Supplemental Online Content

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eAppendix

This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix.

Cohort Analysis

Study Population

Since RZV was expected to replace ZVL in the market,[1] it was not feasible to compare two concurrent cohorts. For the cohort analyses, we identified RZV vaccinations between October 1, 2017 and December 31, 2018 and ZVL vaccinations between October 1, 2012 and September 30, 2017.

To capture any historical event that might be relevant to our study, we required continuous enrollment in Medicare FFS and Part D from 365 days prior to vaccination. Given that both herpes zoster vaccines were recommended for older adults,[1,2] the analysis included beneficiaries who aged into Medicare and were age 65 or older at the time of vaccination. To account for potential confounders, we further excluded vaccinations if there was any GBS diagnosis within a year prior to vaccination, or if the beneficiary was on chronic dialysis therapy, admitted into a nursing home, skilled nursing facility, or received hospice care on the vaccination date. Claims that indicated non-standard administration of the RZV or ZVL vaccine were excluded as possibly duplicated records; we only included the first two eligible administrations of RZV, and the first eligible administration of ZVL vaccine in the following analyses.

We followed each eligible vaccination from date of vaccination to a maximum of 42 days, censoring at the GBS onset date, death, FFS disenrollment, receipt of the other type of herpes zoster vaccine, entrance into a nursing home, skilled nursing facility, or hospice care, or the respective study end date for each cohort.

The GBS algorithm reassigned each case's onset date to the first GBS claim when the onset date occurred within the seven days prior to the GBS hospitalization. Using this earlier date instead of the GBS hospitalization date, when applicable, minimized measurement error.

Statistical Analysis

For the primary analysis, RR was calculated using a Poisson regression model with an offset equal to the natural logarithm of person-time, adjusting for age and sex. Clustered robust standard errors were used to account for multiple RZV doses per beneficiary.[3]

The attributable risk (AR) was calculated by assuming that there were only ZVL vaccinations.[4] We also performed a sensitivity analysis using a Cox proportional hazards model, adjusted for age and sex.

Study Protocols

Please see the following separately submitted documents:

- *Shingrix_GBS_Protocol_v1_4_signed.pdf*
- *Shingrix_GBS_Protocol_Addendum_20200210_signed.pdf*
- *Shingrix_GBS_Protocol_Addendum_v2_20200626_signed.pdf*

A. Medical Record Review

Abstraction

For this study, all records were abstracted by two abstractors, independent of each other, to ensure the accuracy of the abstraction. Because the study had multiple abstractors, the abstraction data underwent an additional level of review to reconcile differences between the abstractions. A final reviewer looked at discrepancies between the two abstractions and then reviewed the medical record themselves to determine the correct response.

Case Classification

Cases identified by this process as Brighton Level 1, 2, or 3 are “chart-confirmed” GBS cases. A level 4 case has insufficient evidence to meet the Brighton criteria but was diagnosed and billed as GBS by a healthcare provider, and a level 5 case is not a case of GBS according to the Brighton criteria but was similarly diagnosed and billed (eTable 5).[5,6] As part of the MRR, information surrounding the onset of neurological symptoms was gathered and additional sensitivity analyses using chart-based time to the onset date of GBS instead of the time to claims-based GBS diagnosis date were completed.

Neurologist Adjudication

To enhance the validity and accuracy of the adjudication process, two neurologists independently adjudicated each case, reviewing all of the abstracted data and consulting the medical charts as needed to determine the most appropriate case classification.

Any discordance between their case classifications was resolved after discussion of the findings of their independent reviews. The neurologists' classification was used as the final case classification for the self-controlled case series (SCCS) sensitivity analysis. In the case that an agreement was not reached for at least one of the cases, we were prepared to conduct additional sensitivity analyses with the different classifications.

Self-Controlled Case Series Analysis

Analysis Assumptions

The assumptions of the SCCS and the adaptations that we made to its implementation are as follows:

(i) Events must be independently recurrent and rare

The original SCCS model was developed to assess the risk of recurrent events. However, due to the rare events assumption, this bias can be safely ignored if these non-recurrent events have a risk of occurrence <10%, as in the case of GBS.

(ii) Occurrence of an event should not affect subsequent exposures or mortality

The standard implementation of SCCS requires that exposure must be exogenous. There is a concern in our study as our event (GBS) is likely to reduce the chance of subsequent exposure. We did not include any control time from before the first dose; this ensured that any cases recorded within our study had occurred subsequent to initial exposure. To accommodate this concern for the second dose, we relied on the rare event assumption. The SCCS method may be applied to unique, non-recurrent outcomes only when the event is rare, like GBS.

