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

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Outline

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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%) [3]

Observed vs. Expected Analysis Summary

Results

	RSVPreF3+AS01	RSVPreF
Inferential Analysis Results		
Observed vs. Expected Analysis	**2.76 (95% CI: 1.32, 5.07)**	**6.94 (95% CI: 3.70, 11.87)**
PPV-Adjusted Analysis	2.75 (95% CI: 0.46, 5.04)	**6.91 (95% CI: 1.85, 11.97)**
GBS Cases per 1 million Doses	10.0	25.1
Descriptive Analysis Results		
Total RSV Vaccine Doses	**2,061,602**	
RSV Vaccine Doses	1,379,335	682,267
Observed GBS cases	<11	13

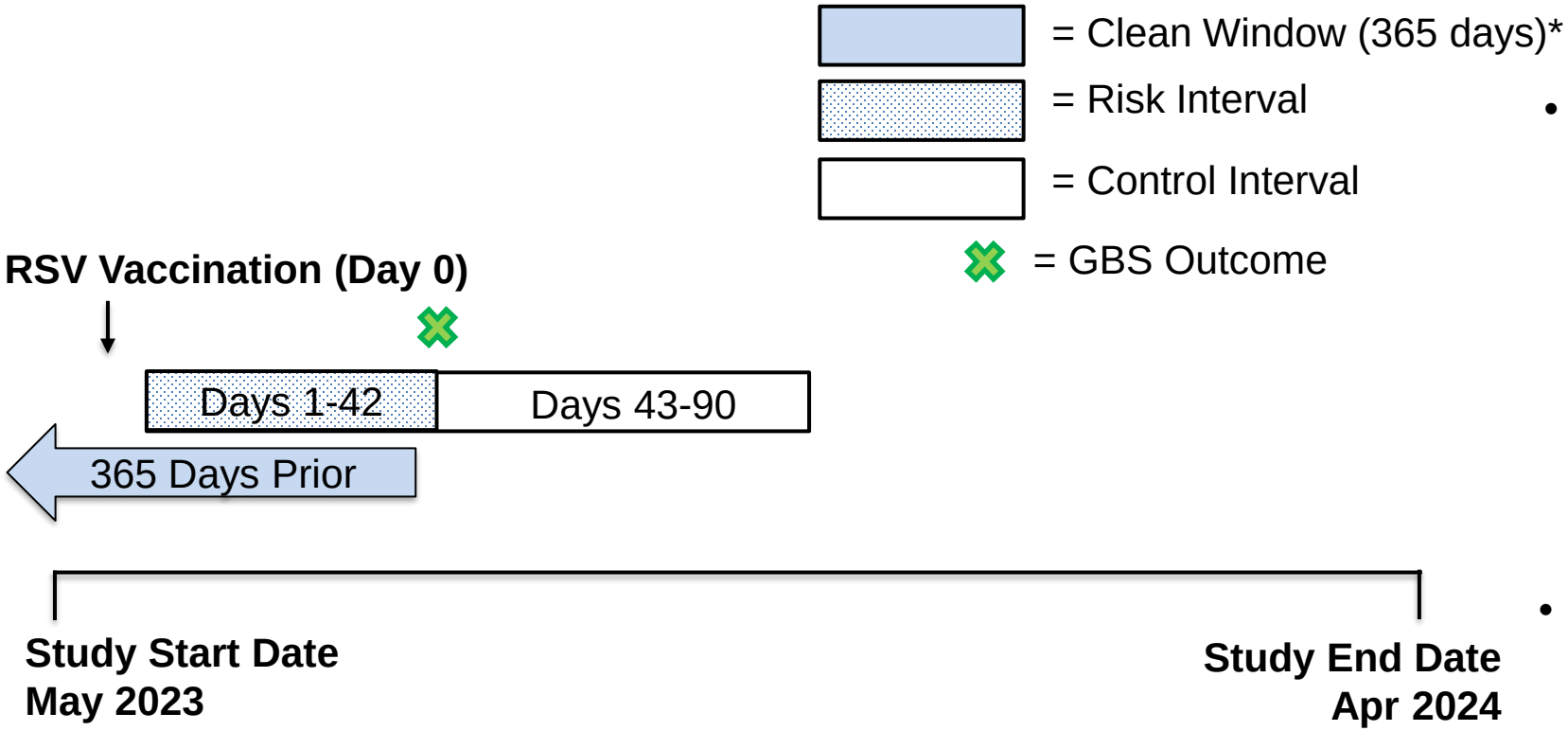
- **An elevated IRR was observed for GBS following RSV vaccination**
- **Only RSVPreF association was statistically significantly elevated in PPV-adjusted analysis**

