenza vaccine between the season start and end dates, as identified by a CPT code or HCPCS code indicating a seasonal influenza vaccination in the PB or OP settings. The complete list of codes is found in Appendix C.

## Concomitant Vaccinations

We will use HCPCS and CPT codes from OP claims to identify concomitantly administered vaccines (pneumococcal, hepatitis B, zoster, and tetanus toxoid-containing vaccines) (Appendix D, Table D-1). We will also search Part D (prescription drug coverage) claims for concomitant vaccine National Drug Codes (NDC) (Appendix D, Table D-2).

## Statistical Analyses

### Descriptive Analyses

We will display demographic characteristics of vaccinated beneficiaries such as age category (65–74, 75–84, and 85+), sex, and concomitant vaccinations, both for the seasonal vaccines and split by vaccine type including high-dose, adjuvanted, quadrivalent (standard dose-split virus), trivalent (standard dose-split virus), recombinant, and cell-cultured vaccines.

We will also display figures showing uptake of vaccines by week and the distribution of observed GBS cases following vaccination.

For the chart-confirmed end-of-season analyses, we will also produce descriptive statistics on confirmed GBS cases with preceding illness 42 days before GBS onset according to the abstraction results. We will search for upper respiratory infection, influenza-like illnesses, cough due to respiratory illness with/without wheeze, fever, gastrointestinal illness, nausea or vomiting, diarrhea, *Campylobactor jejuni*, and *Clostridium difficile*.

### Self-Controlled Assessment of GBS Risk (SCRI analyses)

In the SCRI approach, each influenza-vaccinated beneficiary serves as their own control as we assess a beneficiary’s risk of experiencing an outcome (GBS) after exposure (influenza vaccination) compared to the same beneficiary’s risk of experiencing an outcome during a non-exposed time period. The study population for SCRI includes all exposed individuals ages 65 and older, but only GBS cases contribute to the risk estimation. SCRI implicitly adjusts for time invariant confounders, but is susceptible to time varying confounding, which can be minimized by choosing a short control interval that is close in time to the risk interval.[21](#_ENREF_21)

We will include all GBS cases that occurred within the first 84 days following vaccination, separating cases into the risk and control windows for both the primary risk window and secondary risk window analyses. We will generate population summary statistics for each window.

We will conduct an “early vaccination cut-off” SCRI analysis using data processed through week 31 (March 15, 2019). The vaccination cutoff we will use is week 13 (November 9, 2018), by which point ~84% of vaccinations should have been serviced, translating to an SCRI analysis with approximately 81% of all the control window GBS cases for the 2018–2019 season.

### Primary, Secondary, Sensitivity, and Exploratory Analyses

Primary Analyses

The primary study groups will include (1) FFS beneficiaries 65 years and older at the time of receiving any seasonal influenza vaccine and (2) FFS beneficiaries 65 years and older at the time of receiving high-dose vaccine. Power calculations show that we have 92% power to detect an odds ratio of 3.0 for seasonal vaccines and 94% power to detect an odds ratio of 4.0 for high-dose vaccine in the primary risk window (Appendix E). Descriptive SCRI results and unadjusted and seasonality-adjusted SCRI results will be conducted. These SCRI analyses will be conducted using both claims-based cases and cases considered chart-confirmed using quantitative bias analysis based on positive predictive value.

Upon the conclusion of the influenza season, we will re-run all of the above SCRI analyses using vaccinations administered through June 29, 2019 and data through approximately September 27, 2019. These SCRI analyses will use claims-based cases only.

We will also conduct chart-confirmed end-of-season SCRI analyses including all GBS or Fisher syndrome cases observed in the primary risk (8–21 day) and control windows classified as Brighton Collaboration Levels 1–3.[4](#_ENREF_4) For these analyses, we will assign each case’s “earliest onset date” as the earliest date of onset of neurological symptoms. If the onset date could not be retrieved, we will use date of first diagnosis or date of hospitalization.

Medical record review will be conducted progressively throughout the influenza season, starting with cases identified in the “early vaccination cut-off” analyses (Appendix F-J). All inpatient GBS hospitalizations identified via claims from 1 to 98 days post-vaccination will be included in the review. This period accounts for an earlier GBS claim in any position in the inpatient or outpatient settings in the seven days prior to the primary-coded GBS hospitalization and for the one-week “washout period” following days 1–42 post-vaccination used in one the sensitivity analyses (see below; days 1–42 risk window, 43–49 washout period, 50–91 control window, 92–98 earliest onset date period).

Secondary Analyses

Additional subgroup and concomitant vaccination analyses will be completed following the end of the influenza season. For subgroup analyses (vaccine type, risk window 8–21 days post-vaccination), and analyses with and without concomitant vaccination (influenza, pneumococcal, hepatitis B, tetanus-containing, and/or zoster vaccines, risk window: 8–21 days post-vaccination), SCRI testing will be determined via power analyses based on the number of GBS cases observed within each subgroup (≥80% power to detect an odds ratio of 3.0). Given sufficient power, we propose conducting specific analysis for concomitant Shingrix administration: (1) concomitant administration of any influenza vaccine with the adjuvanted zoster vaccine (Shingrix) and (2) concomitant administration of trivalent adjuvanted influenza vaccine with the adjuvanted zoster vaccine (Shingrix).

An additional risk window of days 1–42 post-vaccination will be considered for our primary and secondary analyses.

Sensitivity Analyses

At the end of the influenza season, we will also conduct chart-confirmed SCRI analyses including all GBS or Fisher syndrome cases observed in the primary risk (8–21 day) and control windows classified as Brighton Collaboration Levels 1–4 and diagnosis made by a neurologist (insufficient diagnostic data available in the medical chart).[7](#_ENREF_7)

We will also conduct chart-confirmed end-of-season SCRI analyses using days 50–91 days post-vaccination as control window. We will include a one-week “washout period” following days 1–42 post-vaccination given that some GBS risk might extend beyond the six weeks after vaccination.

Exploratory Analyses

As an exploratory interim analysis, we will also conduct an analysis using vaccinations administered through March 15, 2019 and claims delay adjustment (section 3.7.5.2). We will also conduct an analysis without claims delay adjustment for comparison.

### Modeling

Odds ratios will be estimated with conditional logistic regression models, which are offset by the length of the observation time. 95% confidence intervals and p-values will be estimated by fitting a conditional logistic regression model; specifically, a two-sided hypothesis test will be performed via conditional logistic regression with GBS as the response variable. The model will include an indicator for the risk window as the predictor variable, an offset equal to the log of the window length, and will condition on an identification variable for the beneficiary. The model can be written as

where *p* is the risk of GBS, *interval* represents the length of the respective window in days. Under this model, our null and alternative hypotheses can be written as:

where gives the odds ratio of GBS in the risk window compared to the control window. Thus, significance of the coefficient on the risk window variable at a pre-specified level will indicate a significant association between influenza vaccination and GBS. Days 8-21 post-vaccination will be used as the primary risk window, and days 1-42 post-vaccination will be used as the secondary risk window, while days 43-84 post-vaccination will be used as the control window.

Attributable risk (per million vaccinations) will be calculated by extracting the probability of having events in the risk and control windows using the odds ratio obtained from conditional logistic regression and multiplying these probabilities by the total number of adjusted[[2]](#footnote-3) GBS cases to obtain the expected number of cases in each period. We then find the difference between the expected number of cases in the risk and control period and divide by the total number of vaccinated beneficiaries.

### SCRI Model Adjustments

#### Seasonality Adjustments

Because wild-type influenza has been seen to be associated with GBS, we will adjust for seasonality as part of the primary (i.e., all vaccines), secondary (i.e., by vaccine types), and sensitivity analyses (i.e., both risk windows).

Seasonality adjustment may be done using weekly rates of confirmed influenza calculated as the proportion of specimens testing positive for influenza among the total number of specimens submitted to the World Health Organization Collaborating Laboratories and the National Enteric Virus Surveillance System in the United States for influenza testing during the 2018-2019 influenza season, if the necessary influenza rates are available.[[3]](#footnote-4) Seasonality of influenza will be measured and introduced into the SCRI analysis in the following manner:

1. Choosing Seasonality Metric: the weekly rate of confirmed influenza, calculated as the total positive influenza count (the sum of positive tests for all sub-strains of influenza (A (H1N1), A (H3), A (unidentified), B, BVic, BYam, H3N2v)) divided by the total number of specimens submitted.
2. Defining “high” and “low” Seasons for Each Region: weeks with a influenza rate in the upper 25th percentile (i.e., 10 weeks) were deemed to be in the “high” influenza season while the remaining weeks (i.e., 30 weeks) were deemed to be in the “low” influenza season, for each HHS region.
3. Estimating Regional Baseline Risk: expected weekly number of GBS cases for each region was estimated using the fitted value from a Poisson regression model.
   1. Influenza season (“high” or “low”), as determined in (2), was the independent variable (dummy for “high” influenza season)
   2. Log of total FFS beneficiaries enrolled for each respective week and region was used as the offset
4. Calculating Weekly GBS Predicted Probability: the weekly number of GBS cases is predicted for each regional model and divided by the number of FFS beneficiaries from that region in that week to get a predicted GBS rate by region and week.
5. Calculating Weighted National GBS Predicted Probability for Each Week: the weekly predicted GBS probabilities from (4) are aggregated by region and weighted using the proportion of observed number of FFS beneficiaries in each region as the weight.
6. Calculating Cumulative Risk: Poisson regression model was used to estimate cumulative risk in risk interval and control interval for each beneficiary included in self-controlled risk interval (SCRI) analysis
   1. Cumulative risk calculated by summing weekly national baseline risk of GBS for risk periods (both primary and secondary) and for control period.
   2. Risk of getting GBS in a particular week was partially dependent on not having gotten it in previous weeks in the corresponding window period (risk or control)
      1. This dependence of risk among weeks was taken into account by multiplying each risk estimate for week *q* by (1 - *pw*) for each *w*, where *pw* is the risk for week *w* and *w* runs from 1 to (*q* - 1)
      2. Using the above-mentioned variables, the cumulative risk for a 6-week risk interval beginning in week 1 was calculated as such:

Cumulative Risk = p1 + (1 – p1)\*p2 + … + (1 – p1)\* … \* (1 – p5)\*p6

1. Running New SCRI Model With Seasonality Measure: a conditional logistic regression used for SCRI analysis conducted as before, with following difference:

New offset term was log of cumulative estimated risk for the interval instead of the log of length of interval in days.

#### Claims-Delay Adjusted Analysis

To include additional beneficiaries after the primary analysis cutoff date that do not have sufficient follow-up time, we will also conduct an SCRI analysis including all eligible vaccinated beneficiaries past the cutoff date adjusted for the claims delay in the risk and control windows.

In this analysis, the follow-up time represented by the offset term in the SCRI model be adjusted to reflect the differential probability that cases are observed. For each beneficiary we calculate the probability a case is observed in the given window (), using the previously generated delay distribution (, where represents the probability that a case is delayed by i weeks, n is the total number of weeks in a study). The adjusted follow-up time would then be the product of the length of window () and the probability that a case is observed in the given window ().

This idea is similar to the approach used by Leite et al. (2017) to account for data accrual delays when conducting near real-time vaccine safety surveillance with administrative claims data, where they also adjusted the follow-up time by the probability that an event would be recorded.22,23

#### Multiplicity Adjustments

In the end-of-season SCRI analyses, for vaccine type subgroup analyses (Figure 1), we will produce multiplicity adjusted p-values using the Benjamini-Hochberg procedure.[22](#_ENREF_22)

#### Quantitative Bias Analysis Based on Positive Predictive Value

In addition to the SCRI analysis on the claims-identified GBS cases, we will also conduct analysis adjusting for the positive predictive value (PPV) of the GBS definition using quantitative bias analysis to reflect the uncertainty in the claims-identified cases. For the early-end-of-season analysis, we will use the PPV resulting from the medical record review process conducted in the 2015–2016 season for the early-end-of-season. For the end-of-season analysis, we will not conduct a quantitative bias analysis, as we expect to have medical records for cases. This adjustment will be used to assess sensitivity to the reliability of the claims-based GBS definition.

