

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
- Presentation of End-of-Season SCCS Analysis Results and Comparison to Early-Season Results
- Discussion
- Conclusions

Introduction



- Three RSV vaccines were approved for use in the U.S. in adults 60 years and older
 - RSVPreF3+AS01 (GSK – AREXVY®) – May 3, 2023
 - RSVPreF (Pfizer – ABRYSVO®) – May 31, 2023
 - mRNA-1345 (Moderna – mRESVIA®) – May 31, 2024*
- Pre-licensure clinical trials identified a small number of GBS cases in RSVPreF3+AS01 and RSVPreF vaccines
- Reports submitted to Vaccine Adverse Events Reporting System (VAERS) identified higher GBS rates post-RSVPreF3+AS01 and RSVPreF vaccination than expected background rates

* The analyses described in this presentation included vaccinations through Jan 2024, which was prior to the approval of mRNA-1345 vaccine



RSV Vaccine Post-Market Analyses

- Post-market analyses* to assess the safety of RSV vaccines among Medicare Fee-for-Service (FFS) beneficiaries ages 65 and older

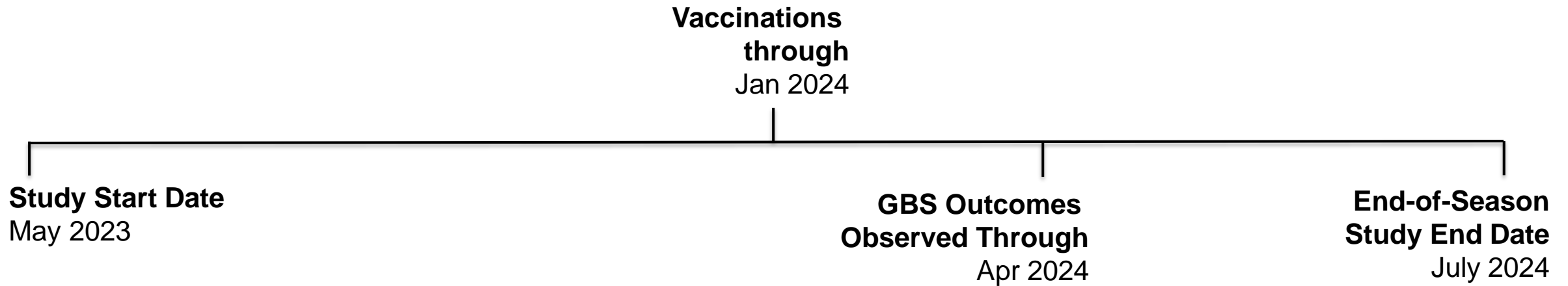
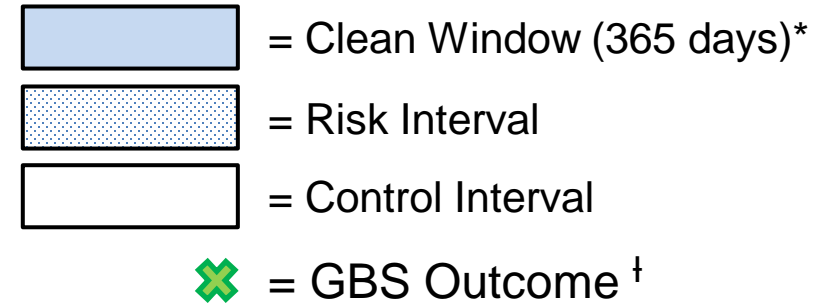
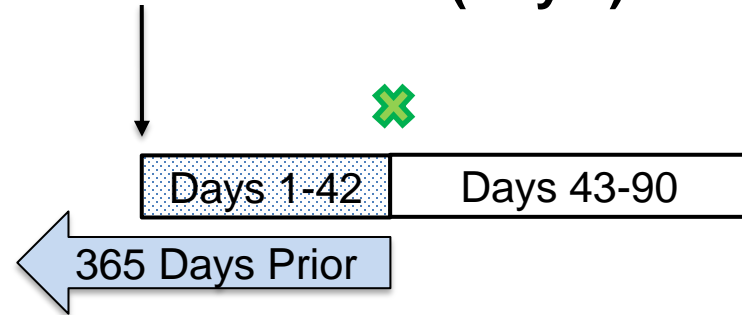
Analyses	Includes Vaccines Administered Through	Data Through Date	Number of Doses		Number GBS Cases
			RSV PreF3+AS01	RSVPreF	
Early-Season SCCS	October 22, 2023	April 6, 2024	872,068	456,107	28
End-of-Season SCCS	January 28, 2024	July 13, 2024	2,202,247	1,024,442	95

* The analyses described in this presentation included vaccinations through Jan 2024, which was prior to the approval of mRNA-1345 vaccine.