(iii) Events cannot happen at the exact same time or age.

We do not have concerns for this assumption in our study.

(iv) Event rates are constant within intervals

While there is some evidence suggesting that GBS risk is non-constant following exposure, we believe that this will introduce only limited bias to our results.

(v) Exposure is transient or intermittent

We do not have concerns for this assumption in our study.

PPV-Based Quantitative Bias Analysis

Our first set of chart-confirmed sensitivity analyses excluded cases whose medical records were not available for MRR, but a portion of them might have been true GBS cases. To ensure comparability of results and address cases for which we did not receive medical charts, we conducted a PPV-based quantitative bias analysis. We calculated the number of cases in the risk and control windows by applying the PPV to the set of non-response cases identified in claims and added them to the chart-confirmed cases. We use PPV of 78.57%.

This resulted in 10.20 cases in the risk window (842.27 days), 6.32 cases falling in the control window (2,378.37 days), and an RR of 4.60 95% CI (1.59-13.30).

Shortened Control Window Sensitivity Analysis

Preliminary onset date investigations suggested that the chart-based onset date generally occurs prior to the claims-based onset date. Thus, using chart-based onset dates had the potential to cause cases to shift from the control window to the risk window or from after the end of the control to within the control window. As we requested cases with a claims-based onset date only up to day 183 post-vaccination for the medical record review, our analyses could have excluded GBS cases that would have otherwise shifted into the 43-183 day control window due to their chart-based onset dates.

To reduce the bias from missing potential cases with chart-based onset dates within our control window, we completed a chart-confirmed SCCS sensitivity analysis where we used the chart-based GBS onset date and shortened the control window by 28 days (i.e., days 43-155 post-vaccination). We used 28 days because available clinical GBS information estimates a 2-4 weeks period between the initial onset of neurological symptoms and nadir of weakness.[5] Shortening the control window by this amount ensures we have full claims and medical records

information for cases whose chart-based onset date may occur between days 43-155 post-vaccination. The case definition followed the main SCCS sensitivity analysis using chart-based onset dates.

Attributable Risk Calculation

We calculated the portion of GBS cases attributable to vaccination with RZV. The excessive number of GBS cases following RZV vaccination can be derived from the conditional Poisson regression model directly, defined as the difference between the sum of model fitted values (i.e., model predicted number of cases), and the sum of expected cases if there were no RZV vaccination (i.e., all observed time is treated as control time). The **unadjusted AR** is the excessive number of GBS cases divided by the number of eligible RZV vaccinations (or eligible follow up dose-years). The standard error (SE) of the unadjusted AR is estimated by bootstrap resampling 10,000 times.[4] For each iteration, we sampled the beneficiaries with GBS with replacement and repeated the AR calculation. The SE is calculated as the square root of the variance of the 10,000 AR values. Using the primary model, we found that for every million doses of RZV administered, we could expect to see 6.47 excessive cases of GBS in the study population.

While the unadjusted ARs are obtained from the claims-based and chart-confirmed analyses directly, they might not be truly representative of the underlying risk of GBS. For claims-based analysis, the rate of GBS might be overestimated without chart confirmation, while chart-confirmed analysis might have a GBS rate that is underestimated, without accounting for unreturned charts.

Accordingly, we calculated a **PPV-adjusted AR**. For analyses using claims information only, such as the claims-based primary analysis (21 cases), we apply a process similar to the PPV-based quantitative bias sensitivity analysis. Taking the primary analysis as an example, we

impute the GBS status of beneficiaries 1,000 times using our PPV (78.57%). On average, we expect to have a total of 16.5 cases (21*78.57%). We repeat the AR calculation for each imputed dataset and the PPV-adjusted AR is defined as the mean of 1,000 AR values divided by the number of eligible Shringrix vaccinations (or the number of eligible dose-years). For each of the 1,000 imputed datasets, we perform bootstrap resampling 10,000 times to obtain the SE in the same way as the unadjusted AR. The overall SE of the PPV-adjusted AR is calculated using Rubin's rule of combining multiply imputed results.[7]

For analyses using MRR information, we follow the same methodology as the PPV-based quantitative bias sensitivity analysis: include all chart-confirmed cases, and impute GBS status of cases whose medical records are not available using the PPV 1,000 times. The AR and SE of AR are calculated as described above.

By imputing GBS status using the PPV, these PPV-adjusted ARs should be closer to the true AR than the unadjusted ARs, and are therefore better inferences for public health information.