Quantitative bias analysis will be conducted by creating multiple datasets where the status of claims-identified GBS cases is imputed by assigning them the status of “chart-confirmed” with probability equal to the PPV. The PPV is calculated as the number of chart-confirmed GBS cases over the total number of charts returned via the abstraction process; cases with “insufficient evidence” are not considered as chart-confirmed. During the 2015-2016 season, the ICD-10 PPV was calculated to be 71.2%. 1,000 Imputed datasets are created. Analyses conducted on each of the individual imputed datasets can be combined using a rule developed by Schenker and Rubin (1986).[23](#_ENREF_23) Assuming normality of the coefficient estimates, the p-values for the imputed analyses are found by dividing the coefficient estimate by the model’s standard error to arrive the z-statistic. We will additionally produce figures displaying distribution of the odds ratios from the imputed datasets resulting from our positive predictive value adjustment.

Seasonality- and multiplicity-adjusted analyses will be completed as needed for the end-of-season SCRI analyses.

**ETHICAL CONSIDERATIONS**

This surveillance was approved by the FDA’s Research Involving Human Subjects Committee. Medicare administrative data were used under a data use agreement with CMS and data use was approved by the Centers’ privacy board.

This study is funded through an inter-agency agreement between the Centers for Medicare & Medicaid Services and the U.S. Food and Drug Administration.

**TIMELINES**

|  |  |
| --- | --- |
| **Task** | **Date** |
| Finalized Protocol | April 10, 2019 |
| Early Season SCRI Results | April 3, 2019 |
| Early Season Results Memo | April 24, 2019 |
| Early Season Results – ACIP | May 8, 2019 |
| Early Season Results Manuscript/Short Communication (ready for clearance) | Summer 2019 |
| Medical Record Review | Rolling |
| End of Season SCRI Results | November 2019 |
| 2018-2019 Season Internal Report | November 2019 |
| 2018-2019 Season Manuscript (ready for clearance) | December 2019 |

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# ACKNOWLEDGEMENT AND CERTIFICATION

## Electronic Signature

By submitting an electronic signature under this Acknowledgement and Certification of Understanding, you are acknowledging that you have read and agree to the contents of this protocol (version 1.2). By signing below, you submit your approval for the analyses described in this protocol.



# APPENDIX

1. Influenza Vaccine Strains

Table A-1. Influenza vaccine strains used in the United States since 2010–2011 season to 2018-2019 season

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Season** | **Trivalent** | |  | **Quadrivalent** | |
| **H1N1** | **H3N2** | **B strain** | | **Additional B strain** |
| 2010-2011 | A/California/7/2009 | A/Perth/16/2009 | B/Brisbane/60/2008 | | -- |
| 2011-2012 | A/California/7/2009 | A/Perth/16/2009 | B/Brisbane/60/2008 | | -- |
| 2012-2013 | A/California/7/2009 | A/Victoria/361/2011 | B/Wisconsin/1/2010 | | -- |
| 2013-2014 | A/California/7/2009 | A/Victoria/361/2011 | B/Massachusetts/2/2012 | | B/Brisbane/60/2008 |
| 2014-2015 | A/California/7/2009 | A/Victoria/361/2011 | B/Massachusetts/2/2012 | | B/Brisbane/60/2008 |
| 2015-2016 | A/California/7/2009 | A/Switzerland/9715293/2013 | B/Phuket/3073/2013 | | B/Brisbane/60/2008 |
| 2016-2017 | A/California/7/2009 | A/Hong Kong/4801/2014 | B/Brisbane/60/2008 | | B/Phuket/3073/2013 |
| 2017-2018 | A/Michigan/45/2015 | A/Hong Kong/4801/2014 | B/Brisbane/60/2008 | | B/Phuket/3073/2013 |
| 2018-2019 | A/Michigan/45/2015 | A/Singapore/INFIMH-16-0019-2016 | B/Colorado/06/2017 | | B/Phuket/3073/2013 |

1. Claims Maturity

Early Season SCRI analyses must account for claims maturity, which is defined as the cumulative probability of observing all GBS cases from vaccinations serviced by our cutoff week (i.e., Nov. 9, 2018) given that GBS occurred 43-84 days post-vaccination.

where vt is the number of vaccinations serviced at time period *t*, T is the observation week, and *pt* is the estimated probability of observing a GBS case in the 43-84 day control window after a vaccination in week *t* by the observation week if it occurred.

The claims delay distribution for the 43-84 day control window was estimated from the clinical delay from the 2015-16 through 2017-18 seasons and the processing delay from the 2017-18 seasons.

The proposed cutoff date for our early season SCRI allows us to capture an estimated 84% of observed vaccinations through our data through date of March 15, 2019 with over 96% claims maturity. In other words, we have a ~96% chance of observing all of the GBS cases that may have occurred before the end of the control window for High Dose vaccinations administered through Nov. 9, 2018.

Table B-1. Count of Vaccinations Serviced per Week Observable by Week 31 in 2017-2018 Season and Cumulative Claims Maturity, High Dose 65+

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **2018-19 Surveillance** | | **Real-Time Surveillance Vaccines Serviced (2017-2018 Season)** | | | **Claims Maturity by Cutoff** |
|
| **Week** | **Cutoff Date** | **# Cumulative** | **# Per Week** | **Cum. %** |
| 1 | 8/17/2018 | 57,991 | 57,991 | 0.7% | 99.3% |
| 2 | 8/24/2018 | 165,736 | 107,745 | 1.9% | 99.2% |
| 3 | 8/31/2018 | 369,097 | 203,361 | 4.2% | 99.2% |
| 4 | 9/7/2018 | 705,503 | 336,406 | 8.0% | 99.0% |
| 5 | 9/14/2018 | 1,267,531 | 562,028 | 14.4% | 98.9% |
| 6 | 9/21/2018 | 1,987,041 | 719,510 | 22.6% | 98.7% |
| 7 | 9/28/2018 | 2,845,638 | 858,597 | 32.3% | 98.5% |
| 8 | 10/5/2018 | 3,904,793 | 1,059,155 | 44.4% | 98.3% |
| 9 | 10/12/2018 | 4,852,582 | 947,789 | 55.1% | 98.0% |
| 10 | 10/19/2018 | 5,699,928 | 847,346 | 64.7% | 97.7% |
| 11 | 10/26/2018 | 6,408,081 | 708,153 | 72.8% | 97.3% |
| 12 | 11/2/2018 | 6,947,824 | 539,743 | 78.9% | 96.9% |
| 13 | 11/9/2018 | 7,371,829 | 424,005 | 83.7% | 96.4% |
| 14 | 11/16/2018 | 7,698,656 | 326,827 | 87.4% | 95.7% |
| 15 | 11/23/2018 | 7,848,280 | 149,624 | 89.1% | 95.3% |
| 16 | 11/30/2018 | 8,038,652 | 190,372 | 91.3% | 94.4% |
| 17 | 12/7/2018 | 8,197,097 | 158,445 | 93.1% | 93.4% |
| 18 | 12/14/2018 | 8,318,010 | 120,913 | 94.5% | 92.4% |
| 19 | 12/21/2018 | 8,396,987 | 78,977 | 95.4% | 91.7% |
| 20 | 12/28/2018 | 8,434,151 | 37,164 | 95.8% | 91.2% |
| 21 | 1/4/2019 | 8,475,023 | 40,872 | 96.3% | 90.8% |
| 22 | 1/11/2019 | 8,547,974 | 72,951 | 97.1% | 89.9% |
| 23 | 1/18/2019 | 8,612,830 | 64,856 | 97.8% | 89.1% |
| 24 | 1/25/2019 | 8,670,294 | 57,464 | 98.5% | 88.4% |
| 25 | 2/1/2019 | 8,730,140 | 59,846 | 99.2% | 87.7% |
| 26 | 2/8/2019 | 8,763,287 | 33,147 | 99.5% | 87.3% |
| 27 | 2/15/2019 | 8,786,603 | 23,316 | 99.8% | 87.0% |
| 28 | 2/22/2019 | 8,797,409 | 10,806 | 99.9% | 86.9% |
| 29 | 3/1/2019 | 8,802,824 | 5,415 | 100.0% | 86.8% |
| 30 | 3/8/2019 | 8,804,210 | 1,386 | 100.0% | 86.8% |
| 31 | 3/15/2019 | 8,804,229 | 19 | 100.0% | 86.8% |

1. Influenza Vaccine Codes

Table C-1. List of influenza vaccine codes included in surveillance for the 2018–2019 season

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Code** | **SCRI Analyses**  **(65+)** | **Description** | **Vaccine Categorization** | | | | |
| **Vaccine Classification** | | **Strain** | **Abbreviation** | **Maps to Multiple Vaccine Types** |
| 90470 | No (pandemic) | H1N1 Immunization administration (intramuscular, intranasal), including counseling when performed | Pandemic | | | | |
| 90630 | No (not in 18-19) | Vaccine for influenza for injection into skin, quadrivalent, preservative free | Inactivated | Intradermal | Quadrivalent | IIV4-ID | No |
| 90653 | Yes | Vaccine for influenza for injection into muscle, inactivated, subunit, adjuvanted | Inactivated | Adjuvanted | Trivalent | aIIV3 | No |
| 90654 | No (not in 18-19) | Vaccine for influenza injection into skin, trivalent, preservative free | Inactivated | Intradermal | Trivalent | IIV3-ID | No |
| 90655 | No (pediatric) | Vaccine for influenza for administration into muscle, 0.25 ml dosage, trivalent, split virus, preservative free (pediatric use) | Inactivated | Standard (split virus) | Trivalent | IIV3 | No |
| 90656 | Yes | Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent, preservative free | Inactivated | Standard (split virus) | Trivalent | IIV3 | No |
| 90657 | No (pediatric) | Vaccine for influenza for administration into muscle, 0.25 ml dosage, trivalent (pediatric use) | Inactivated | Standard (split virus) | Trivalent | IIV3 | No |
| 90658 | Yes | Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent | Inactivated | Standard (split virus) | Trivalent | IIV3 | No |
| 90659 | No (code deleted) | Influenza virus vaccine, whole virus, for intramuscular or jet injection use | Inactivated | Standard (whole virus) | -- | -- | -- |
| 90660 | No (not in 18-19 / ages 2-49 | Vaccine for influenza for nasal administration, trivalent | Live | Attenuated | Trivalent | LAIV3 | No |
| 90661 | No (not in 18-19) | Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent, cell culture-based | Inactivated | Cell-cultured | Trivalent | ccIIV3 | No |
| 90662 | Yes | Vaccine for influenza for injection into muscle, split virus, enhanced immunogenicity via increased antigen content | Inactivated | High-dose | Trivalent | IIV3-HD | No |
| 90663 | No (pandemic) | Influenza virus vaccine, pandemic formulation, H1N1 | Pandemic | | | | |
| 90664 | No (pandemic) | Vaccine for influenza for nasal administration, pandemic formulation | Pandemic | | | | |
| 90666 | No (pandemic) | Vaccine for influenza for injection into muscle, pandemic formulation | Pandemic | | | | |
| 90667 | No (pandemic) | Vaccine for influenza for injection into muscle, pandemic formulation | Pandemic | | | | |
| 90668 | No (pandemic) | Vaccine for influenza for injection into muscle, pandemic formulation | Pandemic | | | | |
| 90672 | No (ages 2-49) | Vaccine for influenza for nasal administration, tetravalent | Live | Attenuated | Quadrivalent | LAIV4 | No |
| 90673 | No (not in 18-19) | Vaccine for influenza administered into muscle, preservative and antibiotic free, trivalent, recombinant DNA-derived | Recombinant | | Trivalent | RIV3 | No |
| 90674 | Yes | Vaccine for influenza for administration into muscle, 0.5 ml dosage, tetravalent, cell-culture based | Inactivated | Cell-cultured | Quadrivalent | ccIIV4 | No |
| 90682 | Yes | Influenza virus vaccine, quadrivalent (RIV4), derived from recombinant DNA, hemagglutinin (HA) protein only, preservative and antibiotic free, for intramuscular use) | Recombinant | | Quadrivalent | RIV4 | No |
| 90685 | No (pediatric) | Vaccine for influenza for administration into muscle, 0.25 ml dosage, quadrivalent, preservative free (pediatric use) | Inactivated | Standard (split virus) | Quadrivalent | IIV4 | No |
| 90686 | Yes | Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent, preservative free | Inactivated | Standard (split virus) | Quadrivalent | IIV4 | No |
| 90687 | No (pediatric) | Vaccine for influenza for administration into muscle, 0.25 ml dosage, quadrivalent (pediatric use) | Inactivated | Standard (split virus) | Quadrivalent | IIV4 | No |
| 90688 | Yes | Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent | Inactivated | Standard (split virus) | Quadrivalent | IIV4 | No |
| 90724 | No (code deleted) | Immunization, active; influenza virus vaccine | General | | -- | -- | Yes |
| 90756 | Yes | Influenza virus vaccine, quadrivalent (ccIIV4), derived from cell cultures, subunit, antibiotic free, 0.5mL dosage, for intramuscular use) | Inactivated | Cell-cultured | Quadrivalent | ccIIV4 | No |
| G0008 | Yes | Administration of influenza virus vaccine | General | | -- | -- | Yes |
| G9141 | No (pandemic) | Influenza a (H1N1) immunization administration (includes the physician counseling the patient/family) | Pandemic | | | | |
| G9142 | No (pandemic) | Influenza a (H1N1) vaccine, any route of administration | Pandemic | | | | |
| Q2033 | No (code deleted) | Influenza vaccine, recombinant hemagglutinin antigens, for intramuscular use (flublok) | Recombinant | | Trivalent | RIV3 | No |
| Q2034 | Yes | Influenza virus vaccine, split virus, for intramuscular use (agriflu) | Inactivated | Standard (split virus) | Trivalent | IIV3 | No |
| Q2035 | Yes | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (afluria) | Inactivated | Standard (split virus) | Trivalent and Quadrivalent | IIV3, IIV4 | Yes |
| Q2036 | Yes | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (flulaval) | Inactivated | Standard (split virus) | Trivalent and Quadrivalent | IIV3, IIV4 | Yes |
| Q2037 | Yes | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (fluvirin) | Inactivated | Standard (split virus) | Trivalent | IIV3 | No |
| Q2038 | Yes | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (fluzone) | Inactivated | Standard (split virus) | Trivalent and Quadrivalent | IIV3, IIV4 | Yes |
| Q2039 | Yes | Influenza virus vaccine, not otherwise specified | General | | -- | -- | Yes |

