Evaluation of Guillain-Barré Syndrome (GBS) following Respiratory Syncytial Virus (RSV) Vaccination Among Adults 65 Years and Older

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MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)  
Respiratory Syncytial Virus (RSV) Vaccine, Adults  
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Outline

• Introduction
• Observed vs. Expected Analysis Summary
  ▪ Study Methods and Results
• Self-Controlled Case Series (SCCS) Analysis
  ▪ Study Methods and Results
• Discussion
• Conclusion
Introduction

• Two* RSV vaccines were approved for use in the U.S. in adults 60 years and older
  ▪ RSVPreF3+AS01 (GSK - AREXVY)
  ▪ RSVPreF (PFIZER - ABRYSVO)

• An imbalance in the rates of Guillain-Barré syndrome (GBS) between vaccine and placebo recipients was identified in clinical trials supporting licensure of RSV vaccines \(^1,^2\)

• FDA is conducting a post-licensure RSV vaccine safety study using two designs:
  ▪ Observed vs. Expected Analysis
  ▪ Self-Controlled Case Series (SCCS) Analysis

\(^*\)mRNA-1345 (Moderna - mRESVIA®) was approved on May 31, 2024.
Observed vs. Expected Analysis Summary

Methods

• Evaluated risk of GBS following one dose of either RSVPreF3+AS01 or RSVPreF vaccines using a retrospective cohort design with the 2022 historical comparator

• Estimated the observed incidence rates (IRs) and compared to historical comparator (expected) rates, to obtain incidence rate ratios (IRRs) with 95% confidence intervals (CIs)

• Estimation of GBS positive-predictive value (PPV)-adjusted rates is based on multiple imputed datasets
  ▪ Chart review, PPV for GBS: 71% (95% CI: 63%, 79%)
# Observed vs. Expected Analysis Summary

## Results

<table>
<thead>
<tr>
<th>Inferential Analysis Results</th>
<th>RSVPreF3+AS01</th>
<th>RSVPreF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed vs. Expected Analysis</td>
<td>2.76 (95% CI: 1.32, 5.07)</td>
<td>6.94 (95% CI: 3.70, 11.87)</td>
</tr>
<tr>
<td>PPV-Adjusted Analysis</td>
<td>2.75 (95% CI: 0.46, 5.04)</td>
<td>6.91 (95% CI: 1.85, 11.97)</td>
</tr>
<tr>
<td>GBS Cases per 1 million Doses</td>
<td>10.0</td>
<td>25.1</td>
</tr>
</tbody>
</table>

## Descriptive Analysis Results

| Total RSV Vaccine Doses                       | 2,061,602   |
| RSV Vaccine Doses                            | 1,379,335   | 682,267 |
| Observed GBS cases                           | <11         | 13      |

- An elevated IRR was observed for GBS following RSV vaccination
- Only RSVPreF association was statistically significantly elevated in PPV-adjusted analysis

Data Through Date: Dec 02, 2023
Motivation for SCCS Study

• The observed vs. expected analysis is a crude method with limited adjustments for confounding, utilizing aggregate historical incidence rates rather than individual historical persons as comparators, increasing the potential for confounding and bias.

• The SCCS is a robust method that controls for time-invariant confounding and does not rely on historical background incidence rates.
Self-Controlled Case Series (SCCS) Design

### Population Inclusion Criteria:
- Enrolled in Medicare Fee-for-Service (FFS) during the clean window
- 65 years of age or older on RSV vaccination date
- No GBS outcome during the clean window

### Population Exclusion Criteria:
- Beneficiaries with no incident GBS outcome in the observation period
  - OR
  - Beneficiaries who do not meet criteria to identify an incident outcome**

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*The clean window is relative to the outcome date; risk and control intervals are relative to the vaccination date
**Outcomes that are considered 'incident' after implementing the outcome-specific cleaning window are included, and only first incident outcome in the observation period are retained
# SCCS Analysis: Study Methods

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Self-Controlled Case Series (SCCS) ⁴, ⁵</th>
</tr>
</thead>
</table>
| **Data Sources and Study Population** | Centers for Medicare & Medicaid Services (CMS) Medicare Beneficiaries ages 65 years and older, enrolled in:  
- Medicare FFS (Parts A and B) and Part D on the date of RSV vaccination  
- Medicare FFS and in 1-year prior |
| **Study Period**     | May 2023* – April 2024**               |
| **GBS Outcome Definition** |  
- Risk Interval: 1 - 42 days  
- Control Interval: 43 - 90 days  
- Care Setting: inpatient – primary position only; ICD-10-CM DGN G61.0 |
| **Statistical Analyses** |  
- IRRs with 95% CIs  
- Absolute Risk: Attributable Risk (AR) with 95% CIs per 100,000 doses and 100,000 person-years (PY)  
- Adjustment for outcome-dependent observation time (Farrington) ⁶, seasonality, PPV |

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*FDA approval dates for RSVPreF3+AS01 and RSVPreF were May 3, 2023 and May 31, 2023, respectively  
*Study end date for initial SCCS analysis was April 6, 2024  
**RSV vaccinations prior to October 8, 2023 to have complete observation in 90 days post-vaccination and is expected to have 90% or greater data-completeness
SCCS Analysis: Vaccination Uptake Trends