Self-Controlled Case Series (SCCS) Design



RSV Vaccination (Day 0)



* The clean window is relative to the outcome date; risk and control intervals are relative to the vaccination date

† Incident GBS identified in inpatient – primary position only; ICD-10-CM DGN G61.0

SCCS Analysis: Study Methods



Study Design	Self-Controlled Case Series (SCCS)
Data Sources /Study Population	<ul style="list-style-type: none"> • Medicare Fee-for-Service (FFS) (Parts A, B and D) beneficiaries aged 65 years and older • Enrolled on date of first observed RSV vaccination and during 1-year prior to vaccination • Incident GBS case during the observation period (i.e., no GBS event in the clean window) • Vaccinated with either RSVPreF3+AS01 or RSVPreF prior to Jan 28, 2024
Study Period	May 2023 – Jul 2024
GBS Outcome Definition	<ul style="list-style-type: none"> • Risk Interval: 1 - 42 days • Control Interval: 43 - 90 days • Care Setting: inpatient – primary position only; ICD-10-CM DGN G61.0
Statistical Analyses	<ul style="list-style-type: none"> • Incidence Rate Ratios (IRR) • Absolute Risk: Attributable Risk (AR) per 100,000 doses and 100,000 person-years (PY) • Adjustment for outcome-dependent observation time (Farrington), seasonality, PPV • Chart-confirmed analysis with Farrington and seasonality adjustments • Secondary analyses: IRR, AR stratified by same day concomitant vaccination with 2023-2024 COVID-19, 2023-2024 influenza, pneumococcal, and shingles vaccines

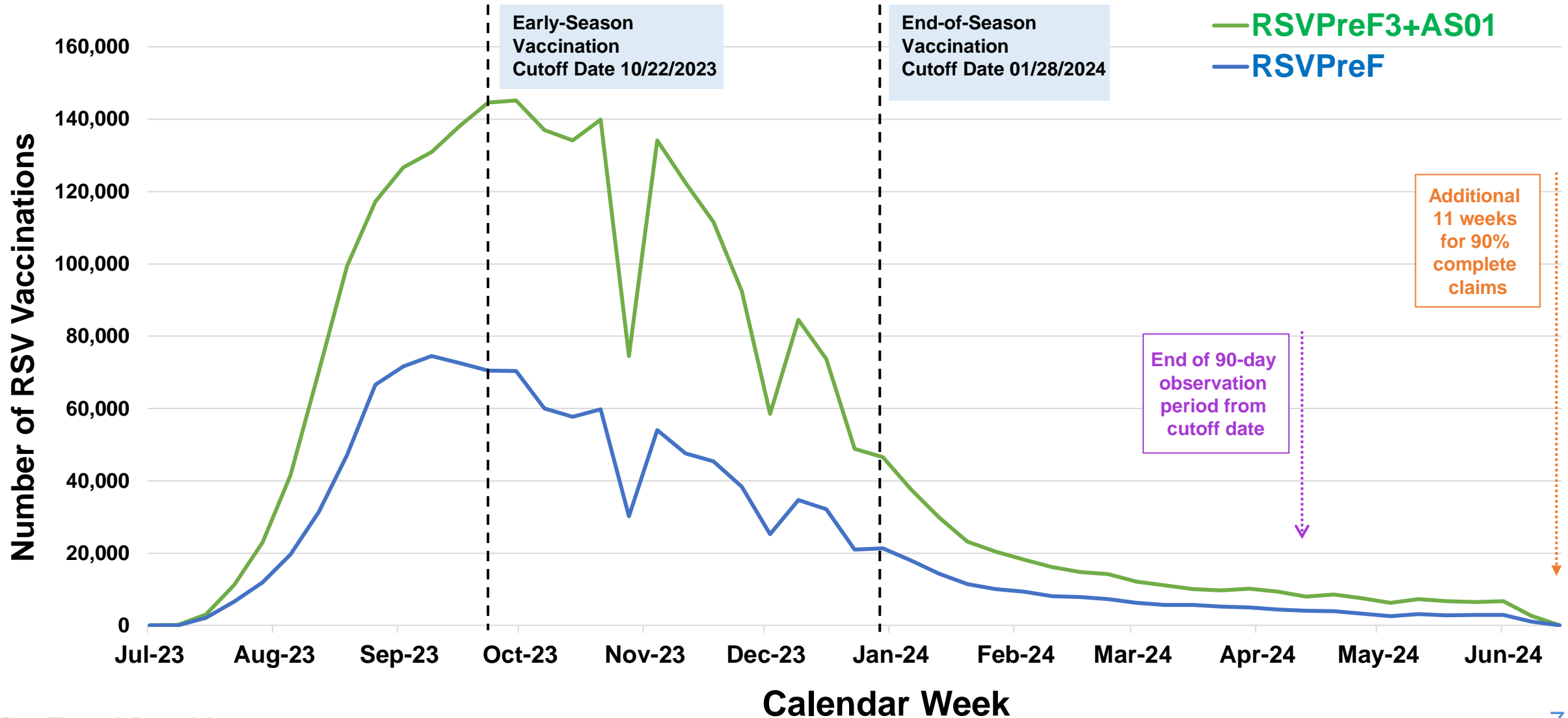
Study end date for End of Season SCCS analysis was July 13, 2024