Seasonality Adjustment

The seasonality adjustment used data from the World Health Organization and the National Enteric Virus Surveillance System to determine weekly influenza rates and determine the expected rate of GBS.[8] Seasonality of influenza was measured and introduced into the SCCS 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 an 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.
    a. Influenza season ("high" or "low"), as determined in (2), was the independent variable (dummy for "high" influenza season)
    b. 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 the SCCS analysis
    a. Cumulative risk calculated by summing weekly national baseline risk of GBS for risk and control period.
    b. 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)
        i. This dependence of risk among weeks was taken into account by multiplying each risk estimate for week q by $(1 - p_w)$ for each w, where p_w is the risk for week w and w runs from 1 to $(q - 1)$
        ii. Using the above-mentioned variables, the cumulative risk for a 6-week risk interval beginning in week 1 was calculated as such:
        Cumulative Risk = $p_1 + (1 – p_1)*p_2 + … + (1 – p_1)* … * (1 – p_5)*p_6$
7) Running New SCCS Model With Seasonality Measure: a conditional Poisson regression used for SCCS analysis conducted as before, with the following difference: new offset term was log of cumulative estimated risk for the interval instead of the log of length of interval in days.

Risk Time Trend Analysis

In the VSD analysis, the observed GBS risk post-Shingrix vaccination decreased over time. To investigate the change in post-vaccination GBS risk over time in Medicare data, we fit the following SCCS model:

$$\log\big(E(Y|X)\big) = \beta_1(risk\_window) + \beta_2(risk\_window * vaccination\_timing) + \log(window\_length) + strata(beneficiary\_id)$$

$$Y = GBS\ outcome\ variable$$

$$risk\_window = binary\ term\ indicating\ GBS\ occurrence\ in\ risk\ window$$

$$vaccination\_timing = days\ since\ Shingrix\ approval\ date$$

$$window\_length = interval\ (risk/control\ window\ length)$$

$$beneficiary\_id = term\ identifying\ the\ beneficiary$$

The model allows the risk of GBS in the risk window to change over calendar time, while assuming it remains constant in the control window over calendar time. Due to the low number of observations, we assumed linearity of change in GBS risk. $Exp(\beta_2)$ represented the change in risk per unit time since Shingrix approval date.

Based off observed vaccinations, the change in RR every additional 30 days after approval derived from the model was 0.99 (95% CI: 0.90-1.09; p=0.771). eFigure 1 displays the change in RR over time.

GBS Case Severity

We used two metrics to measure the severity of GBS cases occurring after Shingrix vaccination: (i) occurrence of respiratory failure or mechanical intubation, and (ii) length of hospital stay.

We produced descriptive statistics determining the number of cases with a claim for respiratory failure or intubation during a hospitalization with a primary GBS diagnosis. We used the codes in eTable 7 to search for intubation and respiratory failure occurring during the same hospital stay as the primary GBS diagnosis.

Cases were additionally assessed for severity based upon the length of stay during a hospitalization with a primary GBS diagnosis. We defined length of stay using the date of admission and the date of discharge. Additionally, we determined which eligible GBS cases had death as the reason for discharge.

Figures and Tables

eTable 1. National Drug Codes Used to Identify Shingrix Vaccinations in Medicare Claims

NDC Code	Description
Supplied as an outer package of 1 dose	
58160-0828-01	Lyophilized gE Antigen Component (Vial 2 of 2)
58160-0829-01	Adjuvant Suspension Component (Vial 1 of 2)
58160-0819-12	Outer Package
Supplied as an outer package of 10 doses	
58160-0828-03	Lyophilized gE Antigen Component (10 vials)
58160-0829-03	Adjuvant Suspension Component (10 vials)
58160-0823-11	Outer Package

eTable 2. National Drug Codes Used to Identify ZVL Vaccinations in Medicare Claims

NDC Code	Description
Merck	
00006-4963-00	1 Vial, Single-Dose in 1 Carton > .65 mL in 1 Vial, Merck
00006-4963-01	Zoster Vaccine Live for Injection, .65 mL, Merck
00006-4963-41	10 Vial, Single-Dose in 1 Carton > .65 mL in 1 Vial, Merck
Other Supplier	
54868-5703-00	Zoster Vaccine Live for Injection, .65 mL, Physicians Total Care
68258-8908-00	Zoster Vaccine Live for Injection, .65 mL, Dispensing Solutions, Inc.
68258-8908-01	Zoster Vaccine Live for Injection, .65 mL, Dispensing Solutions, Inc.