**Figure 1. Categories for analyses by vaccine type/class**

The primary SCRI analysis will be conducted for all seasonal vaccines combined and for high-dose vaccines.

1. Concomitant Vaccine Codes for SCRI Analyses

Table D-1. Concomitant Vaccine CPT/HCPCS Code List

|  |  |  |  |
| --- | --- | --- | --- |
| **Code Type** | **Code** | **Include In SCRI** | **Description** |
| **Pneumococcal** | |  |  |
| CPT | 90669 | No | Pneumococcal conjugate vaccine, polyvalent, for children under 5 years, for intramuscular use |
| 90670 | Yes | Pneumococcal conjugate vaccine, 13 valent, for intramuscular use |
| 90732 | Yes | Pneumococcal polysaccharide vaccine, 23-valent, adult or immunosuppressed patient dosage, when administered to individuals 2 years or older, for subcutaneous or intramuscular use |
| J6065 | No | Pneumococcal vaccine |
| HCPCS | G0009 | Yes | Administration of pneumococcal vaccine |
| G8864 | No | Pneumococcal vaccine administered or previously received |
| G8867 | No | Pneumococcal vaccine not administered or previously received, reason not otherwise specified |
| G9279 | No | Pneumococcal screening performed and documentation of vaccination received prior to discharge |
| G9280 | No | Pneumococcal vaccination not administered prior to discharge, reason not specified |
| S0195 | No | Pneumococcal conjugate vaccine, polyvalent, intramuscular, for children from five years to nine years of age who have not previously received the vaccine |
| **Hepatitis B** | |  |  |
| CPT | 4149F | No | Hepatitis b vaccine injection administered or previously received (hep-c, hiv) (ibd) |
| 4275F | No | Hepatitis b vaccine injection administered or previously received (hiv)5 |
| 90371 | No | Hepatitis B immune globulin for injection into muscle |
| 90636 | Yes | Vaccine for Hepatitis A and Hepatitis B injection into muscle, adult dosage |
| 90697 | No | Vaccine for diphtheria, tetanus toxoids, acellular pertussis (whooping cough), haemophilus influenza type B, hepatitis B and polio for injection into muscle |
| 90723 | No | Vaccine for diphtheria, tetanus toxoids, acellular pertussis (whooping cough), hepatitis b, and polio for injection into muscle |
| 90731 | No | Immunization, active; hepatitis b vaccine |
| 90739 | Yes | Vaccine for Hepatitis B adult dosage (2 dose schedule) injection into muscle |
| 90740 | Yes | Vaccine for Hepatitis B (3 dose schedule) for injection into muscle, dialysis or immunosuppressed patient |
| 90742 | No | Immunization, passive; specific hyperimmune serum globulin (eg, hepatitis b, measles, pertussis, rabies, rho(d), tetanus, vaccinia, varicella-zoster) |
| 90743 | No | Vaccine for Hepatitis B (2 dose schedule) for injection into muscle, adolescent patient |
| 90744 | No | Vaccine for Hepatitis B (3 dose schedule) for injection into muscle, pediatric and adolescent patients |
| 90745 | No | Hepatitis b vaccine, adolescent/high risk infant dosage, for intramuscular use |
| 90746 | Yes | Vaccine for Hepatitis B adult dosage (3 dose schedule) injection into muscle |
| 90747 | Yes | Vaccine for Hepatitis B (4 dose schedule) for injection into muscle, dialysis or immunosuppressed patient |
| 90748 | No | Vaccine for Hepatitis B and Hemophilus influenza B for injection into muscle |
| J1571 | No | Injection, hepatitis b immune globulin (hepagam b), intramuscular, 0.5 ml |
| J1573 | No | Injection, hepatitis b immune globulin (hepagam b), intravenous, 0.5 ml |
| HCPCS | G0010 | Yes | Administration of hepatitis b vaccine |
| Q3023 | No | Injection, hepatitis b vaccine, immunosuppressed patients (including renal dialysis patients), per dose |
| Q4090 | No | Injection, hepatitis b immune globulin (hepagam b), intramuscular, 0.5 ml |
| **Tetanus Toxoids** | |  |  |
| CPT | 90296 | No | Diphtheria equine antitoxin |
| 90389 | No | Tetanus immune globulin for injection into muscle |
| 90696 | No | Vaccine for diphtheria, tetanus toxoids, acellular pertussis (whooping cough), and polio for injection into muscle, patient 4 through 6 years of age |
| 90697 | No | Diphtheria, tetanus toxoids, acellular pertussis vaccine, inactivated poliovirus vaccine, Haemophilus influenzae type b PRP-OMP conjugate vaccine, and hepatitis B vaccine (DTaP-IPV-Hib-HepB), for intramuscular use |
| 90698 | No | Vaccine for diphtheria, tetanus toxoids, acellular pertussis (whooping cough), haemophilus influenza type B, and polio for injection into muscle |
| 90700 | No | Vaccine for diphtheria, tetanus, and acellular pertussis (whooping cough) injection into muscle, child younger than 7 years |
| 90701 | No | Diphtheria, tetanus toxoids, and whole cell pertussis vaccine (dtp), for intramuscular use |
| 90702 | No | Vaccine for diphtheria and tetanus toxoids injection into muscle, patient younger than 7 years of age |
| 90703 | No | Tetanus toxoid injection into muscle |
| 90711 | No | Immunization, active; diphtheria, tetanus toxoids, and pertussis (dtp) and injectable poliomyelitis vaccine |
| 90714 | Yes | Vaccine for tetanus and diphtheria toxoids injection into muscle, patient 7 years or older |
| 90715 | Yes | Tetanus, diphtheria toxoids and acellular pertussis vaccine (Tdap), when administered to individuals 7 years or older, for intramuscular use |
| 90718 | No | Tetanus and diphtheria toxoids (td) adsorbed when administered to individuals 7 years or older, for intramuscular use |
| 90719 | No | Vaccine for diphtheria toxoid injection into muscle |
| 90720 | No | Vaccine for diphtheria, tetanus toxoids, whole cell pertussis (whooping cough), and Hemophilus influenza B injection into muscle |
| 90721 | No | Vaccine for diphtheria, tetanus toxoids, acellular pertussis (whooping cough), and Hemophilus influenza B injection into muscle |
| 90723 | No | Vaccine for diphtheria, tetanus toxoids, acellular pertussis (whooping cough), Hepatitis B, and polio for injection into muscle |
| J1670 | No | Injection, tetanus immune globulin, human, up to 250 units |
| J3180 | No | Injection, tetanus toxoid, up to 1 ml |
| **Herpes Zoster (Shingles)** | | |  |
| CPT | 90736 | Yes | Zoster (shingles) vaccine (HZV), live, for subcutaneous injection |
| 90750 | Yes | Zoster (shingles) vaccine (hzv), recombinant, sub-unit, adjuvanted, for intramuscular injection |

