



Risk of Guillain-Barré syndrome (GBS) following Recombinant Zoster Vaccine (RZV)

Advisory Committee on Immunization Practices meeting
February 24-25, 2021

Background

- Upon detection of the statistical signal for GBS following RZV in the Vaccine Safety Datalink (VSD) Rapid Cycle Analysis (RCA) in the fall of 2018, CDC consulted with FDA on additional analyses in other databases
- Subsequently, FDA in collaboration with CDC and CMS initiated an assessment of risk of GBS following RZV in Medicare data
- Analyses completed
 - Cohort analysis to replicate original VSD RCA
 - Claims Based Self-Controlled Analysis for **Oct 2017 – Mar 2019**
 - Medical Record Review (MRR) Self-Controlled Analysis for **Oct 2017 – Mar 2019**
 - Extended Claims Based Self-Controlled Analysis for **Oct. 1, 2017 – Feb. 29, 2020**

Methods – Self-Controlled Analysis

- Self-Controlled Case Series (SCCS) analysis to compare relative risk within an individual
- Population
 - **Exposure:** Vaccinations identified using National Drug Codes (NDCs) in Part D
 - RZV vaccination window: **Oct 2017 – Mar 2019**
 - **Outcome:** Primary inpatient Guillain-Barré syndrome (GBS) diagnosis
 - ICD-10: G61.0
 - Aged into Medicare (65 years or older)
 - Continuous enrollment in Medicare Parts A, B and D for 183 days prior to vaccination
 - Clean period: No GBS in 183 days prior to vaccination date
- **Risk Window:** Days 1-42 post-vaccination
- **Control Window:** Days 43-183 post-first dose (or until they receive their second dose) and days 43-183 post-second dose (or until end of study period/disenrollment/death).
- **Poisson Model:** $\log(E(Y|X)) = \beta_1(\text{risk_window}) + \log(t) + \text{strata}(\text{beneficiary_id})$
 - Y = GBS outcome variable*
 - risk_window = binary term indicating GBS occurrence in risk window*
 - t = interval*
 - beneficiary_id = term identifying the beneficiary*

Results – Self-Controlled Analysis

Table 2. GBS outcome rates and unadjusted model results

	Primary Analysis (All doses)				Sensitivity Analysis (First dose only)			
<i>Conditional Poisson Regression</i>								
<i>Cases in Risk Window (Days 1-42)</i>	13				13			
<i>Cases in Control Window (Days 43-183)</i>	8				4			
<i>Risk Days</i>	1,092				714			
<i>Control Days</i>	2,928				2,090			
<i>Unadjusted Model Results</i>	<i>RR</i>	<i>95% CI</i>		<i>P-Value</i>	<i>RR</i>	<i>95% CI</i>		<i>P-Value</i>
	4.30	1.76	10.53	0.001	9.30	3.00	28.84	<0.001



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	4.30	1.76	10.53	0.001	9.30	3.00	28.84	<0.001
Attributable Risk								
<i>RZV Doses</i>	1,541,267				950,797			
<i>Risk Days (million)</i>	63.89				39.46			
<i>Control Days (million)</i>	119.62				63.72			
<i>Attributable Risk per 100,000 Person Years</i>	<i>AR</i>	<i>95% CI</i>		<i>P-Value</i>	<i>AR</i>	<i>95% CI</i>		<i>P-Value</i>
	1.98	0.75	3.22	0.002	4.10	2.46	5.75	<0.001
<i>Attributable Risk per million Doses</i>	<i>AR</i>	<i>95% CI</i>		<i>P-Value</i>	<i>AR</i>	<i>95% CI</i>		<i>P-Value</i>
	6.47	2.47	10.47	0.002	12.20	7.34	17.06	<0.001

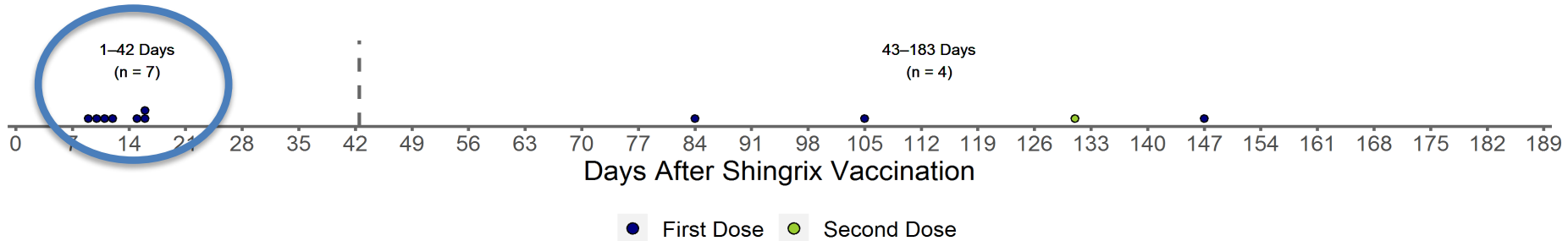
Summary – Self-Controlled Analysis

- Interim results of the FDA SCCS analysis of post-vaccination GBS rate in the vaccinated RZV population between the selected risk and control periods indicate:
 - An elevated unadjusted rate ratio = **4.30 (95% CI 1.76, 10.53), p=0.001**