eTable 3. Cohort Creation Table for RZV and ZVL Vaccinated Populations

Study Eligibility Criteria		RZV				ZVL			
		Vaccination		Beneficiary		Vaccination		Beneficiary	
		#	%	#	%	#	%	#	%
A	Number of Distinct Vaccination Dates in Study Period	2,908,302	100.00%	1,881,203	100.00%	5,475,092	100.00%	5,406,306	100.00%
B	Number of Vaccinations Satisfying (A) and having Continuous Part A/B Enrollment for 365 days prior to vaccination date	1,515,529	52.11%	977,940	51.98%	2,480,022	45.30%	2,454,048	45.39%
C	Number of Vaccinations Satisfying (B) and having Continuous Part D Enrollment for 365 days prior to vaccination date	1,489,808	51.23%	961,535	51.11%	2,271,684	41.49%	2,248,197	41.58%
D	Number of Vaccinations Satisfying (C) and Age 65+ on vaccination date	1,414,851	48.65%	911,995	48.48%	2,066,933	37.75%	2,046,737	37.86%
E	Number of Vaccinations Satisfying (D) and Aged into Medicare, with or without ESRD	1,323,710	45.51%	851,268	45.25%	1,848,945	33.77%	1,831,841	33.88%
F	Number of Vaccinations Satisfying (E) and not on Chronic Dialysis in 7 days prior to vaccination date	1,323,207	45.50%	851,044	45.24%	1,847,847	33.75%	1,830,770	33.86%
G	Number of Vaccinations Satisfying (F) and not in Nursing Home on vaccination date	1,321,269	45.43%	849,814	45.17%	1,834,915	33.51%	1,818,222	33.63%
H	Number of Vaccinations Satisfying (G) and not in Skilled Nursing Facility on vaccination date	1,321,237	45.43%	849,791	45.17%	1,834,887	33.51%	1,818,194	33.63%
I	Number of Vaccinations Satisfying (H) and not in Hospice on vaccination date	1,320,964	45.42%	849,622	45.16%	1,834,258	33.50%	1,817,579	33.62%
J	Number of Vaccinations Satisfying (I) and not having the *Same* Zoster Vaccine in 42 days prior to vaccination date	1,318,622	45.34%	849,609	45.16%	1,832,618	33.47%	1,817,520	33.62%
	Number of Vaccinations Satisfying (I) and not having the *Other* Zoster Vaccine in 42 days prior to vaccination date	1,318,507	45.34%	849,556	45.16%				
K	Number of Vaccinations Satisfying (J) and not having GBS history in 365 days prior to vaccination date	1,318,248	45.33%	849,397	45.15%	1,832,194	33.46%	1,817,099	33.61%
L	Number of Vaccinations Satisfying (K) and are the First/Second Eligible Dose of RZV or the First Eligible Dose of ZVL	1,318,004	45.32%	849,397	45.15%	1,817,099	33.19%	1,817,099	33.61%

eTable 4. Cohort Creation Table for GBS Population

Study Eligibility Criteria		RZV Beneficiaries			
		Main Analysis		Extended Analysis	
		#	%	#	%
A	Number of Beneficiaries in Study Period	2,192,079	100.00%	5,627,836	100.00%
B	Number of Beneficiaries Satisfying (A) and having Continuous Part A/B Enrollment for 183 days prior to vaccination date	1,173,195	53.52%	2,854,323	50.72%
C	Number of Beneficiaries Satisfying (B) and having Continuous Part D Enrollment between RZV approval (October 2017) and vaccination date	1,116,360	50.93%	2,526,916	44.90%
D	Number of Beneficiaries Satisfying (C) and Age 65+ on vaccination date	1,059,900	48.35%	2,410,016	42.82%
	Number of Beneficiaries Satisfying (C) and Age 65+ at RZV approval (October 2017)	1,051,684	47.98%	2,383,563	42.35%
E	Number of Beneficiaries Satisfying (D) and Aged into Medicare, with or without ESRD	988,822	45.11%	2,248,194	39.95%
F	Number of Beneficiaries Satisfying (E) and not on Chronic Dialysis in Study Period	986,919	45.02%	2,243,110	39.86%
G	Number of Beneficiaries Satisfying (F) and not in Nursing Home in Study Period	958,896	43.74%	2,147,877	38.17%
H	Number of Beneficiaries Satisfying (G) and not in Skilled Nursing Facility in Study Period	956,939	43.65%	2,139,232	38.01%
I	Number of Beneficiaries Satisfying (H) and not in Hospice in Study Period	954,120	43.53%	2,128,170	37.82%
J	Number of Beneficiaries Satisfying (I) and having One/Two Doses of RZV	953,146	43.48%	2,119,380	37.66%
K	Number of Beneficiaries Satisfying (J) and not having two RZV Vaccinations within 42 days	950,911	43.38%	2,114,012	37.56%
L	Number of Beneficiaries Satisfying (K) and not having GBS history in 183 days prior to vaccination date	950,797	43.37%	2,113,758	37.56%
M	Number of Beneficiaries Satisfying (L) and having GBS Outcome in Study Period	21	0.00%	44	0.00%