Table D-2. Concomitant Vaccine NDC Code List

|  |  |  |  |
| --- | --- | --- | --- |
| **Code Type** | **Code** | **Include In SCRI** | **Description** |
| **Tetanus Toxoids** | |  |  |
| NDC | 00006-4133-01 | Yes | Tetanus-diphtheria toxoids (td) inj 2-2 lf/0.5ml |
| 00006-4133-41 | Yes | Tetanus-diphtheria toxoids (td) inj 2-2 lf/0.5ml |
| 00008-0339-03 | Yes | Tetanus toxoid,adsorbed |
| 00008-0340-01 | Yes | Tetanus toxoid,fluid |
| 00026-0634-02 | No | Tetanus immune globulin (human) inj 250 unit/ml |
| 13533-0131-00 | Yes | Tetanus diphtheria toxoids (td) inj 2 2 lf 0.5ml |
| 13533-0131-01 | Yes | Tetanus diphtheria toxoids (td) inj 2 2 lf 0.5ml |
| 13533-0634-02 | No | Tetanus immune globulin (human) inj 250 unit/ml |
| 13533-0634-20 | No | Tetanus immune globulin (human) inj 250 unit/ml |
| 14362-0111-01 | Yes | Tetanus-diphtheria toxoids (td) inj 2-2 lf/0.5ml |
| 14362-0111-03 | Yes | Tetanus-diphtheria toxoids (td) inj 2-2 lf/0.5ml |
| 14362-0111-04 | Yes | Tetanus and diphtheria toxoids adult |
| 17478-0130-10 | Yes | Tetanus-diphtheria toxoids (td) inj 2-2 lf/0.5ml |
| 17478-0131-00 | Yes | Tetanus and diphtheria toxoids adult |
| 17478-0131-01 | Yes | Tetanus-diphtheria toxoids (td) inj 2-2 lf/0.5ml |
| 21695-0413-01 | Yes | Tetanus-diphtheria toxoids (td) inj 2-2 lf/0.5ml |
| 21695-0608-01 | Yes | Tetanus toxoid adsorbed inj 5 lf |
| 21695-0608-05 | Yes | Tetanus toxoid adsorbed inj 5 lf |
| 21695-0609-01 | Yes | Tetanus-diphtheria toxoids (td) inj 5-2 lfu |
| 21695-0609-05 | Yes | Tetanus-diphtheria toxoids (td) inj 5-2 lfu |
| 23490-2010-01 | Yes | Tet tox-diph-acell pertuss ad inj 5-2-15.5 lf-lf-mcg/0.5ml |
| 23490-2011-01 | Yes | Tet tox-diph-acell pertuss ad inj 5-2-15.5 lf-lf-mcg/0.5ml |
| 23490-2033-01 | Yes | Tetanus-diphtheria toxoids (td) inj 5-2 lfu |
| 23490-2033-02 | Yes | Tetanus-diphtheria toxoids (td) inj 5-2 lfu |
| 49281-0215-10 | Yes | Tetanus-diphtheria toxoids (td) inj 5-2 lfu |
| 49281-0215-15 | Yes | Tetanus-diphtheria toxoids (td) inj 5-2 lfu |
| 49281-0215-58 | Yes | Tetanus-diphtheria toxoids (td) inj 5-2 lfu |
| 49281-0215-88 | Yes | Tetanus-diphtheria toxoids (td) inj 5-2 lfu |
| 49281-0225-10 | Yes | Diphtheria-tetanus tox adsorbed (dt) im inj 25-5 unit/0.5ml |
| 49281-0225-58 | Yes | Diphtheria-tetanus tox adsorbed (dt) im inj 25-5 unit/0.5ml |
| 49281-0271-10 | Yes | Tetanus-diphtheria toxoids (td) inj 5-2 lfu |
| 49281-0271-83 | Yes | Tetanus-diphtheria toxoids (td) inj 5-2 lfu |
| 49281-0275-10 | Yes | Diphtheria-tetanus toxoids (dt) inj 6.7-5 lfu/0.5ml |
| 49281-0278-10 | Yes | Diphtheria-tetanus toxoids (dt) inj 6.7-5 lfu/0.5ml |
| 49281-0286-05 | Yes | Diph, acellular pert & tet tox inj 15 lf-10 mcg-5 lf/0.5ml |
| 49281-0286-10 | Yes | Diph, acellular pert & tet tox inj 15 lf-10 mcg-5 lf/0.5ml |
| 49281-0286-58 | Yes | Diph, acellular pert & tet tox inj 15 lf-10 mcg-5 lf/0.5ml |
| 49281-0291-10 | Yes | Tetanus-diphtheria toxoids (td) inj 5-2 lfu |
| 49281-0291-83 | Yes | Tetanus-diphtheria toxoids (td) inj 5-2 lfu |
| 49281-0298-10 | Yes | Diph, acellular pert & tet tox inj 6.7 lf-46.8 mcg-5lf/0.5ml |
| 49281-0400-10 | Yes | Tet tox-diph-acell pertuss ad inj 5-2-15.5 lf-lf-mcg/0.5ml |
| 49281-0400-15 | Yes | Tet tox-diph-acell pertuss ad inj 5-2-15.5 lf-lf-mcg/0.5ml |
| 49281-0400-20 | Yes | Tet tox diph acell pertuss ad inj 5 2 15.5 lf lf mcg 0.5ml |
| 49281-0400-58 | Yes | Tet tox-diph-acell pertuss ad inj 5-2-15.5 lf-lf-mcg/0.5ml |
| 49281-0400-88 | Yes | Tet tox-diph-acell pertuss ad inj 5-2-15.5 lf-lf-mcg/0.5ml |
| 49281-0400-89 | Yes | Tet tox diph acell pertuss ad inj 5 2 15.5 lf lf mcg 0.5ml |
| 49281-0510-05 | No | Diph-ac per-tet tox ad-poliov-haemoph b poly vac for im susp |
| 49281-0560-05 | No | Diph,pertus(acel),tet,polio/pf |
| 49281-0562-10 | No | Diph tetanus tox ad acell pert polio virus ipv vac inj |
| 49281-0562-58 | No | Diph tetanus tox ad acell pert polio virus ipv vac inj |
| 49281-0597-05 | No | Diph, acell pert, tet tox & haemophil b poly vac for inj kit |
| 49281-0800-83 | Yes | Tetanus toxoid adsorbed inj 5 lf |
| 49281-0812-84 | Yes | Tetanus toxoid fluid inj 4 lf |
| 49281-0820-10 | Yes | Tetanus toxoid adsorbed inj 5 lf |
| 50090-1079-00 | No | Tet Tox Diph Acell Pertuss Ad Inj 5 2 15.5 LF LF MCG 0.5ML |
| 50090-1377-00 | No | Tet Tox Diph Acell Pertuss Ad Inj 5 2.5 18.5 LF LF MCG 0.5ML |
| 50090-1377-01 | No | Tet Tox Diph Acell Pertuss Ad Inj 5 2.5 18.5 LF LF MCG 0.5ML |
| 54569-1458-00 | Yes | Tetanus toxoid adsorbed inj 5 lf |
| 54569-1459-00 | Yes | Tetanus toxoid fluid inj 5 lf |
| 54569-1460-00 | Yes | Tetanus-diphtheria toxoids (td) inj 5-2 lfu |
| 54569-3875-00 | Yes | Tetanus diphtheria toxoids (td) inj 5 2 lfu |
| 54569-4398-00 | No | Tetanus immune globulin (human) inj 250 unit/ml |
| 54569-4399-00 | No | Tetanus immune globulin (human) inj 250 unit/ml |
| 54569-4969-00 | Yes | Diph, acellular pert & tet tox inj 25 lf-58 mcg-10 lf/0.5ml |
| 54569-5486-00 | No | Diph-tetanus tox-acell pert-hepatitis b-polio ipv vac inj |
| 54569-5989-00 | Yes | Tet tox-diph-acell pertuss ad inj 5-2-15.5 lf-lf-mcg/0.5ml |
| 54569-6082-00 | Yes | Tetanus-diphtheria toxoids (td) inj 2-2 lf/0.5ml |
| 54569-6386-00 | Yes | Diphth,pertuss(acell),tet vac |
| 54569-6426-00 | Yes | Tetanus toxoid adsorbed inj 5 lf |
| 54569-6440-00 | Yes | Tet tox-diph-acell pertuss ad inj 5-2.5-18.5 lf-lf-mcg/0.5ml |
| 54569-6440-01 | Yes | Tet tox-diph-acell pertuss ad inj 5-2.5-18.5 lf-lf-mcg/0.5ml |
| 54868-0571-06 | Yes | Tetanus-diphtheria toxoids (td) inj 5-2 lfu |
| 54868-3197-00 | Yes | Tetanus toxoid adsorbed inj 10 lf |
| 54868-3394-00 | Yes | Diphtheria, pertussis & tetanus toxoids inj 6.7-4-5 lfu |
| 54868-3394-01 | Yes | Diphtheria, pertussis & tetanus toxoids inj 6.7-4-5 lfu |
| 54868-3490-00 | No | Diph, pertussis, tetanus tox & haemophilus b olig vac inj |
| 54868-3597-00 | Yes | Tetanus toxoid adsorbed inj 5 lf |
| 55045-3550-01 | Yes | Tet tox-diph-acell pertuss ad inj 5-2-15.5 lf-lf-mcg/0.5ml |
| 55045-3945-01 | Yes | Tetanus-diphtheria toxoids (td) inj 2-2 lf/0.5ml |
| 58160-0801-11 | No | Meningococcal (c y) haemophilus b tet tox conj vac for inj |
| 58160-0806-05 | No | Haemophilus b polysaccharide conjugate vac for inj 10 mcg |
| 58160-0809-01 | No | Meningococcal (c y) haemophilus b tet tox conj vac for inj |
| 58160-0809-05 | No | Meningococcal vaccine c y haemophilus b conj tetanus tox pf |
| 58160-0810-01 | Yes | Diph,pertuss(acell),tet ped/pf |
| 58160-0810-11 | Yes | Diph, acellular pert & tet tox inj 25 lf-58 mcg-10 lf/0.5ml |
| 58160-0810-41 | Yes | Diph, acellular pert & tet tox inj 25 lf-58 mcg-10 lf/0.5ml |
| 58160-0810-43 | Yes | Diph, acellular pert & tet tox inj 25 lf-58 mcg-10 lf/0.5ml |
| 58160-0810-46 | Yes | Diph, acellular pert & tet tox inj 25 lf-58 mcg-10 lf/0.5ml |
| 58160-0810-51 | Yes | Diph, acellular pert & tet tox inj 25 lf-58 mcg-10 lf/0.5ml |
| 58160-0810-52 | Yes | Diph, acellular pert & tet tox inj 25 lf-58 mcg-10 lf/0.5ml |
| 58160-0811-11 | No | Diph-tetanus tox-acell pert-hepatitis b-polio ipv vac inj |
| 58160-0811-43 | No | Diph tetanus tox acell pert hepatitis b polio ipv vac inj |
| 58160-0811-46 | No | Diph-tetanus tox-acell pert-hepatitis b-polio ipv vac inj |
| 58160-0811-51 | No | Diph-tetanus tox-acell pert-hepatitis b-polio ipv vac inj |
| 58160-0811-52 | No | Diph-tetanus tox-acell pert-hepatitis b-polio ipv vac inj |
| 58160-0812-01 | No | Diph,pertus(acel),tet,polio/pf |
| 58160-0812-11 | No | Diph-tetanus tox ad-acell pert & polio virus, ipv vac inj |
| 58160-0812-43 | No | Diph,pertus(acel),tet,polio/pf |
| 58160-0812-46 | No | Diph-tetanus tox ad-acell pert & polio virus, ipv vac inj |
| 58160-0812-51 | No | Diph-tetanus tox ad-acell pert & polio virus, ipv vac inj |
| 58160-0812-52 | No | Diph-tetanus tox ad-acell pert & polio virus, ipv vac inj |
| 58160-0840-01 | Yes | Diph,pertuss(acell),tet ped/pf |
| 58160-0840-11 | Yes | Diph, acellular pert & tet tox inj 25 lf-58 mcg-10 lf/0.5ml |
| 58160-0840-46 | Yes | Diph, acellular pert & tet tox inj 25 lf-58 mcg-10 lf/0.5ml |
| 58160-0841-11 | No | Diph-tetanus tox-acell pert-hepatitis b-polio ipv vac inj |
| 58160-0841-46 | No | Diph-tetanus tox-acell pert-hepatitis b-polio ipv vac inj |
| 58160-0842-01 | Yes | Diphth,pertuss(acell),tet vac |
| 58160-0842-05 | Yes | Diphtheria pertussis(acellular) tetanus vaccine |
| 58160-0842-11 | Yes | Tet tox-diph-acell pertuss ad inj 5-2.5-18.5 lf-lf-mcg/0.5ml |
| 58160-0842-32 | Yes | Tet tox-diph-acell pertuss ad inj 5-2.5-18.5 lf-lf-mcg/0.5ml |
| 58160-0842-34 | Yes | Tet tox diph acell pertuss ad inj 5 2.5 18.5 lf lf mcg 0.5ml |
| 58160-0842-43 | Yes | Diphth,pertuss(acell),tet vac |
| 58160-0842-46 | Yes | Tet tox-diph-acell pertuss ad inj 5-2.5-18.5 lf-lf-mcg/0.5ml |
| 58160-0842-51 | Yes | Tet tox-diph-acell pertuss ad inj 5-2.5-18.5 lf-lf-mcg/0.5ml |
| 58160-0842-52 | Yes | Tet tox-diph-acell pertuss ad inj 5-2.5-18.5 lf-lf-mcg/0.5ml |
| 58337-1301-01 | Yes | Tetanus toxoid adsorbed inj 10 lf |
| 58337-1301-02 | Yes | Tetanus toxoid adsorbed inj 10 lf |
| 68258-8939-01 | Yes | Tetanus toxoid adsorbed inj 5 lf |
| 68258-8939-05 | Yes | Tetanus toxoid adsorbed inj 5 lf |
| 68258-8970-05 | Yes | Tet tox-diph-acell pertuss ad inj 5-2-15.5 lf-lf-mcg/0.5ml |
| **Herpes Zoster (Shingles)** | |  |  |
| NDC | 00006-4963-00 | Yes | Zoster vaccine live for inj 19400 unit 0.65ml |
| 00006-4963-01 | Yes | Zoster vaccine live for inj 19400 unit 0.65ml |
| 00006-4963-41 | Yes | Zoster vaccine live for inj 19400 unit 0.65ml |
| 52769-0118-01 | No | Varicella zoster immune glob |
| 52769-0118-02 | No | Varicella zoster immune globulin (human ) inj 125 unit 2.5ml |
| 52769-0118-10 | No | Varicella zoster immune globulin (human ) inj 625 unit 10ml |
| 52769-0574-11 | No | Varicella zoster immune glob |
| 52769-0574-66 | No | Varicella zoster immune globulin (human ) inj 125 unit 2.5ml |
| 53270-0125-01 | No | Varicella zoster immune glob (human) for im inj 125 unit |
| 53270-0125-02 | No | Varicella zoster immune globulin (human ) for inj 125 unit |
| 53270-0126-01 | No | Varicella zoster immune glob (human) im inj 125 unit 1.2ml |
| 53270-0126-02 | No | Varicella zoster immune glob (human) im inj 125 unit 1.2ml |
| 54868-5703-00 | Yes | Zoster vaccine live for inj 19400 unit 0.65ml |
| 58160-0819-12 | Yes | Zoster vaccine recombinant adjuvanted for im inj 50 mcg; SHINGRIX |
| 58160-0823-11 | Yes | Zoster vaccine recombinant adjuvanted for im inj 50 mcg; SHINGRIX |
| 58160-0828-01 | Yes | Varicella zoster virus glycoprotein e rec component 2 of 2; SHINGRIX |
| 58160-0828-03 | Yes | Varicella zoster virus glycoprotein e rec component 2 of 2; SHINGRIX |
| 58160-0829-01 | Yes | Vaccine adjuvant system as01b pf component vial 1 of 2; SHINGRIX |
| 58160-0829-03 | Yes | Vaccine adjuvant system as01b pf component vial 1 of 2; SHINGRIX |
| 68258-8908-00 | Yes | Zoster vaccine live for inj 19400 unit 0.65ml |
| 68258-8908-01 | Yes | Zoster vaccine live for inj 19400 unit 0.65ml |
| 70504-0126-01 | No | Varicella zoster immune glob (human) im inj 125 unit 1.2ml |
| 70504-0126-02 | No | Varicella zoster immune glob (human) im inj 125 unit 1.2ml |