RZV-GBS Medical Record Review

- Records for all GBS cases following RZV or ZVL vaccination were requested from providers (36 total)
- Brighton Collaboration's GBS Case Definition applied to data abstracted from records
- Additional layer of adjudication performed by subject matter expert neurologists

Temporal Distribution of MRR GBS Cases





Results – MRR Self-Controlled Analysis

Table 4. GBS outcome rates and for neurologist-confirmed cases*

* Uses chart-based onset date

	Primary Analysis (All doses)				Sensitivity Analysis (First dose only)			
Conditional Poisson Regression								
Cases in Risk Window (Days 1-42)	7				7			
Cases in Control Window (Days 43-183)	4				3			
Risk Days	546				420			
Control Days	1,557				1,302			
Unadjusted Model Results	RR	95% CI		P-Value	RR	95% CI		P-Value
	4.96	1.43	17.27	0.012	7.06	1.80	27.71	0.005
Attributable Risk								
RZV Doses	1,541,267				950,797			
Risk Days (million)	63.89				39.46			
Control Days (million)	119.62				63.72			
Attributable Risk per 100,000 Person Years	AR	95% CI		P-Value	AR	95% CI		P-Value
	1.11	0.25	1.97	0.011	2.13	0.79	3.46	0.002
Attributable Risk per million Doses	AR	95% CI		P-Value	AR	95% CI		P-Value
	3.63	0.83	6.43	0.011	6.32	2.36	10.28	0.002

Results – Extended Self-Controlled Analysis

Table 5. GBS outcome rates for extended analysis

* Uses chart-based onset date

Analysis	Risk Case	Control Cases	Risk Days	Control Days	Rate Ratio (95% CI)	Attributable Risk Per Million Doses
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)	3.13 (0.62, 5.64)
Secondary Analysis (First dose only)	21	8	1,191	3,675	7.72 (3.39, 17.60)	6.48 (3.36, 9.60)
Secondary Analysis (Second dose only)	3	12	626	1,453	0.22 (0.04, 1.22)	Unstable

None of the pre-planned sensitivity analyses led to a different conclusion

Model (log scale) RR Lower Upper

All Doses

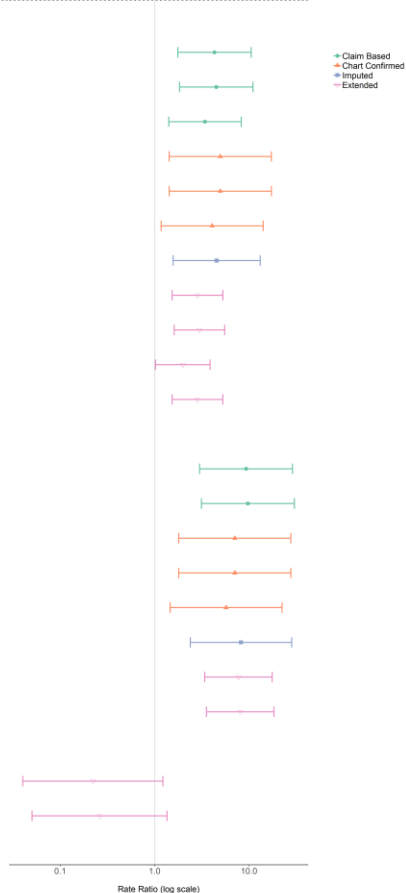
Model (log scale)	RR	Lower	Upper
Primary Analysis	4.30	1.76	10.53
Claim Identified Cases, Adjusted for Seasonality	4.50	1.84	11.00
Claim Identified Cases, Adjusted for Rare Exposure Post Outcome	3.42	1.42	8.26
Chart-Confirmed Cases, Chart-Based Onset Date	4.96	1.43	17.27
Chart-Confirmed Cases, Claim-Based Onset Date	4.96	1.43	17.27
Chart-Confirmed Cases, Control Days 43-155	4.06	1.17	14.10
PPV-Based Quantitative Bias Analysis	4.54	1.57	13.14
Extended Period, Unadjusted	2.84	1.53	5.27
Extended Period, Adjusted for Seasonality	2.98	1.61	5.53
Extended Period, Adjusted for Rare Exposure Post Outcome	1.99	1.02	3.86
Extended Period, Assuming Full Observability	2.84	1.53	5.27