Note: RSV vaccinations observed prior to Jan 28, 2024 were needed for 90% complete observation in 90 days post vaccination

End-of-Season SCCS Analysis



Weekly Uptake Trends in for RSVPreF3+AS01 and RSVPreF Vaccines



Data Through Date: July 13, 2024

SCCS Analysis: Descriptive Results



Case Counts for GBS following RSV vaccination by Vaccine Type

Case Population Eligibility Criteria	Early-Season SCCS Analysis		End-of-Season SCCS Analysis	
	RSV Vaccinations (n = 1.3 M doses)*		RSV Vaccinations (n = 3.2 M doses)*	
	RSVPreF3+AS01 (n = ~872k doses)*	RSVPreF (n = ~456k doses)*	RSVPreF3+AS01 (n = 2.2 M doses)*	RSVPreF (n = 1.0 M doses)*
Total GBS cases [total number of days in study period]	160 [339 days]	92 [311 days]	236 [437 days]	130 [409 days]
GBS cases during 90-day observation period	105	74	119	89
Incident GBS cases after applying clean window restriction	55	36	<70	<50
GBS cases qualifying for SCCS analyses	11	17	56	39

*n = Medicare beneficiaries that received one RSV vaccination and eligible for early- and end-of-season SCCS analysis are presented. Product-specific and total dose counts may not equal due to rounding

† Cell suppressed to protect patient confidentiality

Early-Season Data Through Date: April 6, 2024

End-of-Season Data Through Date: July 13, 2024



GBS Medical Record Review (MRR) Results

Case Classification of GBS Medical Records

GBS MRR	Overall
Total GBS Cases and Records Requested	95
Records Received and Adjudicated	75
Chart-Confirmed GBS Cases* (Level 1, Level 2, Level 3)	51
Insufficient Evidence or Not a Case* (Level 4, Level 5)	24
Records Not Returned	20

* Medical records were adjudicated per the Brighton Collaboration clinical case definition for GBS

Positive Predictive Value (PPV) of GBS

Category	PPV** with 95% Confidence Interval (CI)
Overall	68.0% (56.8%, 77.5%)
Risk Interval	62.3% (48.8%, 74.1%)
Control Interval	81.8% (61.5%, 92.7%)