1. SCRI Power

Table E-1. Estimated Power of the SCRI to Detect Odds Ratios Using Vaccinations Serviced Before 10/12/2018 Cutoff\*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Population** | **Risk Window** | **GBS Cases** | **Odds Ratio to Detect** | **Power** |
| High Dose | 8 - 21 | 27 | 1.5 | 16% |
| High Dose | 8 - 21 | 27 | 2 | 39% |
| High Dose | 8 - 21 | 27 | 3 | 78% |
| High Dose | 8 - 21 | 27 | 4 | 94% |
| High Dose | 8 - 21 | 27 | 5 | 98% |
| High Dose | 8 - 21 | 27 | 6 | 100% |
| High Dose | 8 - 21 | 27 | 7 | 100% |
| High Dose | 8 - 21 | 27 | 8 | 100% |
| High Dose | 8 - 21 | 27 | 9 | 100% |
| High Dose | 8 - 21 | 27 | 10 | 100% |
| Seasonal | 8 - 21 | 35 | 1.5 | 25% |
| Seasonal | 8 - 21 | 35 | 2 | 56% |
| Seasonal | 8 - 21 | 35 | 3 | 92% |
| Seasonal | 8 - 21 | 35 | 4 | 99% |
| Seasonal | 8 - 21 | 35 | 5 | 100% |
| Seasonal | 8 - 21 | 35 | 6 | 100% |
| Seasonal | 8 - 21 | 35 | 7 | 100% |
| Seasonal | 8 - 21 | 35 | 8 | 100% |
| Seasonal | 8 - 21 | 35 | 9 | 100% |
| Seasonal | 8 - 21 | 35 | 10 | 100% |
| High Dose | 1 - 42 | 39 | 1.5 | 24% |
| High Dose | 1 - 42 | 39 | 2 | 57% |
| High Dose | 1 - 42 | 39 | 3 | 92% |
| High Dose | 1 - 42 | 39 | 4 | 99% |
| High Dose | 1 - 42 | 39 | 5 | 100% |
| High Dose | 1 - 42 | 39 | 6 | 100% |
| High Dose | 1 - 42 | 39 | 7 | 100% |
| High Dose | 1 - 42 | 39 | 8 | 100% |
| High Dose | 1 - 42 | 39 | 9 | 100% |
| High Dose | 1 - 42 | 39 | 10 | 100% |
| Seasonal | 1 - 42 | 56 | 1.5 | 31% |
| Seasonal | 1 - 42 | 56 | 2 | 70% |
| Seasonal | 1 - 42 | 56 | 3 | 98% |
| Seasonal | 1 - 42 | 56 | 4 | 100% |
| Seasonal | 1 - 42 | 56 | 5 | 100% |
| Seasonal | 1 - 42 | 56 | 6 | 100% |
| Seasonal | 1 - 42 | 56 | 7 | 100% |
| Seasonal | 1 - 42 | 56 | 8 | 100% |
| Seasonal | 1 - 42 | 56 | 9 | 100% |
| Seasonal | 1 - 42 | 56 | 10 | 100% |

*\* Two-sided test where alpha = 0.05, # of simulations = 10,000*

1. Medical Record Review

During the influenza season any GBS cases identified through Medicare claims may be sent through the medical record review process (“abstraction”). This abstraction process entails detailed review of the medical charts for all beneficiaries who were diagnosed with GBS to determine whether they truly have GBS. Once the count of true GBS cases and non-cases are returned, a chart-confirmed end-of-season SCRI analysis is completed using only the true GBS cases.

When conducted, the complete abstraction process entails (i) developing an abstraction tool that isolates the information from medical records needed to confirm a GBS diagnosis, (ii) testing the abstraction tool to ensure that it functions as intended, (iii) developing a user guide for abstractors, (iv) requesting records for claims-identified GBS cases, (v) abstracting records using the tool, (vi) calculating Brighton Scores using abstraction results, and (vii) resolving Brighton Score discrepancies. Steps (i), (ii), and (iii) have already been completed and do not need to be repeated for future iterations of abstraction. Moving forward, if the abstraction process is completed, there are four main steps:

1. **Requesting records**: After identifying the cases of interest (i.e., the beneficiaries with a GBS diagnosis claim), that list of beneficiaries is sent to a contractor, which then asks the associated medical facilities to share records corresponding to the hospitalization for GBS for each of the identified beneficiaries. It is noted if facilities do not respond to the contractor’s record request.
2. **Abstracting records**: Upon receiving records, trained abstractors use the abstraction tool to complete a detailed review of the medical charts to determine whether the necessary clinical and diagnostic criteria required for a GBS diagnoses are met. Abstractors use the following Abstraction Manual:
3. **Calculating Brighton Scores**:The Brighton Collaboration's case definitions for GBS and Fisher Syndrome are used;[4](#_ENREF_4) classification criteria are detailed in Appendix G, Table 5. Each returned record is categorized as either Brighton level 1, 2, or 3, not a case, or as having insufficient evidence to determine a definitive GBS of Fisher Syndrome case. Brighton level 1 cases meet all necessary clinical criteria and further have both cerebrospinal fluid (CSF) and electrophysiological test findings consistent with GBS; level 2 cases meet all necessary clinical criteria and have evidence of GBS from only one of these tests; level 3 cases only meet the clinical criteria. Records classified as Brighton Level 1, 2, or 3 are deemed as “chart-confirmed” GBS cases, while "insufficient evidence" and "not a case" records are labeled as non-cases. We use a tool housed by The Brighton Collaboration to calculate Brighton Score.
4. **Resolving Discrepancies:** If there are multiple abstractors reviewing each record, and their conclusions differ (e.g., one abstractor indicates a medical record does show the presence of a condition and the other abstractor disagrees), then one additional person reviews the record to decide which abstractor is correct.
5. Clinical Case Definitions for GBS and Fisher Syndrome

Table G-1. Clinical case detailing the definitions used to classify medically reviewed cases of claims-identified GBS cases among the U.S. Medicare Population.[4](#_ENREF_4)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Syndrome** | **Diagnostic  Criterion** | **Brighton Level 1 Diagnostic Certainty** | **Brighton Level 2 Diagnostic Certainty** | **Brighton Level 3 Diagnostic Certainty** |
| Guillain-Barré Syndrome |  |  |  |  |
|  | Flaccidity | Bilateral and flaccid paresis of the limbs | Bilateral and flaccid paresis of the limbs | Bilateral and flaccid paresis of the limbs |
|  | Reflexes | Decreased or absent deep tendon reflexes in affected limbs | Decreased or absent deep tendon reflexes in affected limbs | Decreased or absent deep tendon reflexes in affected limbs |
|  | Monophasic illness | Monophasic illness pattern and interval between onset and nadir of weakness between 12 hours and 28 days and subsequent clinical plateau | Monophasic illness pattern and interval between onset and nadir of weakness between 12 hours and 28 days and subsequent clinical plateau | Monophasic illness pattern and interval between onset and nadir of weakness between 12 hours and 28 days and subsequent clinical plateau |
|  | Diagnostic studies | Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above the laboratory normal value and CSF total white blood cell count <50 cells/mm3) | CSF total white blood cell count <50 cells/mm3 (with or without CSF protein level above the laboratory normal value) or if CSF not collected or results not available, electrophysiological studies consistent with GBS |  |
|  |  | Electrophysiological findings consistent with GBS |  |  |
|  | Alternative  diagnoses | Absence of an identified alternative diagnosis for weakness | Absence of identified alternative diagnosis for weakness | Absence of identified alternative diagnosis for weakness |
| Fisher  Syndrome |  |  |  |  |
|  | Ophthalmoparesis, hyporeflexia, and ataxia | Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes and ataxia | Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes and ataxia | Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes and ataxia |
|  | Limb weakness | Absence of limb weakness | Absence of limb weakness | Absence of limb weakness |
|  | Monophasic illness | Monophasic illness pattern and interval between onset and nadir of weakness between 12 hours and 28 days and subsequent clinical plateau | Monophasic illness pattern and interval between onset and nadir of weakness between 12 hours and 28 days and subsequent clinical plateau | Monophasic illness pattern and interval between onset and nadir of weakness between 12 hours and 28 days and subsequent clinical plateau |
|  | Diagnostic studies | Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above the laboratory normal and total CSF white blood cell count <50 cells/mm3) | CSF total white blood cell count <50 cells/mm3 (with or without CSF protein level above the laboratory normal value) or nerve conduction studies are normal or indicate involvement of sensory nerves only |  |
|  |  | Nerve conduction studies are normal or indicate involvement of sensory nerves only |  |  |
|  | Altered consciousness or corticospinal tract signs | No alterations in consciousness or corticospinal tract signs | No alterations in consciousness or corticospinal tract signs | No alterations in consciousness or corticospinal tract signs |
|  | Alternative diagnoses | Absence of identified alternative diagnosis | Absence of identified alternative diagnosis | Absence of identified alternative diagnosis |

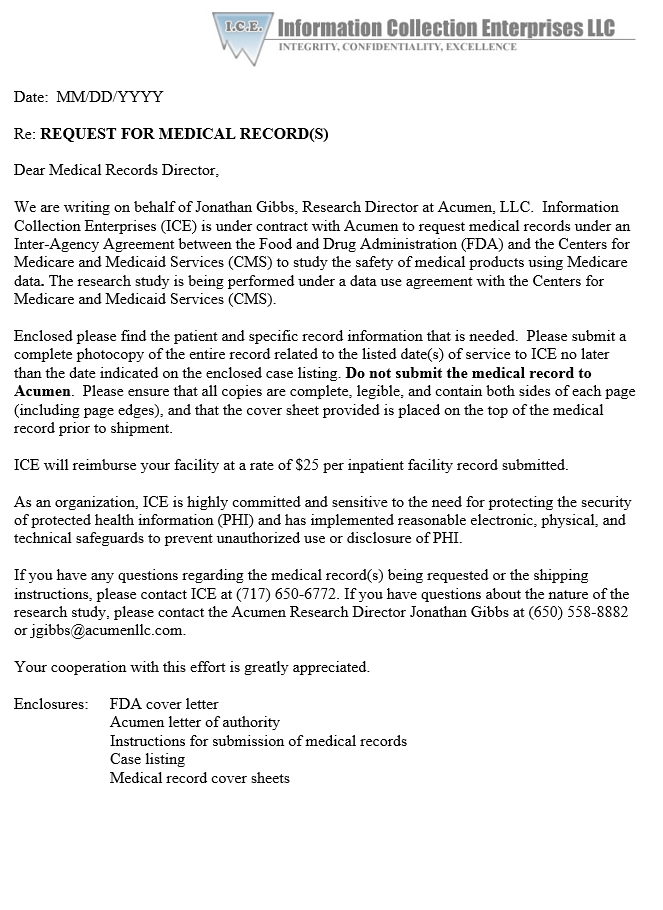
1. GBS Abstraction Manual

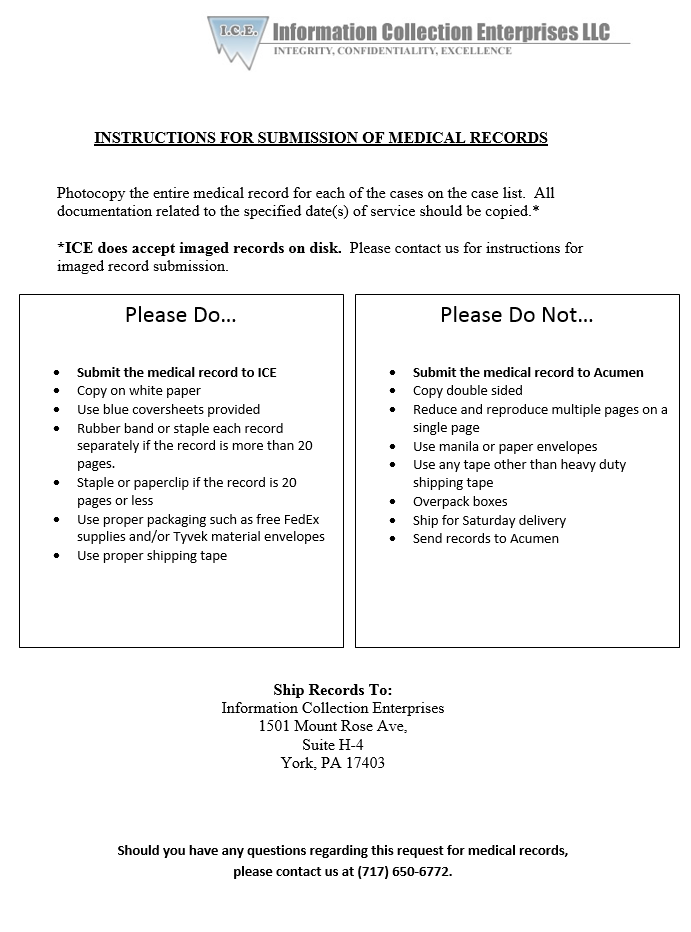
Abstraction manual removed for submission to *Journal of Infectious Diseases*.