eTable 5. Brighton Collaboration Case Classifications and Criteria for Guillain Barré Syndrome

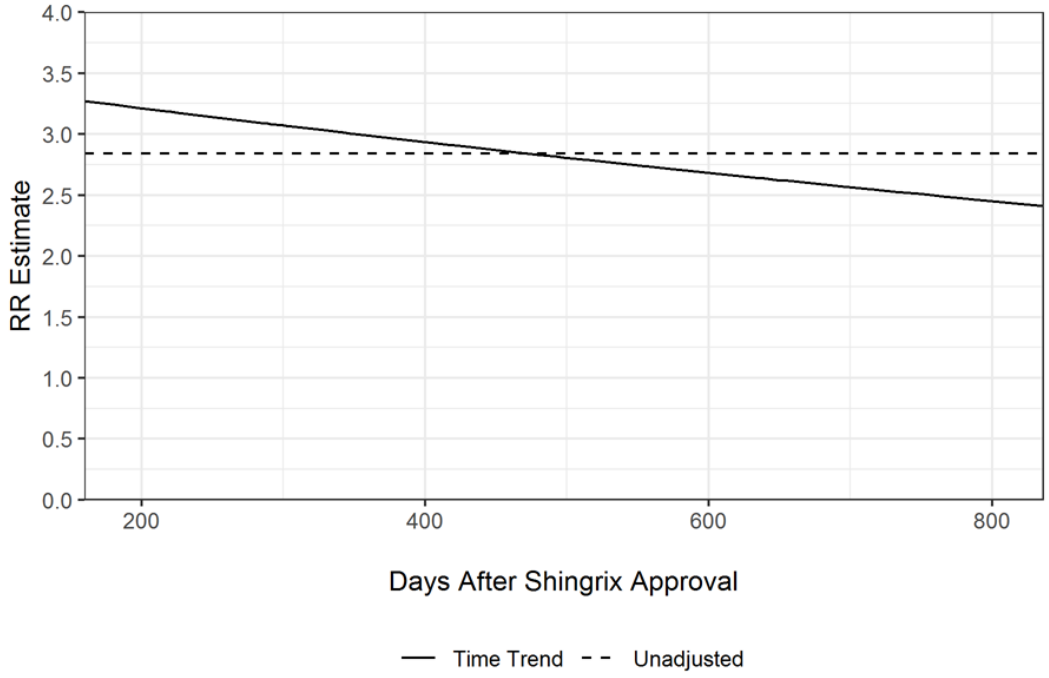
Level	Requirements
Level 1 (Highest Level of Certainty)	1. Bilateral AND flaccid weakness of the limbs 2. Decreased or absent deep tendon reflexes in weak limbs 3. Monophasic illness pattern AND interval between onset and nadir of weakness between 12h and 28 days AND subsequent clinical plateau. The eventual outcome is either stabilization at nadir OR subsequent improvement OR death 4. Electrophysiologic findings consistent with GBS 5. Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/μl) 6. Absence of identified alternative diagnosis for weakness
Level 2	1. Bilateral AND flaccid weakness of the limbs 2. Decreased or absent deep tendon reflexes in weak limbs 3. Monophasic illness pattern AND interval between onset and nadir of weakness between 12h and 28 days AND subsequent clinical plateau. 4. CSF total white cell count <50 cells/μl (with or without CSF protein elevation above laboratory normal value) OR If CSF not collected or results not available, electrophysiologic studies consistent with GBS 5. Absence of identified alternative diagnosis for weakness
Level 3	1. Bilateral AND flaccid weakness of the limbs 2. Decreased or absent deep tendon reflexes in weak limbs 3. Monophasic illness pattern AND interval between onset and nadir of weakness between 12h and 28 days AND subsequent clinical plateau. 4. Absence of identified alternative diagnosis for weakness
Level 4 (Lowest Level of Certainty)	1. A case was classified as having “insufficient evidence” if a physician’s diagnosis of GBS was made, but evidence was insufficient to classify the patient at any higher level of diagnostic certainty (i.e., the abstraction data for that case does not contradict any of the level 3 criteria but is missing information for at least one of the level 3 criteria) 2. Absence of identified alternative diagnosis for weakness
Level 5 (Not A Case)	1. If a case did not meet the criteria necessary for classification as Brighton level 1, 2, or 3, was not diagnosed with GBS by a physician, or had a definitive alternate diagnosis documented in the chart, the patient was classified as “not GBS”