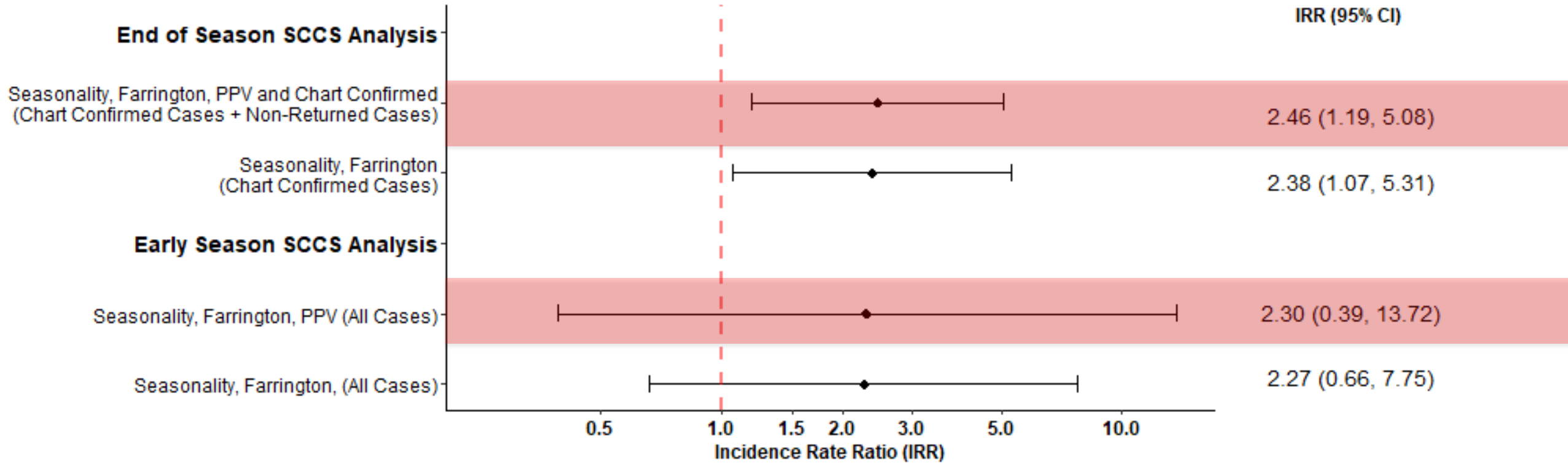
** PPV calculations include all GBS case records assigned a case classification based on the MRR in the denominator



Comparison of Early vs. End of Season Results

GBS and **RSVPreF3+AS01**

Incidence Rate Ratio (IRR) with 95% Confidence Intervals (95% CI)



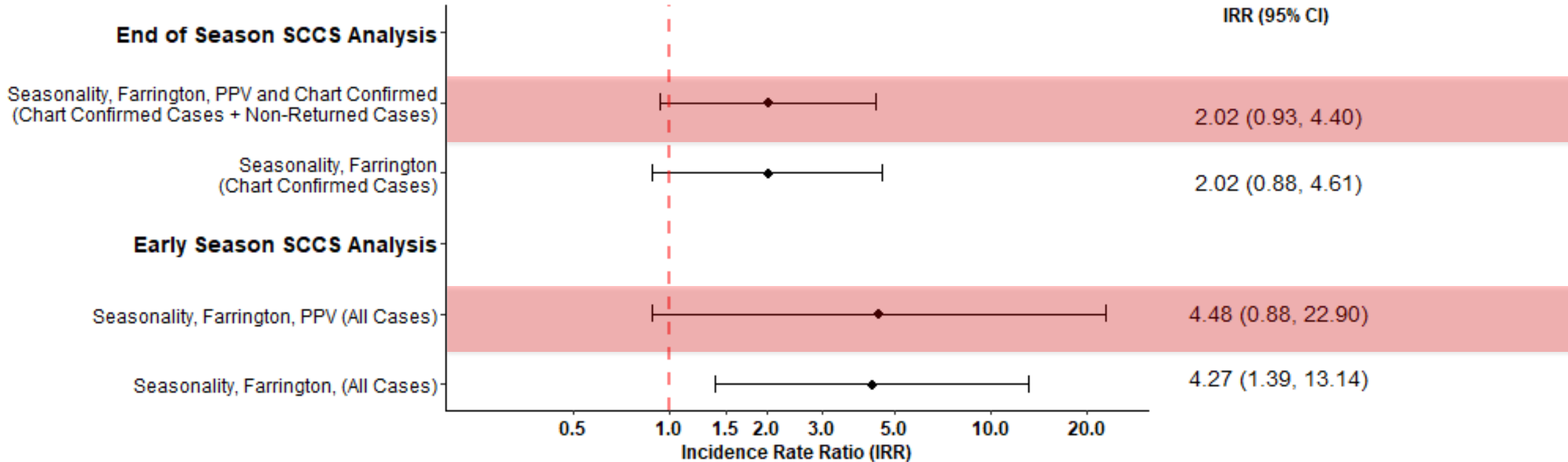
A statistically significant elevation in GBS risk was observed with seasonality, Farrington, PPV adjusted analysis that included chart-confirmed and non-returned cases:

RSVPreF3+AS01
2.46 (95% CI: 1.19, 5.08)

Comparison of Early vs. End of Season Results

GBS and RSVPreF

IRR with 95% CI



An elevated but non-statistically significant IRR was observed for GBS with seasonality, Farrington, PPV adjusted analysis that included chart-confirmed and non-returned cases:

RSVPreF
2.02 (95% CI: 0.93, 4.40)



End-of-Season SCCS Results: GBS and RSV Vaccination

IRR and Attributable Risk (AR)

Seasonality, Farrington Analysis, and PPV-Based Multiple Imputation – Chart Confirmed + Not Returned Cases

Inferential Analysis Results	RSVPreF3+AS01	RSVPreF
Eligible Vaccines	2,202,247	1,024,442
*Cases in the Risk Interval	24	18
*Cases in the Control Interval	11	<11
IRR (95% CI)	2.46 (1.19, 5.08)	2.02 (0.93, 4.40)
AR per 100,000 Doses (95% CI)	0.65 (0.18, 1.12)	0.90 (-0.02, 1.81)
AR Per 100,000 PY (95% CI)	5.71 (1.61, 9.80)	7.82 (-0.17, 15.81)

**Cases in risk and control intervals are the average number of true cases in the multiple imputation process
Small cell sizes <11; suppressed to protect patient confidentiality*

PY = Person-Years



End-of-Season Descriptive Results: Concomitant Vaccination among GBS Cases

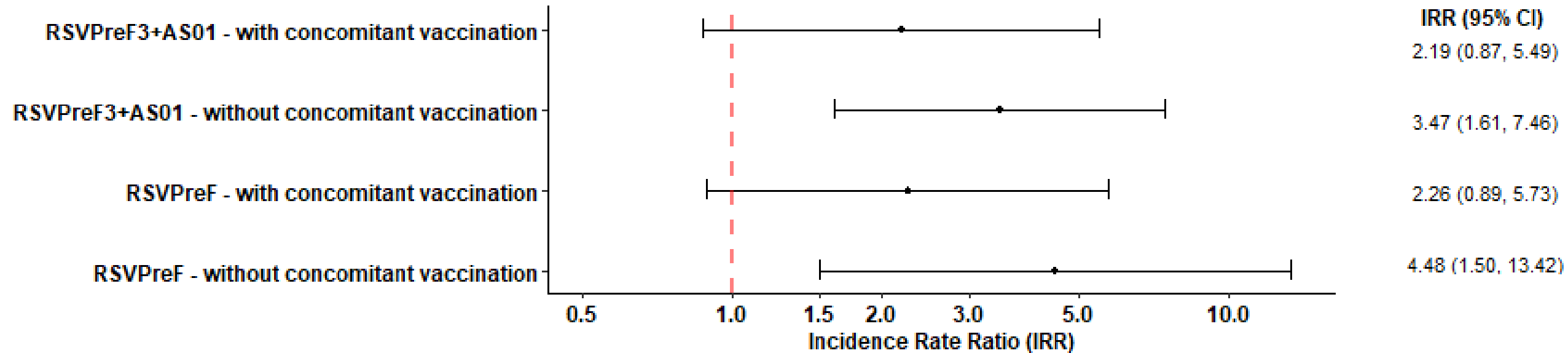
	RSVPreF3+AS01	RSVPreF
Eligible Vaccines	2,202,247	1,024,442
Total GBS Cases	56	39
Number (%) with any concomitant vaccination	20 (35.7%)	19 (48.7%)

Concomitant vaccination is defined as vaccination on the same day as RSV vaccination with at least one of 2023-2024 COVID-19, 2023-2024 influenza, pneumococcal, and shingles vaccines.



