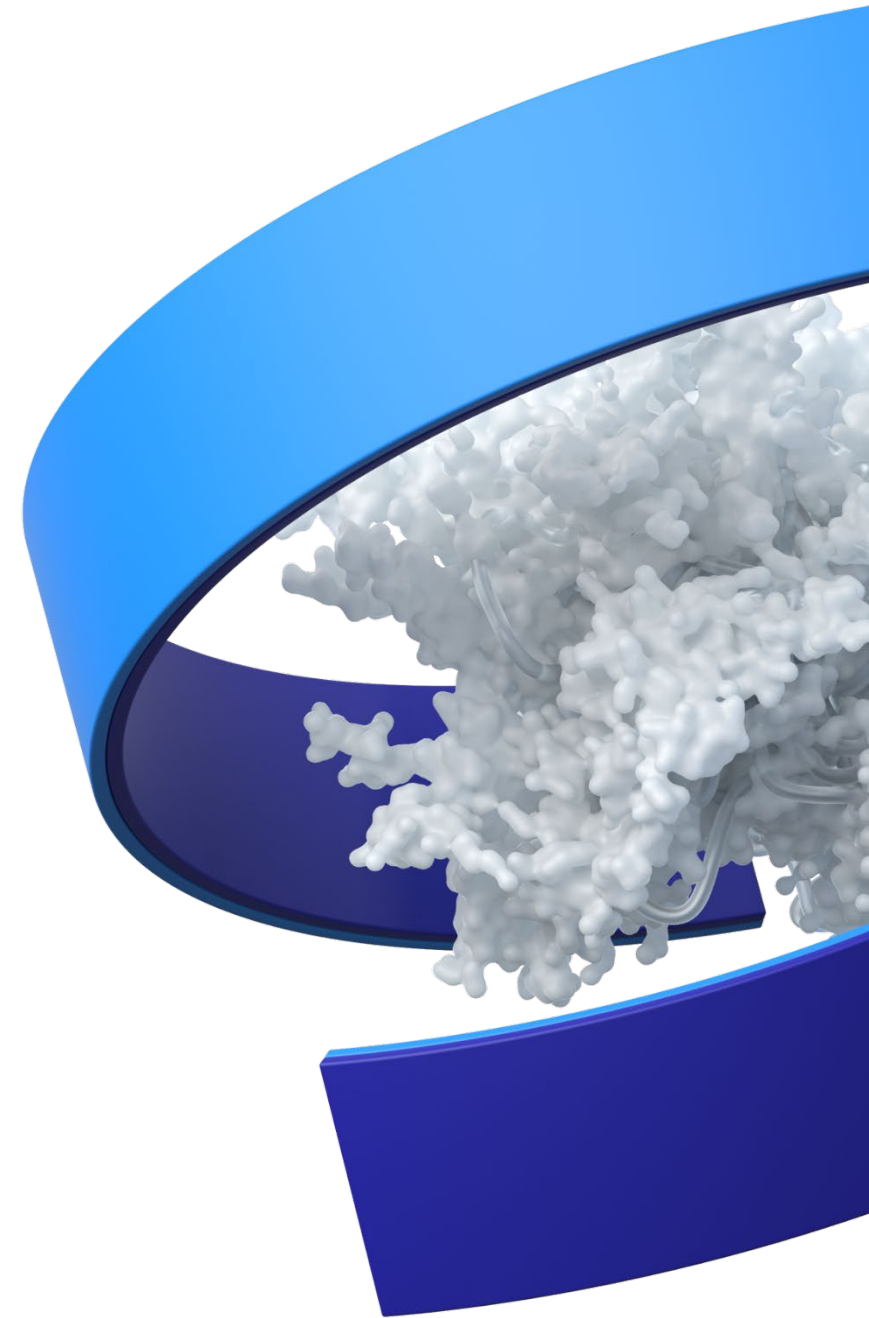


Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: [ocod@fda.hhs.gov](mailto:ocod@fda.hhs.gov) and include 508 Accommodation and the title of the document in the subject line of your e-mail.