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



- **<u>Population Inclusion Criteria:</u>**
  - 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
- **<u>Population Exclusion Criteria:</u>**
  - Beneficiaries with no incident GBS outcome in the observation period

  OR
  - Beneficiaries who do not meet criteria to identify an incident outcome**

**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

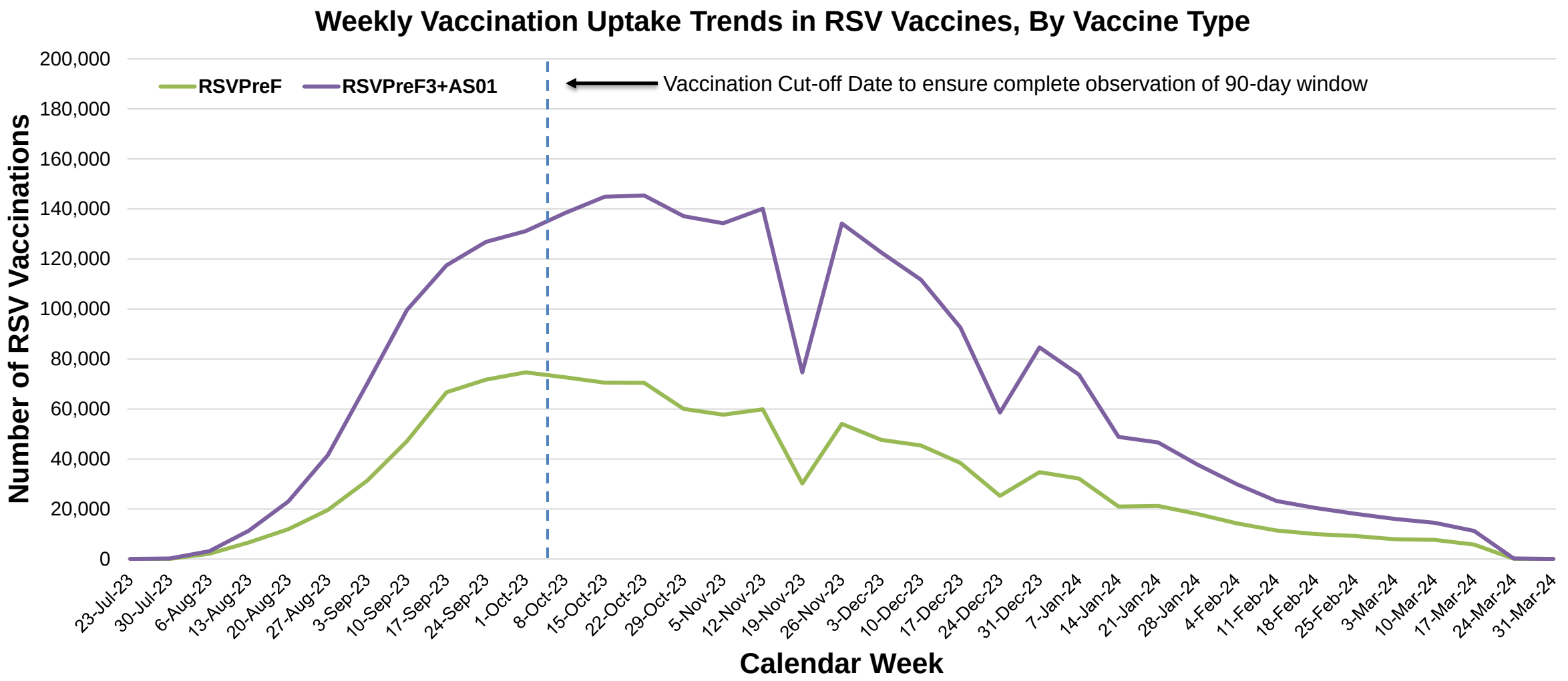
Study Design	Self-Controlled Case Series (SCCS) [4, 5]
Data Sources and Study Population	Centers for Medicare & Medicaid Services (CMS) Medicare Beneficiaries ages 65 years and older, enrolled in: ▪ Medicare FFS (Parts A and B) and Part D on the date of RSV vaccination ▪ Medicare FFS and in 1-year prior
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