First Dose Only

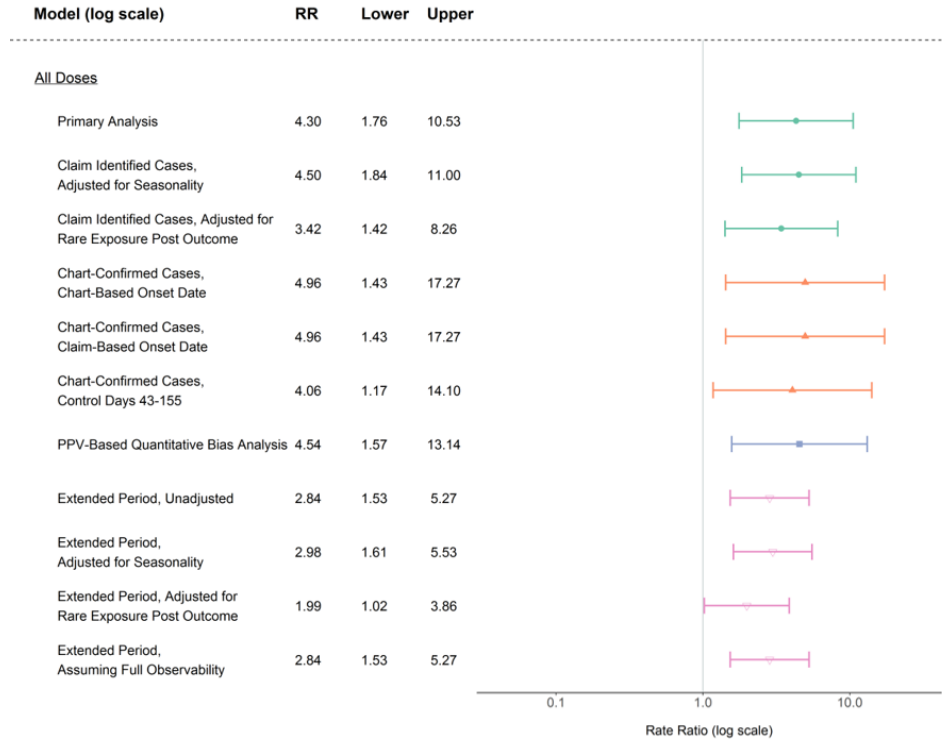
Model (log scale)	RR	Lower	Upper
Secondary Analysis	9.30	3.00	28.84
Claim Identified Cases, Adjusted for Seasonality	9.73	3.14	30.18
Chart-Confirmed Cases, Chart-Based Onset Date	7.06	1.80	27.71
Chart-Confirmed Cases, Claim-Based Onset Date	7.06	1.80	27.71
Chart-Confirmed Cases, Control Days 43-155	5.72	1.46	22.38
PPV-Based Quantitative Bias Analysis	8.22	2.39	28.30
Extended Period, Unadjusted	7.72	3.39	17.60
Extended Period, Adjusted for Seasonality	8.06	3.54	18.37

Second Dose Only

Model (log scale)	RR	Lower	Upper
Extended Period, Unadjusted	0.22	0.04	1.22
Extended Period, Adjusted for Seasonality	0.26	0.05	1.35

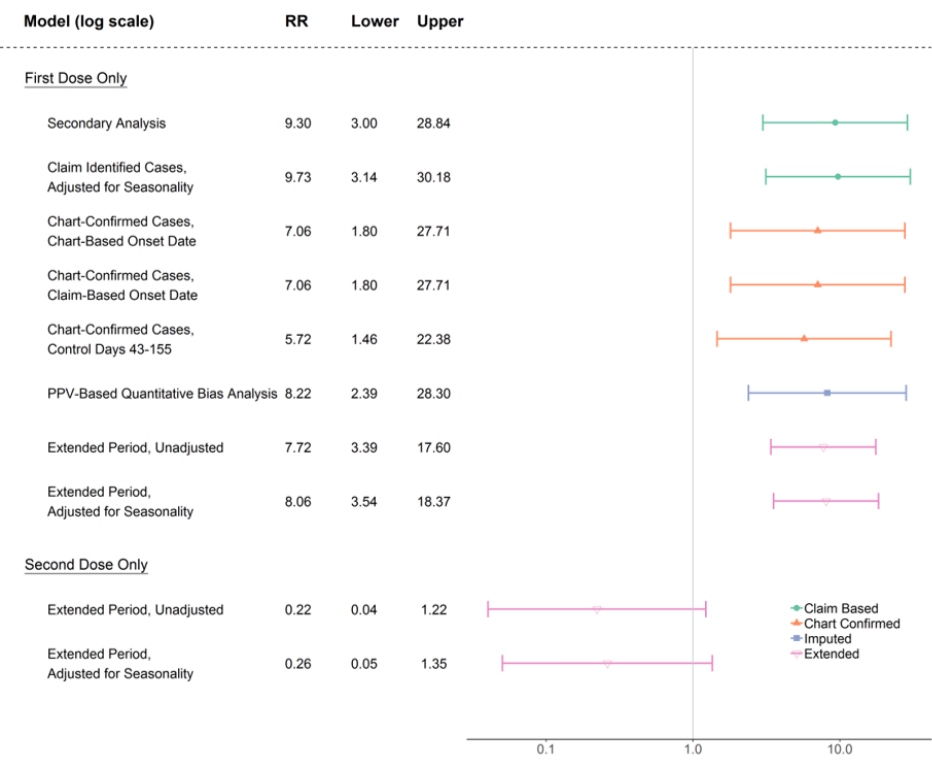


Forest Plot of Results



Forest Plot
for All Doses

Forest Plot by First and Second Dose



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