eTable 6. List of influenza vaccine codes included in surveillance for the 2017-2018, 2018–2019 season*

Code	Code Type	Vaccine Type	Vaccine Category
90630	CPT	IIV4-ID	Other
90654	CPT	IIV3-ID	Other
90661	CPT	ccIIV3	Other
90664	CPT	Pandemic	Pandemic
90666	CPT	Pandemic	Pandemic
90667	CPT	Pandemic	Pandemic
90668	CPT	Pandemic	Pandemic
90689	CPT	IIV4	Standard Dose
90673	CPT	RIV3	Other
G9141	HCPCS	Pandemic	Pandemic
G9142	HCPCS	Pandemic	Pandemic
Q2033	HCPCS	RIV3	Other
90653	CPT	aIIV3	Adjuvanted
90656	CPT	IIV3	Standard Dose
90658	CPT	IIV3	Standard Dose
90662	CPT	IIV3-HD	High Dose
90674	CPT	ccIIV4	Other
90682	CPT	RIV4	Other
90686	CPT	IIV4	Standard Dose
90688	CPT	IIV4	Standard Dose
90756	CPT	ccIIV4	Other
G0008	HCPCS	Admin	Other
Q2034	HCPCS	IIV3	Standard Dose
Q2035	HCPCS	IIV3_IIV4	Standard Dose
Q2036	HCPCS	IIV3_IIV4	Standard Dose
Q2037	HCPCS	IIV3	Standard Dose
Q2038	HCPCS	IIV3_IIV4	Standard Dose
Q2039	HCPCS	General	Other

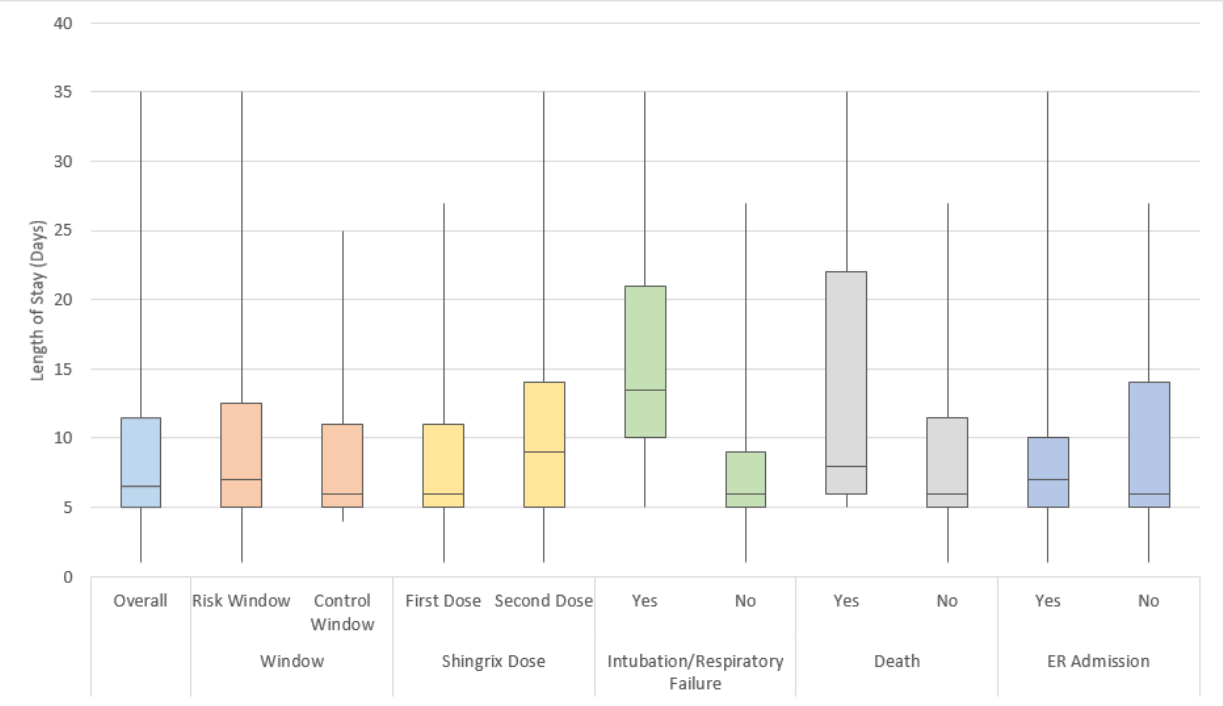
** Codes searched in OP or PB care settings*