1. Abstraction Tool

Abstraction tool screenshots removedfor submission to *Journal of Infectious Diseases*.

1. Medical Record Request Letter





# Table S-3. Count of vaccinations and cumulative claims maturity observable by week 31 in the 2018–2019 influenza season, high-dose influenza vaccine, Medicare Fee-for-Service Population

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **2018-19 Surveillance** | | **Real-Time Surveillance Vaccines Serviced (2018-2019 Season)** | | | **Claims Maturity by Cutoff** |
| **Week** | **Cutoff Date** | **# Cumulative** | **# Per Week** | **Cum. %** |
| 1 | 8/17/2018 | 57,991 | 57,991 | 0.7% | 99.3% |
| 2 | 8/24/2018 | 165,736 | 107,745 | 1.9% | 99.2% |
| 3 | 8/31/2018 | 369,097 | 203,361 | 4.2% | 99.2% |
| 4 | 9/7/2018 | 705,503 | 336,406 | 8.0% | 99.0% |
| 5 | 9/14/2018 | 1,267,531 | 562,028 | 14.4% | 98.9% |
| 6 | 9/21/2018 | 1,987,041 | 719,510 | 22.6% | 98.7% |
| 7 | 9/28/2018 | 2,845,638 | 858,597 | 32.3% | 98.5% |
| 8 | 10/5/2018 | 3,904,793 | 1,059,155 | 44.4% | 98.3% |
| 9 | 10/12/2018 | 4,852,582 | 947,789 | 55.1% | 98.0% |
| 10 | 10/19/2018 | 5,699,928 | 847,346 | 64.7% | 97.7% |
| 11 | 10/26/2018 | 6,408,081 | 708,153 | 72.8% | 97.3% |
| 12 | 11/2/2018 | 6,947,824 | 539,743 | 78.9% | 96.9% |
| 13 | 11/9/2018 | 7,371,829 | 424,005 | 83.7% | 96.4% |
| 14 | 11/16/2018 | 7,698,656 | 326,827 | 87.4% | 95.7% |
| 15 | 11/23/2018 | 7,848,280 | 149,624 | 89.1% | 95.3% |
| 16 | 11/30/2018 | 8,038,652 | 190,372 | 91.3% | 94.4% |
| 17 | 12/7/2018 | 8,197,097 | 158,445 | 93.1% | 93.4% |
| 18 | 12/14/2018 | 8,318,010 | 120,913 | 94.5% | 92.4% |
| 19 | 12/21/2018 | 8,396,987 | 78,977 | 95.4% | 91.7% |
| 20 | 12/28/2018 | 8,434,151 | 37,164 | 95.8% | 91.2% |
| 21 | 1/4/2019 | 8,475,023 | 40,872 | 96.3% | 90.8% |
| 22 | 1/11/2019 | 8,547,974 | 72,951 | 97.1% | 89.9% |
| 23 | 1/18/2019 | 8,612,830 | 64,856 | 97.8% | 89.1% |
| 24 | 1/25/2019 | 8,670,294 | 57,464 | 98.5% | 88.4% |
| 25 | 2/1/2019 | 8,730,140 | 59,846 | 99.2% | 87.7% |
| 26 | 2/8/2019 | 8,763,287 | 33,147 | 99.5% | 87.3% |
| 27 | 2/15/2019 | 8,786,603 | 23,316 | 99.8% | 87.0% |
| 28 | 2/22/2019 | 8,797,409 | 10,806 | 99.9% | 86.9% |
| 29 | 3/1/2019 | 8,802,824 | 5,415 | 100.0% | 86.8% |
| 30 | 3/8/2019 | 8,804,210 | 1,386 | 100.0% | 86.8% |
| 31 | 3/15/2019 | 8,804,229 | 19 | 100.0% | 86.8% |

# Table S-4. Number of vaccinations meeting surveillance population eligibility criteria at various steps in the Medicare Fee-for-Service population cohort development process

|  |  |  |
| --- | --- | --- |
|  | **Early-Season** | **End-of-Season** |
| **Vaccine recipients** | **17,214,390** | **17,606,043** |
| Vaccination between August 11, 2018 to November 9, 2018 (early-season analysis) or June 29, 2019 (end-of-season analysis) | 14,560,821 | 17,606,043 |
| Age ≥65 years at time of vaccination | 13,197,043 | 15,796,783 |
| First vaccination for beneficiary in study period | 13,148,308 | 15,682,935 |
| Enrolled in FFS from 183 days prior to vaccination through 84 days after vaccination, unless death occurs between vaccination and 84 days post-vaccination | 12,159,346 | 14,437,945 |
| **Eligible seasonal vaccines** | **12,159,346** | **14,437,945** |
| **Eligible high-dose Vaccines** | **7,453,690** | **8,667,640** |

# Table S-5. Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT) codes from outpatient claims to identify influenza vaccinations in the 2018–2019 influenza season, Medicare Fee-for-Service self-controlled risk interval analyses

|  |  |  |
| --- | --- | --- |
| **HCPCS/CPT code** | **HCPCS/CPT code description** | **Classification** |
|
| 90653 | Vaccine for influenza for injection into muscle, inactivated, subunit, adjuvanted | Adjuvanted (aIIV3) |
| 90656 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent, preservative free | Standard (split virus) (IIV3) |
| 90658 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, trivalent | Standard (split virus) (IIV3) |
| 90662 | Vaccine for influenza for injection into muscle, split virus, enhanced immunogenicity via increased antigen content | High-dose (IIV3-HD) |
| 90674 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, tetravalent, cell-culture based | Cell-cultured (ccIIV4) |
| 90682 | Influenza virus vaccine, quadrivalent (RIV4), derived from recombinant DNA, hemagglutinin (HA) protein only, preservative and antibiotic free, for intramuscular use) | Recombinant (RIV4) |
| 90686 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent, preservative free | Standard (split virus) (IIV4) |
| 90688 | Vaccine for influenza for administration into muscle, 0.5 ml dosage, quadrivalent | Standard (split virus) (IIV4) |
| 90756 | Influenza virus vaccine, quadrivalent (ccIIV4), derived from cell cultures, subunit, antibiotic free, 0.5mL dosage, for intramuscular use) | Cell-cultured (ccIIV4) |
| G0008 | Administration of influenza virus Vaccine | General |
| Q2034 | Influenza virus vaccine, split virus, for intramuscular use (Agriflu) | Standard (split virus) (IIV3) |
| Q2035 | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Afluria) | Standard (split virus) (IIV3, IIV4) |
| Q2036 | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Flulaval) | Standard (split virus) (IIV3, IIV4) |
| Q2037 | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Fluvirin) | Standard (split virus) (IIV3) |
| Q2038 | Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Fluzone) | Standard (split virus) (IIV3, IIV4) |
| Q2039 | Influenza virus vaccine, not otherwise specified | General |

# Table S-6. Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT) codes from outpatient claims to identify concomitantly administered vaccines in the 2018–2019 influenza season, Medicare Fee-for-Service self-controlled risk interval analyses

|  |  |  |
| --- | --- | --- |
| ***Code Type*** | ***Code*** | ***Description*** |
| **Pneumococcal vaccines** | |  |
| CPT | 90670 | Pneumococcal conjugate vaccine, 13 valent, for intramuscular use |
| 90732 | Pneumococcal polysaccharide vaccine, 23-valent, adult or immunosuppressed patient dosage, when administered to individuals 2 years or older, for subcutaneous or intramuscular use |
| HCPCS | G0009 | Administration of pneumococcal vaccine |
| **Hepatitis B vaccines** | |  |
| CPT | 90636 | Vaccine for Hepatitis A and Hepatitis B injection into muscle, adult dosage |
| 90739 | Vaccine for Hepatitis B adult dosage (2 dose schedule) injection into muscle |
| 90740 | Vaccine for Hepatitis B (3 dose schedule) for injection into muscle, dialysis or immunosuppressed patient |
| 90746 | Vaccine for Hepatitis B adult dosage (3 dose schedule) injection into muscle |
| 90747 | Vaccine for Hepatitis B (4 dose schedule) for injection into muscle, dialysis or immunosuppressed patient |
| HCPCS | G0010 | Administration of hepatitis b vaccine |
| **Tetanus toxoids-containing vaccines** | | |
| CPT | 90714 | Vaccine for tetanus and diphtheria toxoids injection into muscle, patient 7 years or older |
| 90715 | Tetanus, diphtheria toxoids and acellular pertussis vaccine (Tdap), when administered to individuals 7 years or older, for intramuscular use |
| **Herpes Zoster vaccines** | | |
| CPT | 90736 | Vaccine for shingles injection beneath skin |
| 90750 | Zoster (shingles) vaccine (HZV), recombinant, sub-unit, adjuvanted, for intramuscular injection |

# Table S-7. National Drug Codes (NDC) to identify concomitantly administered vaccines in the 2018–2019 influenza season, Medicare Fee-for-Service self-controlled risk interval analyses