**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



Data Through Date: Apr 06, 2024

SCCS Analysis: Descriptive Results

Case Counts for GBS following RSV vaccination by Vaccine Type

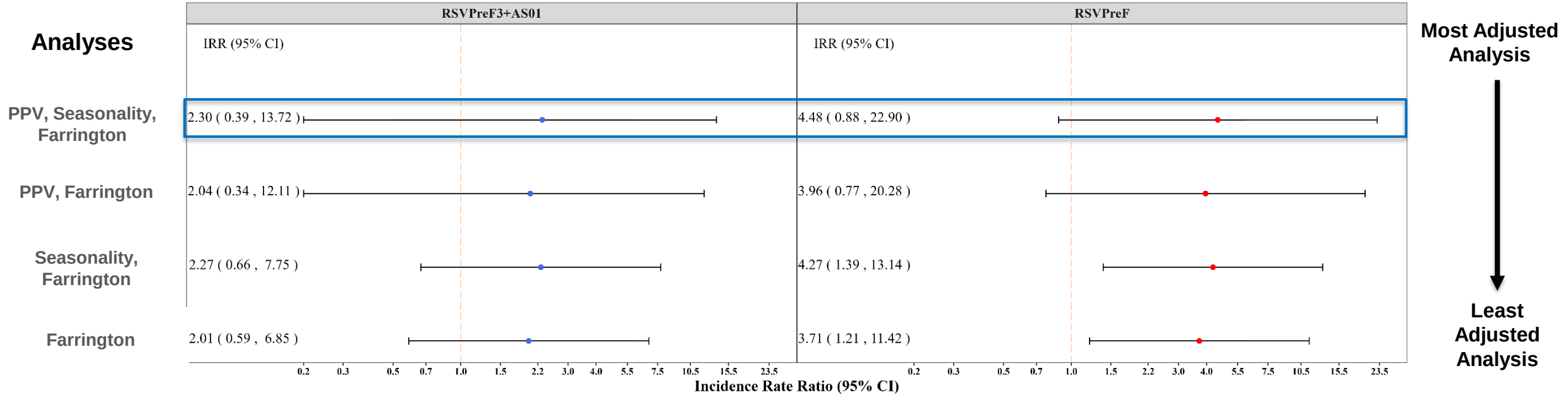
Case Population Eligibility Criteria	RSV Vaccinations (n=1.33 M individuals; 1.33 M doses)*	
	RSVPreF3+AS01 (n= ~872k doses)*	**RSVPreF (n= ~456k doses)***
Total GBS cases and total number of days in study period	160 cases [339 days]	92 cases [311 days]
GBS cases during 90-day observation period	105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

** 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



- 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)**

Data Through Date: Apr 06, 2024

SCCS Analysis including most adjustments are highlighted in Blue
Farrington-Adjusted Analysis = Outcome-Dependent Observation Time Adjustment

SCCS Analysis: Results for GBS and RSV vaccination

Incidence Rate Ratio (IRR) and Attributable Risk (AR) of GBS - Adjusted for PPV, Seasonality and Outcome-Dependent Observation Time

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

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?