eFigure 1. Self-Controlled Case Series GBS Risk Ratio Over Time (All Doses)



The unadjusted line displays the average RR among all doses during the study period. The time trend line uses the risk window term and the time trend interaction term to display the change in RR over time throughout the study period.

eFigure 2. Length of Stay for Shingrix-Vaccinated GBS Cases (Oct 2017 – Feb 2020)



eTable 7. Respiratory Failure and Intubation Codes

Code	Code Type	Description
31500	CPT	Emergent insertion of breathing tube into windpipe cartilage using an endoscope
J9600	ICD-10	Acute respiratory failure, unspecified whether with hypoxia or hypercapnia
J9601	ICD-10	Acute respiratory failure with hypoxia
J9602	ICD-10	Acute respiratory failure with hypercapnia
J9690	ICD-10	Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia
J9691	ICD-10	Respiratory failure, unspecified with hypoxia
J9692	ICD-10	Respiratory failure, unspecified with hypercapnia

eTable 8. Shingrix-Vaccinated GBS Cases with Respiratory Failure After GBS

GBS Category	GBS Cases (Oct 2017 – Feb 2020)			
	Risk Window (Days 1-42)		Control Window (Days 43-183)	
	#	%	#	%
Total GBS Cases	**24**	**100%**	**20**	**100%**
With Respiratory Failure	5	21%	7	35%
Without Respiratory Failure	19	79%	13	65%

Note: For cases in the risk window, respiratory failure was reported for two cases on day 0, for two cases on day 3, and one case on day 21 post-GBS onset.
Note: For cases in the control window, respiratory failure was reported for four cases on day 0, for two cases on day 2, and one case on day 5 post-GBS onset.

eTable 9. Length of Stay for Shingrix-Vaccinated GBS Cases (Oct 2017 – Feb 2020)

Category	Length of Stay*			
	Min	Max	Mean	Std. Dev.
Total GBS Cases	**1**	**35**	**9.55**	**7.22**
Window				
Risk Window	1	35	9.88	8.14
Control Window	4	25	9.15	6.12
Shingrix Dose				
First Dose	1	27	8.69	5.67
Second Dose	1	35	11.20	9.56
Intubation/Respiratory Failure				
Yes	5	35	15.58	5.15
No	1	27	7.28	8.62
Death**				
Yes	5	35	14.00	6.32
No	1	27	9.10	14.09
ER Admission				
Yes	1	35	9.59	7.44
No	1	27	9.47	7.03