|  |  |
| --- | --- |
| **Code** | **Description** |
| 00006-4133-01 | Tetanus-diphtheria toxoids (td) injection 2-2 lf/0.5ml |
| 00006-4133-41 | Tetanus-diphtheria toxoids (td) injection 2-2 lf/0.5ml |
| 00008-0339-03 | Tetanus toxoid, adsorbed |
| 00008-0340-01 | Tetanus toxoid, fluid |
| 13533-0131-00 | Tetanus diphtheria toxoids (td) injection 2 2 lf 0.5ml |
| 13533-0131-01 | Tetanus diphtheria toxoids (td) injection 2 2 lf 0.5ml |
| 14362-0111-01 | Tetanus-diphtheria toxoids (td) injection 2-2 lf/0.5ml |
| 14362-0111-03 | Tetanus-diphtheria toxoids (td) injection 2-2 lf/0.5ml |
| 14362-0111-04 | Tetanus and diphtheria toxoids adsorbed |
| 17478-0130-10 | Tetanus-diphtheria toxoids (td) injection 2-2 lf/0.5ml |
| 17478-0131-00 | Tetanus and diphtheria toxoids adsorbed |
| 17478-0131-01 | Tetanus-diphtheria toxoids (td) injection 2-2 lf/0.5ml |
| 21695-0413-01 | Tetanus-diphtheria toxoids (td) injection 2-2 lf/0.5ml |
| 21695-0608-01 | Tetanus toxoid adsorbed injection 5 lf |
| 21695-0608-05 | Tetanus toxoid adsorbed injection 5 lf |
| 21695-0609-01 | Tetanus-diphtheria toxoids (td) injection 5-2 lfu |
| 21695-0609-05 | Tetanus-diphtheria toxoids (td) injection 5-2 lfu |
| 23490-2010-01 | Tet toxoid-Diphtheria-acellular pertuss adsorbed injection 5-2-15.5 lf-lf-mcg/0.5ml |
| 23490-2011-01 | Tet toxoid-Diphtheria-acellular pertuss adsorbed injection 5-2-15.5 lf-lf-mcg/0.5ml |
| 23490-2033-01 | Tetanus-diphtheria toxoids (td) injection 5-2 lfu |
| 23490-2033-02 | Tetanus-diphtheria toxoids (td) injection 5-2 lfu |
| 49281-0215-10 | Tetanus-diphtheria toxoids (td) injection 5-2 lfu |
| 49281-0215-15 | Tetanus-diphtheria toxoids (td) injection 5-2 lfu |
| 49281-0215-58 | Tetanus-diphtheria toxoids (td) injection 5-2 lfu |
| 49281-0215-88 | Tetanus-diphtheria toxoids (td) injection 5-2 lfu |
| 49281-0225-10 | Diphtheria-tetanus toxoid adsorbed (dt) im injection 25-5 unit/0.5ml |
| 49281-0225-58 | Diphtheria-tetanus toxoid adsorbed (dt) im injection 25-5 unit/0.5ml |
| 49281-0271-10 | Tetanus-diphtheria toxoids (td) injection 5-2 lfu |
| 49281-0271-83 | Tetanus-diphtheria toxoids (td) injection 5-2 lfu |
| 49281-0275-10 | Diphtheria-tetanus toxoids (dt) injection 6.7-5 lfu/0.5ml |
| 49281-0278-10 | Diphtheria-tetanus toxoids (dt) injection 6.7-5 lfu/0.5ml |
| 49281-0286-05 | Diphtheria, acellular pertussis & tetanus toxoids injection 15 lf-10 mcg-5 lf/0.5ml |
| 49281-0286-10 | Diphtheria, acellular pertussis & tetanus toxoids injection 15 lf-10 mcg-5 lf/0.5ml |
| 49281-0286-58 | Diphtheria, acellular pertussis & tetanus toxoids injection 15 lf-10 mcg-5 lf/0.5ml |
| 49281-0291-10 | Tetanus-diphtheria toxoids (td) injection 5-2 lfu |
| 49281-0291-83 | Tetanus-diphtheria toxoids (td) injection 5-2 lfu |
| 49281-0298-10 | Diphtheria, acellular pertussis & tetanus toxoids injection 6.7 lf-46.8 mcg-5lf/0.5ml |
| 49281-0400-10 | Tetanus toxoids-diphtheria-acellular pertussis adsorbed injection 5-2-15.5 lf-lf-mcg/0.5ml |
| 49281-0400-15 | Tetanus toxoids-diphtheria-acellular pertussis adsorbed injection 5-2-15.5 lf-lf-mcg/0.5ml |
| 49281-0400-20 | Tetanus toxoids-diphtheria-acellular pertussis adsorbed injection 5 2 15.5 lf mcg 0.5ml |
| 49281-0400-58 | Tetanus toxoids-diphtheria-acellular pertussis adsorbed injection 5-2-15.5 lf-lf-mcg/0.5ml |
| 49281-0400-88 | Tetanus toxoids-diphtheria-acellular pertussis adsorbed injection 5-2-15.5 lf-lf-mcg/0.5ml |
| 49281-0400-89 | Tetanus toxoids-diphtheria-acellular pertussis adsorbed injection 5 2 15.5 lf mcg 0.5ml |
| 49281-0800-83 | Tetanus toxoid adsorbed injection 5 lf |
| 49281-0812-84 | Tetanus toxoid fluid injection 4 lf |
| 49281-0820-10 | Tetanus toxoid adsorbed injection 5 lf |
| 54569-1458-00 | Tetanus toxoid adsorbed injection 5 lf |
| 54569-1459-00 | Tetanus toxoid fluid injection 5 lf |
| 54569-1460-00 | Tetanus-diphtheria toxoids (td) injection 5-2 lfu |
| 54569-3875-00 | Tetanus diphtheria toxoids (td) injection 5 2 lfu |
| 54569-4969-00 | Diphtheria, acellular pertussis & tetanus toxoids injection 25 lf-58 mcg-10 lf/0.5ml |
| 54569-5989-00 | Tetanus toxoids-diphtheria-acellular pertussis adsorbed injection 5-2-15.5 lf-lf-mcg/0.5ml |
| 54569-6082-00 | Tetanus-diphtheria toxoids (td) injection 2-2 lf/0.5ml |
| 54569-6386-00 | Diphtheria, pertussis (acellular), tetanus vaccine |
| 54569-6426-00 | Tetanus toxoid adsorbed injection 5 lf |
| 54569-6440-00 | Tetanus toxoids-diphtheria-acellular pertussis adsorbed injection 5-2.5-18.5 lf-lf-mcg/0.5ml |
| 54569-6440-01 | Tetanus toxoids-diphtheria-acellular pertussis adsorbed injection 5-2.5-18.5 lf-lf-mcg/0.5ml |
| 54868-0571-06 | Tetanus-diphtheria toxoids (td) injection 5-2 lfu |
| 54868-3197-00 | Tetanus toxoid adsorbed injection 10 lf |
| 54868-3394-00 | Diphtheria, pertussis & tetanus toxoids injection 6.7-4-5 lfu |
| 54868-3394-01 | Diphtheria, pertussis & tetanus toxoids injection 6.7-4-5 lfu |
| 54868-3597-00 | Tetanus toxoid adsorbed injection 5 lf |
| 55045-3550-01 | Tetanus toxoids-diphtheria-acellular pertussis adsorbed injection 5-2-15.5 lf-lf-mcg/0.5ml |
| 55045-3945-01 | Tetanus-diphtheria toxoids (td) injection 2-2 lf/0.5ml |
| 58160-0810-01 | Diphtheria, pertussis (acellular), tetanus ped/pf |
| 58160-0810-11 | Diphtheria, acellular pertussis & tetanus toxoids injection 25 lf-58 mcg-10 lf/0.5ml |
| 58160-0810-41 | Diphtheria, acellular pertussis & tetanus toxoids injection 25 lf-58 mcg-10 lf/0.5ml |
| 58160-0810-43 | Diphtheria, acellular pertussis & tetanus toxoids injection 25 lf-58 mcg-10 lf/0.5ml |
| 58160-0810-46 | Diphtheria, acellular pertussis & tetanus toxoids injection 25 lf-58 mcg-10 lf/0.5ml |
| 58160-0810-51 | Diphtheria, acellular pertussis & tetanus toxoids injection 25 lf-58 mcg-10 lf/0.5ml |
| 58160-0810-52 | Diphtheria, acellular pertussis & tetanus toxoids injection 25 lf-58 mcg-10 lf/0.5ml |
| 58160-0840-01 | Diphtheria, pertussis (acellular), Tetanus ped/pf |
| 58160-0840-11 | Diphtheria, acellular pertussis & tetanus toxoid injection 25 lf-58 mcg-10 lf/0.5ml |
| 58160-0840-46 | Diphtheria, acellular pertussis & tetanus toxoid injection 25 lf-58 mcg-10 lf/0.5ml |
| 58160-0842-01 | Diphtheria, pertussis (acellular), tetanus vaccine |
| 58160-0842-05 | Diphtheria pertussis (acellular) tetanus vaccine |
| 58160-0842-11 | Tetanus toxoid-Diphtheria-acellular pertussis adsorbed injection 5-2.5-18.5 lf-lf-mcg/0.5ml |
| 58160-0842-32 | Tetanus toxoid-Diphtheria-acellular pertussis adsorbed injection 5-2.5-18.5 lf-lf-mcg/0.5ml |
| 58160-0842-34 | Tetanus toxoid Diphtheria acellular pertussis adsorbed injection 5 2.5 18.5 lf lf-mcg/ 0.5ml |
| 58160-0842-43 | Diphtheria, pertussis (acellular), tet vaccine |
| 58160-0842-46 | Tetanus toxoid-Diphtheria-acellular pertussis adsorbed injection 5-2.5-18.5 lf-lf-mcg/0.5ml |
| 58160-0842-51 | Tetanus toxoid-Diphtheria-acellular pertussis adsorbed injection 5-2.5-18.5 lf-lf-mcg/0.5ml |
| 58160-0842-52 | Tetanus toxoid-Diphtheria-acellular pertussis adsorbed injection 5-2.5-18.5 lf-lf-mcg/0.5ml |
| 58337-1301-01 | Tetanus toxoid adsorbed injection 10 lf |
| 58337-1301-02 | Tetanus toxoid adsorbed injection 10 lf |
| 68258-8939-01 | Tetanus toxoid adsorbed injection 5 lf |
| 68258-8939-05 | Tetanus toxoid adsorbed injection 5 lf |
| 68258-8970-05 | Tetanus toxoid-Diphtheria-acellular pertussis adsorbed injection 5-2-15.5 lf-lf-mcg/0.5ml |
| 00006-4963-00 | Zoster vaccine live for injection 19400 unit 0.65ml |
| 00006-4963-01 | Zoster vaccine live for injection 19400 unit 0.65ml |
| 00006-4963-41 | Zoster vaccine live for injection 19400 unit 0.65ml |
| 54868-5703-00 | Zoster vaccine live for injection 19400 unit 0.65ml |
| 58160-0819-12 | Zoster vaccine recombinant adjuvanted for intramuscular injection 50 mcg; SHINGRIX |
| 58160-0823-11 | Zoster vaccine recombinant adjuvanted for intramuscular injection 50 mcg; SHINGRIX |
| 58160-0828-01 | Varicella zoster virus glycoprotein e rec component 2 of 2 |
| 58160-0828-03 | Varicella zoster virus glycoprotein e rec component 2 of 2 |
| 58160-0829-01 | Vaccine adjuvant system as01b pf component vial 1 of 2; SHINGRIX |
| 58160-0829-03 | Vaccine adjuvant system as01b pf component vial 1 of 2; SHINGRIX |
| 68258-8908-00 | Zoster vaccine live for injection 19400 unit 0.65ml |
| 68258-8908-01 | Zoster vaccine live for injection 19400 unit 0.65ml |

# Table S-8. Power calculations, Medicare Fee-for-Service population self-controlled risk interval analyses

## Table S-8.1. Estimated power of the SCRI to detect odds ratios using vaccinations serviced before 10/12/2018 cutoff for number of GBS cases in the 8–21-day risk window and 43–84-day control window, alpha = 0.05 (1,000 simulations)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Population** | **Risk Window** | **GBS Cases** | **Odds Ratio to Detect** | **Power** |
| IIV3-HD | 8 - 21 | 27 | 1.5 | 16% |
| IIV3-HD | 8 - 21 | 27 | 2 | 39% |
| IIV3-HD | 8 - 21 | 27 | 3 | 78% |
| IIV3-HD | 8 - 21 | 27 | 4 | 94% |
| IIV3-HD | 8 - 21 | 27 | 5 | 98% |
| IIV3-HD | 8 - 21 | 27 | 6 | 100% |
| IIV3-HD | 8 - 21 | 27 | 7 | 100% |
| IIV3-HD | 8 - 21 | 27 | 8 | 100% |
| IIV3-HD | 8 - 21 | 27 | 9 | 100% |
| IIV3-HD | 8 - 21 | 27 | 10 | 100% |
| Seasonal | 8 - 21 | 35 | 1.5 | 25% |
| Seasonal | 8 - 21 | 35 | 2 | 56% |
| Seasonal | 8 - 21 | 35 | 3 | 92% |
| Seasonal | 8 - 21 | 35 | 4 | 99% |
| Seasonal | 8 - 21 | 35 | 5 | 100% |
| Seasonal | 8 - 21 | 35 | 6 | 100% |
| Seasonal | 8 - 21 | 35 | 7 | 100% |
| Seasonal | 8 - 21 | 35 | 8 | 100% |
| Seasonal | 8 - 21 | 35 | 9 | 100% |
| Seasonal | 8 - 21 | 35 | 10 | 100% |