Weekly Vaccination Uptake Trends in RSV Vaccines, By Vaccine Type

- RSVPreF
- RSVPreF3+AS01

Vaccination Cut-off Date to ensure complete observation of 90-day window

Data Through Date: Apr 06, 2024
### SCCS Analysis: Descriptive Results

**Case Counts for GBS following RSV vaccination by Vaccine Type**

<table>
<thead>
<tr>
<th>Case Population Eligibility Criteria</th>
<th>RSV Vaccinations (n=1.33 M individuals; 1.33 M doses)*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RSVPreF3+AS01 (n= ~872k doses)*</td>
<td>RSVPreF (n= ~456k doses)*</td>
</tr>
<tr>
<td>Total GBS cases and total number of days in study period</td>
<td>160 cases [339 days]</td>
<td>92 cases [311 days]</td>
</tr>
<tr>
<td>GBS cases during 90-day observation period</td>
<td>105</td>
<td>74</td>
</tr>
<tr>
<td>Incident GBS cases after applying clean window restriction</td>
<td>55</td>
<td>36</td>
</tr>
<tr>
<td>GBS cases qualifying for SCCS analysis (vaccinated before Oct 8, 2023)</td>
<td>11</td>
<td>17</td>
</tr>
</tbody>
</table>

* n = Medicare Beneficiaries that received RSV vaccination and eligible for SCCS analysis are presented

Data Through Date: Apr 06, 2024
SCCS Analysis: Results for GBS

IRR with 95% CI of GBS following RSV Vaccination Adjusted for Combinations of PPV, Seasonality with Outcome-Dependent Observation Time

<table>
<thead>
<tr>
<th>Analyses</th>
<th>RSVPreF3+ASH (IRR (95% CI))</th>
<th>RSVPreF (IRR (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV, Seasonality, Farrington</td>
<td>2.30 (0.39, 13.72)</td>
<td>4.48 (0.88, 22.90)</td>
</tr>
<tr>
<td>PPV, Farrington</td>
<td>2.04 (0.34, 12.11)</td>
<td>3.96 (0.77, 20.28)</td>
</tr>
<tr>
<td>Seasonality, Farrington</td>
<td>2.27 (0.66, 7.75)</td>
<td>4.27 (1.39, 13.14)</td>
</tr>
<tr>
<td>Farrington</td>
<td>2.01 (0.59, 6.85)</td>
<td>3.71 (1.21, 11.42)</td>
</tr>
</tbody>
</table>

- An elevated IRR was observed for GBS following RSVPreF vaccination with two analyses that had the least adjustments.
- Results additionally adjusted for PPV were no longer statistically significant:
  - PPV, Seasonality with Farrington-Adjusted Analysis: 4.48 (95% CI: 0.88, 22.90)
  - PPV, with Farrington-Adjusted Analysis: 3.96 (95% CI: 0.77, 20.28)
SCCS Analysis: Results for GBS and RSV vaccination

Inferential Analysis Results - Adjusted for PPV, Seasonality and Outcome-Dependent Observation Time

<table>
<thead>
<tr>
<th>Inferential Analysis Results</th>
<th>RSVPreF3+AS01</th>
<th>RSVPreF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible Vaccinees</td>
<td>872,068</td>
<td>456,107</td>
</tr>
<tr>
<td>Cases in the Risk and Control Intervals</td>
<td>&lt;11</td>
<td>12.1</td>
</tr>
<tr>
<td>IRR (95% CI)</td>
<td>2.30 (0.39, 13.72)</td>
<td>4.48 (0.88, 22.90)</td>
</tr>
<tr>
<td>AR per 100,000 Doses (95% CI)</td>
<td>0.32 (-0.30, 0.95)</td>
<td>1.57 (0.30, 2.85)</td>
</tr>
<tr>
<td>AR Per 100,000 PY (95% CI)</td>
<td>2.81 (-2.64, 8.26)</td>
<td>13.69 (2.59, 24.79)</td>
</tr>
</tbody>
</table>

Data Through Date: Apr 06, 2024
Discussion

Strengths

• SCCS study design provides robust adjustment for potential time-invariant confounding

• Large database facilitates more precise evaluation of health outcomes

• Study findings are generalizable to U.S. population 65 years and older

Limitations

• Potential outcome misclassification

• Potential misspecification of risk and control intervals

• Potential for residual confounding
Discussion

Observed vs. Expected Analysis

• An elevated IRR was observed for GBS following RSV vaccination, but only RSVPreF association was statistically significantly elevated PPV (chart review) adjustment

• Crude method that utilized aggregate historical comparator rates rather than individuals, increasing the potential for confounding

• Statistically significant results of GBS do not establish a causal association between RSV vaccines and GBS
Discussion

SCCS Analysis

• Although, an elevated IRR was observed for GBS following RSVPreF vaccination for two analyses that had fewer adjustments, the results were not statistically significant when adjusted for PPV.

• Only cases, i.e., persons with an incident outcome contribute to the SCCS analysis.

• Estimation of outcome risk occurs within, rather than between individuals, adjusting for time-invariant confounding.
Conclusion

• The results from two different types of analyses of potential GBS risk following RSV vaccination are mixed and highly uncertain.

• These analyses do not provide clear, conclusive evidence of an elevated risk of GBS and an elevated risk cannot be ruled out at this time.

• FDA is conducting medical chart review on GBS cases and will continue to evaluate the safety of RSV vaccines as more data are available.

• FDA maintains that the benefits of RSV vaccination in preventing RSV hospitalizations outweigh the potential risks associated with the vaccines.
References


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Questions?