** Determined using date of admission and date of discharge.*
*** As reason for discharge.*

eTable 10. Full Set of Self-Controlled GBS Case Series Results

Analysis	Risk Case	Control Cases	Risk Days	Control Days	Rate Ratio (95% CI)	Attributable Risk†			
						Per Million Doses		Per 100,000 Person-Years	
						Unadjusted‡ (95% CI)	PPV-Adjusted§ (95% CI)	Unadjusted‡ (95% CI)	PPV-Adjusted§ (95% CI)
Main SCCS Results (Oct. 1, 2017 to Mar. 31, 2019)									
Primary Analysis (all doses)	13	8	1,092	2,928	4.30 (1.76, 10.53)**	6.47 (2.50, 10.45)**	5.08 (1.04, 9.11)*	1.98 (0.77, 3.20)**	1.56 (0.32, 2.79)*
Secondary Analysis (first dose only)	13	4	714	2,090	9.30 (3.00, 28.84)***	12.20 (7.41, 17.00)***	9.50 (4.35, 14.66)***	4.10 (2.49, 5.72)***	3.20 (1.46, 4.93)***
Seasonality Adjustment (all doses)	13	8	1,092	2,928	4.50 (1.84, 11.00)**	6.56 (2.63, 10.49)**	5.15 (1.13, 9.18)*	2.01 (0.81, 3.22)**	1.58 (0.35, 2.81)*
Farrington Method (all doses)	13	8	1,092	2,928	3.42 (1.42, 8.26)**				
Chart-confirmed Sensitivity Analysis‖ (both neurologists + one neurologist & Brighton algorithm agreement) (Risk 1-42; Control 43-183)	7	4	546	1,557	4.96 (1.43, 17.27)*		5.17 (1.50, 8.84)**		1.59 (0.46, 2.71)**
Chart-confirmed Sensitivity Analysis¶ (both neurologists + one neurologist & Brighton algorithm agreement) (Risk 1-42; Control 43-183)	7	4	546	1,557	4.96 (1.43, 17.27)*		5.13 (1.44, 8.82)**		1.57 (0.44, 2.70)**
Chart-confirmed Sensitivity Analysis# (both neurologists + one neurologist & Brighton algorithm agreement) (Risk 1-42; Control 43-155)	7	4	546	1,277	4.06 (1.17, 14.10)*		4.92 (1.12, 8.73)*		1.61 (0.36, 2.85)*
Extended SCCS Results (Oct. 1, 2017 to Feb. 29, 2020)									
Primary Analysis (all doses)	24	20	2,489	6,157	2.84 (1.53, 5.27)**	4.17 (1.65, 6.69)**	3.13 (0.62, 5.64)*	1.25 (0.49, 2.00)**	0.93 (0.18, 1.68)*
Secondary Analysis (first dose only)	21	8	1,191	3,675	7.72 (3.39, 17.60)***	8.65 (5.74, 11.56)***	6.48 (3.36, 9.60)***	3.06 (2.03, 4.08)***	2.29 (1.19, 3.39)***
Secondary Analysis (second dose only)	3	12	626	1,453	0.22 (0.04, 1.22)				
Claims-based Sensitivity Analysis (all doses, full observability)	24	20	2,520	6,603	3.19 (1.74, 5.83)***	4.42 (1.93, 6.90)***	3.47 (0.99, 5.94)**	1.32 (0.58, 2.06)***	1.04 (0.30, 1.78)**
Seasonality Adjustment (all doses)	24	20	2,489	6,157	2.98 (1.61, 5.53)**	4.28 (1.81, 6.75)**	3.22 (0.74, 5.69)*	1.28 (0.54, 2.02)**	0.96 (0.22, 1.70)*
Seasonality Adjustment (first dose only)	21	8	1,191	3,675	8.06 (3.54, 18.37)***	8.70 (5.82, 11.58)***	6.49 (3.42, 9.57)***	3.07 (2.06, 4.09)***	2.29 (1.21, 3.38)***
Seasonality Adjustment (second dose only)	3	12	626	1,453	0.26 (0.05, 1.35)				

** p < 0.05; ** p < 0.01; *** p < 0.001*

† *When calculating second dose only ARs, we observed a high variance among the estimates from the bootstrapping simulations; the AR estimate for the individual who dies before the beginning of the control window can be infinity, resulting in drastically inflated CI estimates. We have suppressed second dose only AR estimates for this reason.*

‡ *Unadjusted attributable risk estimates are derived using only the claims-based case classifications and does not take into account the outcome PPV or chart return rate.*

§ *PPV-adjusted attributable risk was calculated by imputing GBS status using the same PPV for all analyses, to account for chart confirmation in claims-based analyses and unreturned charts in chart-confirmed analyses.*

‖ *This Chart-confirmed Sensitivity Analyses classifies cases based on neurologist and Brighton algorithm agreement, using chart-based onset dates. The other sensitivity analysis included cases with neurologist agreement + one neurologist yielded the same results.*

This Chart-confirmed Sensitivity Analyses classifies cases based on neurologist and Brighton algorithm agreement, using claims-based onset dates.

¶ *The control window is shortened in this analysis to reduce the bias from missing potential cases with chart-based onset dates within the control window.*

eTable 11. Preceding Illnesses According to Abstraction Results for Chart-confirmed GBS Cases

Preceding Illnesses	Total Number of GBS Cases	Number of GBS Cases	
		Days 1-42 Risk Window	Days 43-183 Control Window
No	12	12	0
Cohort	11	11	--
Cohort-ZVL	4	4	--
Cohort-RZV	7	7	--
SCCS	5	5	0
Yes	10	6	4
Cohort	6	6	--
Cohort-ZVL	3	3	--
Cohort-RZV	3	3	--
SCCS	6	2	4

Note: Cohort cases are included in the 1-42 day risk window by default.

B. References

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