## Table S-8.2. Estimated power of the SCRI to detect odds ratios using vaccinations serviced before 10/12/2018 cutoff for number of GBS cases in the 1–42-day risk window and 43–84-day control window, alpha = 0.05 (1,000 simulations)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Population** | **Risk Window** | **GBS Cases** | **Odds Ratio to Detect** | **Power** |
| IIV3-HD | 1 - 42 | 39 | 1.5 | 24% |
| IIV3-HD | 1 - 42 | 39 | 2 | 57% |
| IIV3-HD | 1 - 42 | 39 | 3 | 92% |
| IIV3-HD | 1 - 42 | 39 | 4 | 99% |
| IIV3-HD | 1 - 42 | 39 | 5 | 100% |
| IIV3-HD | 1 - 42 | 39 | 6 | 100% |
| IIV3-HD | 1 - 42 | 39 | 7 | 100% |
| IIV3-HD | 1 - 42 | 39 | 8 | 100% |
| IIV3-HD | 1 - 42 | 39 | 9 | 100% |
| IIV3-HD | 1 - 42 | 39 | 10 | 100% |
| Seasonal | 1 - 42 | 56 | 1.5 | 31% |
| Seasonal | 1 - 42 | 56 | 2 | 70% |
| Seasonal | 1 - 42 | 56 | 3 | 98% |
| Seasonal | 1 - 42 | 56 | 4 | 100% |
| Seasonal | 1 - 42 | 56 | 5 | 100% |
| Seasonal | 1 - 42 | 56 | 6 | 100% |
| Seasonal | 1 - 42 | 56 | 7 | 100% |
| Seasonal | 1 - 42 | 56 | 8 | 100% |
| Seasonal | 1 - 42 | 56 | 9 | 100% |
| Seasonal | 1 - 42 | 56 | 10 | 100% |

# Table S-9. Demographic characteristics of the Medicare Fee-for-Service, influenza-vaccinated populations ages ≥65 years from August 11, 2018 to June 29, 2019

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **All influenza-vaccinated beneficiaries¥** | | **Vaccine type** | | | | | | | | | | | | | |
| **High-dose**  **(IIV3-HD)** | | **Standard-dose** | | | | | | **Adjuvanted**  **(aIIV3)** | | **Cell-cultured (ccIIV4)** | | **Recombinant**  **(RIV4)** | |
| **Trivalent (IIV3)** | | **Quadrivalent (IIV4)** | | **IIV3/IIV4\*** | |
| **#** | **%** | **#** | **%** | **#** | **%** | **#** | **%** | **#** | **%** | **#** | **%** | **#** | **%** | **#** | **%** |
| **Influenza-vaccinated beneficiaries** | 14,437,945 | 100% | 8,667,640 | 100% | 180,839 | 100% | 1,722,673 | 100% | 2,166,339 | 100% | 2,272,036 | 100% | 906,297 | 100% | 281,475 | 100% |
| **Age (years)** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mean (SD) | 75.8 (7.6) | - | 75.7 (7.5) | - | 78.2 (8.7) | - | 75.7 (7.8) | - | 76.2 (8.1) | - | 75.6 (7.4) | - | 76.5 (8.0) | - | 75.6 (7.6) | - |
| Median (IQR) | 74 (70-81) | - | 74 (70-81) | - | 77 (71-85) | - | 74 (69-81) | - | 75 (69-82) | - | 74 (70-80) | - | 75 (70-82) | - | 74 (69-81) | - |
| 65–74 | 7,270,649 | 50.4% | 4,408,182 | 50.9% | 71,760 | 39.7% | 885,288 | 51.4% | 1,062,986 | 49.1% | 1,161,808 | 51.1% | 425,259 | 46.9% | 144,690 | 51.4% |
| 75–84 | 4,979,473 | 34.5% | 3,007,896 | 34.7% | 62,436 | 34.5% | 567,365 | 32.9% | 718,730 | 33.2% | 791,297 | 34.8% | 317,250 | 35.0% | 95,688 | 34.0% |
| ≥85 | 2,187,823 | 15.2% | 1,251,562 | 14.4% | 46,643 | 25.8% | 270,020 | 15.7% | 384,623 | 17.8% | 318,931 | 14.0% | 163,788 | 18.1% | 41,097 | 14.6% |
| **Sex** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Male | 6,029,665 | 41.8% | 3,653,319 | 42.1% | 70,082 | 38.8% | 706,020 | 41.0% | 876,643 | 40.5% | 954,592 | 42.0% | 369,554 | 40.8% | 117,835 | 41.9% |
| Female | 8,408,280 | 58.2% | 5,014,321 | 57.9% | 110,757 | 61.2% | 1,016,653 | 59.0% | 1,289,696 | 59.5% | 1,317,444 | 58.0% | 536,743 | 59.2% | 163,640 | 58.1% |
| **Concomitant vaccination** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| No | 13,105,220 | 90.8% | 7,802,544 | 90.0% | 171,858 | 95.0% | 1,578,879 | 91.7% | 1,998,942 | 92.3% | 2,067,014 | 91.0% | 855,642 | 94.4% | 253,382 | 90.0% |
| Any | 1,332,725 | 9.2% | 865,096 | 10.0% | 8,981 | 5.0% | 143,794 | 8.3% | 167,397 | 7.7% | 205,022 | 9.0% | 50,655 | 5.6% | 28,093 | 10.0% |

*¥The total number of influenza-vaccinated beneficiaries includes those beneficiaries with general or administration codes only or multiple vaccination types on the same day*

*\*The IIV3/IIV4 category is inclusive of standard-dose vaccine codes for IIV3 and IIV4 vaccines, but additionally includes those standard-dose vaccine codes for which it is unclear whether they were specifically trivalent or quadrivalent (See Table S-4)*

*Abbreviations: IQR, interquartile range; SD, standard deviation.*

# Table S-10. Medicare Fee-for-Service population early-season and end-of-season self-controlled seasonality-adjusted risk interval analysis results: Odds ratios and attributable risks among influenza-vaccinated beneficiaries ages ≥65 years, 2018–2019

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Population** | **Number of GBS cases** | | **Odds ratio** | **Odds ratio 95% CI** | **p-value\*** | **Attributable risk (per million vaccinations)** | **Attributable risk (per million vaccinations) 95% CI** |
| **Risk window** | **Control window** |
| **Early-Season: High-dose influenza-vaccinated beneficiaries** | | |  |  |  |  |  |
| ***Risk window: days 8–21 post-vaccination*** | | |  |  |  |  |  |
| Claims-based, seasonality-adjusted | 16 | 26 | 1.85 | (0.99, 3.44) | 0.054 | 0.98 | (-0.02, 1.82) |
| PPV imputed quantitative bias analysis, seasonality-adjusted | 11.38 | 18.47 | 1.84 | (0.78, 4.31) | 0.162 | 0.69 | (-0.29, 1.47) |
| ***Risk window: days 1–42 post-vaccination*** | |  |  |  |  |  |  |
| Claims-based, seasonality-adjusted | 34 | 26 | 1.31 | (0.79, 2.18) | 0.302 | 1.08 | (-0.97, 2.99) |
| PPV imputed quantitative bias analysis, seasonality-adjusted | 24.21 | 18.58 | 1.31 | (0.65, 2.61) | 0.448 | 0.76 | (-1.20, 2.56) |
| **End-of-Season: High-dose influenza-vaccinated beneficiaries** | | |  |  |  |  |  |
| ***Risk window: days 8–21 post-vaccination*** | | |  |  |  |  |  |
| Claims-based, seasonality-adjusted | 18 | 33 | 1.64 | (0.93, 2.92) | 0.090 | 0.81 | (-0.13, 1.64) |
| ***Risk window: days 1–42 post-vaccination*** | |  |  |  |  |  |  |
| Claims-based, seasonality-adjusted | 37 | 33 | 1.13 | (0.70, 1.80) | 0.620 | 0.48 | (-1.40, 2.31) |
| **Early-Season: Influenza-vaccinated beneficiaries**Δ | |  |  |  |  |  |  |
| ***Risk window: days 8–21 post-vaccination*** | | |  |  |  |  |  |
| Claims-based, seasonality-adjusted | 22 | 42 | 1.57 | (0.94, 2.63) | 0.086 | 0.66 | (-0.09, 1.33) |
| PPV imputed quantitative bias analysis, seasonality-adjusted | 15.67 | 29.93 | 1.56 | (0.78, 3.15) | 0.210 | 0.46 | (-0.26, 1.09) |
| ***Risk window: days 1–42 post-vaccination*** | |  |  |  |  |  |  |
| Claims-based, seasonality-adjusted | 52 | 42 | 1.24 | (0.82, 1.86) | 0.302 | 0.82 | (-0.74, 2.32) |
| PPV imputed quantitative bias analysis, seasonality-adjusted | 37.06 | 30.01 | 1.24 | (0.71, 2.14) | 0.448 | 0.58 | (-0.92, 2.00) |
| **End-of-Season: Influenza-vaccinated beneficiariesΔ** | |  |  |  |  |  |  |
| ***Risk window: days 8–21 post-vaccination*** | | |  |  |  |  |  |
| Claims-based, seasonality-adjusted | 28 | 53 | 1.58 | (1.00, 2.50) | 0.049\* | 0.71 | (0.00, 1.36) |
| ***Risk window: days 1–42 post-vaccination*** | |  |  |  |  |  |  |
| Claims-based, seasonality-adjusted | 63 | 53 | 1.19 | (0.82, 1.71) | 0.356 | 0.69 | (-0.77, 2.11) |

*\* Significant at p<0.05*

*Δ With any influenza vaccine (including high-dose influenza vaccine)*

# S-11. Chart-confirmed end-of-season SCRI Analyses

Following the completion of the medical record review, we conducted SCRI analyses subset to those cases that were confirmed to be GBS according to the Brighton Collaboration’s case definition. We requested 145 charts, 98 of which were returned, resulting in a response rate of 67.59%. Of these 98 cases, 64 were confirmed as a level 1-3 GBS case according to the Brighton Collaboration’s case definition, resulting in a PPV of 65.31%. Using these chart-confirmed cases, we re-ran the SCRI analyses using both the primary and secondary risk windows; the results of these analyses are included in Table S-11.1 below.

We further conducted various sensitivity analyses which varied (1) the source of GBS onset date (i.e., claims-based vs. chart-based) and (2) the risk and control window periods adjusted for the use of claim-based onset date (results not shown). All of the results were consistent with our main chart-confirmed results. See the study protocol addendum in Section S-2 for full details.

## Table S-11.1 Medicare Fee-for-Service population chart-confirmed end-of-season self-controlled risk interval analysis results: Odds ratios and attributable risks among influenza-vaccinated beneficiaries ages ≥65 years, 2018–2019

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Population** | **Number of GBS cases** | | **Odds ratio** | **Odds ratio 95% CI** | **p-value\*** | **Attributable risk (per million vaccinations)** | **Attributable risk (per million vaccinations) 95% CI** |
| **Risk window** | **Control window** |
| **End-of-Season: Influenza-vaccinated beneficiariesΔ** | |  |  |  |  |  |  |
| ***Risk window: days 8–21 post-vaccination*** | | |  |  |  |  |  |
| Chart-confirmed | 10 | 24 | 1.25 | (0.60, 2.61) | 0.553 | 0.72 | (0.00, 1.36) |
| ***Risk window: days 1–42 post-vaccination*** | |  |  |  |  |  |  |
| Chart-confirmed | 28 | 24 | 1.17 | (0.68, 1.71) | 0.579 | 0.28 | (-0.70, 1.21) |
| **End-of-Season: High-dose Influenza-vaccinated beneficiaries** | | |  |  |  |  |  |
| ***Risk window: days 8–21 post-vaccination*** | | |  |  |  |  |  |
| Chart-confirmed | *Insufficient power to detect an OR of 3.0* | | | | | | |
| ***Risk window: days 1–42 post-vaccination*** | |  |  |  |  |  |  |
| Chart-confirmed | 16 | 14 | 1.14 | (0.56, 2.34) | 0.715 | 0.23 | (-0.98, 1.39) |

*\* Significant at p<0.05*

*Δ With any influenza vaccine (including high-dose influenza vaccine*

1. https://www.cdc.gov/flu/protect/vaccine/guillainbarre.htm [↑](#footnote-ref-2)
2. When calculating the attributable risk for the primary risk window of 8-21 days following vaccination, the number of cases in the control window must be divided by 3 to normalize the length of the risk period to the length of the control period. This is not done for the secondary risk window of 1-42 days following vaccination. [↑](#footnote-ref-3)
3. <https://gis.cdc.gov/grasp/fluview/fluportaldashboard.html> [↑](#footnote-ref-4)