Secondary End-of-Season SCCS Results: GBS risk by vaccine type and concomitant vaccination IRR and 95% CI

Seasonality and Farrington Adjusted Analysis, All Cases



There was no evidence of difference in GBS risk among persons with and without same day concomitant vaccination with RSV vaccines



Secondary End-of-Season SCCS Results:

Concomitant Vaccination among GBS cases vaccinated with **RSVPreF3+AS01** – IRR and AR

Seasonality and Farrington Adjusted Analysis

Inferential Analysis Results	With Concomitant Vaccination	Without Concomitant Vaccination
Eligible Vaccines	833,067	1,369,180
Cases in the Risk Interval	<15	<30
Cases in the Control Interval	<11	<11
IRR (95% CI)	2.19 (0.87, 5.49)	3.47 (1.61, 7.46)
AR per 100,000 Doses (95% CI)	0.85 (-0.09, 1.79)	1.40 (0.72, 2.09)
AR Per 100,000 PY* (95% CI)	7.40 (-0.79, 15.59)	12.27 (6.26, 18.28)

Small cell sizes <11; suppressed to protect patient confidentiality

*PY = Person-Years



Secondary End-of-Season SCCS Results:

Concomitant Vaccination among GBS cases vaccinated with **RSVPreF** – IRR and AR

Seasonality and Farrington Adjusted Analysis

Inferential Analysis Results	With Concomitant Vaccination	Without Concomitant Vaccination
Eligible Vaccines	420,764	603,678
Cases in the Risk Interval	<15	<20
Cases in the Control Interval	<11	<11
IRR (95% CI)	2.26 (0.89, 5.73)	4.48 (1.50, 13.42)
AR per 100,000 Doses (95% CI)	1.59 (-0.18, 3.35)	2.06 (0.99, 3.12)
AR Per 100,000 PY* (95% CI)	13.85 (-1.55, 29.25)	18.01 (8.70, 27.31)

Small cell sizes <11; suppressed to protect patient confidentiality

*PY = Person-Years

SCCS Design: Strengths and Limitations



Strengths

- SCCS study design provides robust adjustment for potential time-invariant confounding
- Large database facilitates more precise evaluation of GBS
- Study findings are generalizable to U.S. population 65 years and older
- Medical Record Review improved classification of GBS

Limitations

- Potential misclassification of GBS in administrative claims data
- The study is not intended to compare GBS risk between the two vaccine products
- IRR estimates may be sensitive to the number of records returned and adjudicated through MRR
- Potential misspecification of post-RSV vaccination risk and control intervals for GBS
- Potential for residual confounding
- Attributable risk based on small number of cases may be difficult to interpret

Discussion

- **Observed vs. Expected Analysis**

- An elevated risk of GBS was observed following both RSV vaccines
- Results were not statistically significant for RSVPreF3+AS01 when adjusting for PPV

- **Early-Season SCCS**

- Statistically significant elevation in GBS risk was observed following RSVPreF vaccine
- Results did not remain statistically significant for RSVPreF vaccine when adjusting for PPV-based multiple imputations

- **End-of-Season SCCS**

- A statistically significant elevated IRR was observed for GBS following vaccination with RSVPreF3+AS01; GBS risk was elevated yet not statistically significant following RSVPreF vaccination
- Results remained the same when restricting to confirmed GBS cases through MRR
- There was no evidence of difference in GBS risk among persons with and without same day concomitant vaccination with RSV vaccines

Conclusions



- Our findings suggest an increased GBS risk following RSVPreF3+AS01 and RSVPreF among adults aged 65 years and older
- These results are consistent with pre-licensure clinical trials and surveillance systems such as VAERS
- End-of-season SCCS analyses results are largely chart-confirmed from MRR and include approximately three times more vaccine doses and GBS cases compared to the early season SCCS results
- GBS risk following vaccination with RSVPreF3+AS01 and RSVPreF is rare, with less than 10 cases per 1 million vaccinations
- There is no difference in GBS risk among persons with and without same day concomitant vaccination with RSV vaccines

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