# Bivalent RSV Prefusion F Vaccine for Maternal Immunization to Protect Infants

Vaccines and Related Biological  
Products Advisory Committee

May 18, 2023





# **RSV Disease and Pfizer's RSVpreF Vaccine**

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**Bill Gruber, MD, FAAP, FIDSA, FPIDS**

Senior Vice President Vaccine Clinical R&D  
Pfizer

# Presentation Agenda

## Introduction



**William Gruber, MD**

## Unmet Medical Need



**Eric Simões, MB, BS, DCH, MD**  
Professor of Pediatrics and Epidemiology

## Clinical Development Plan



- Clinical Safety
- Pivotal Trial Efficacy

**Iona Munjal, MD**  
Senior Director, Pfizer Vaccines

## Pharmacovigilance & Surveillance



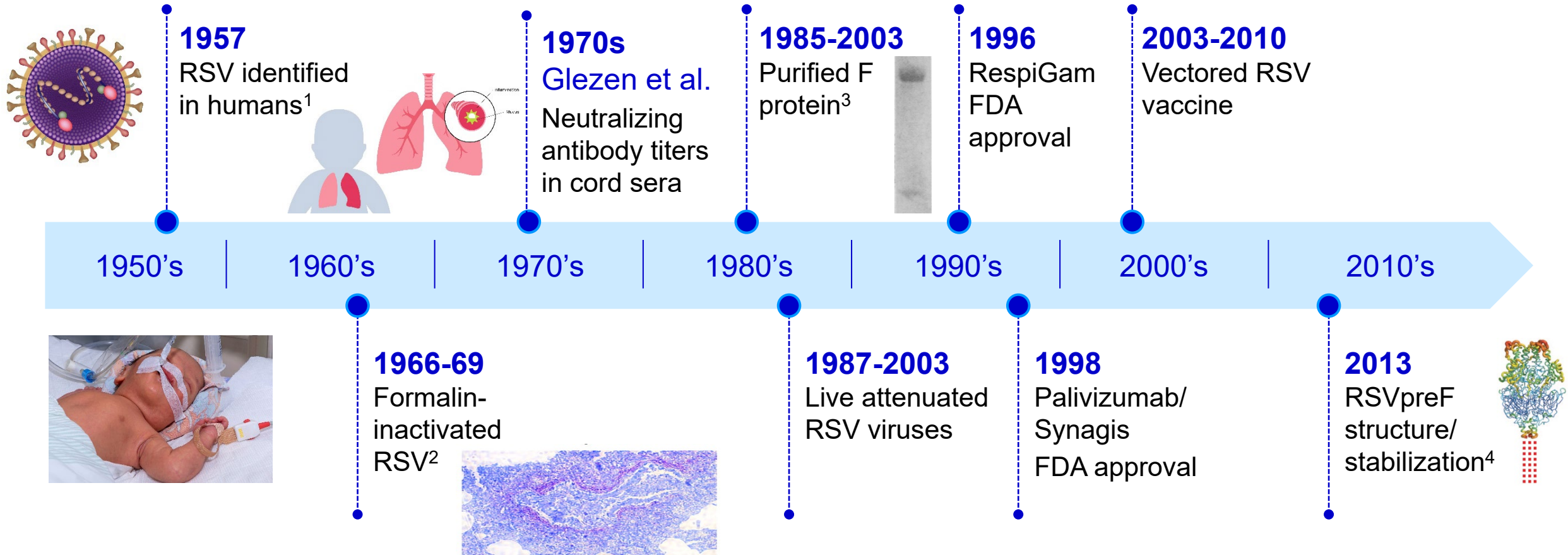
**Jamie Wilkins, PharmD**  
Senior Director, Worldwide Safety

## Benefit-Risk & Conclusions



**William Gruber, MD**

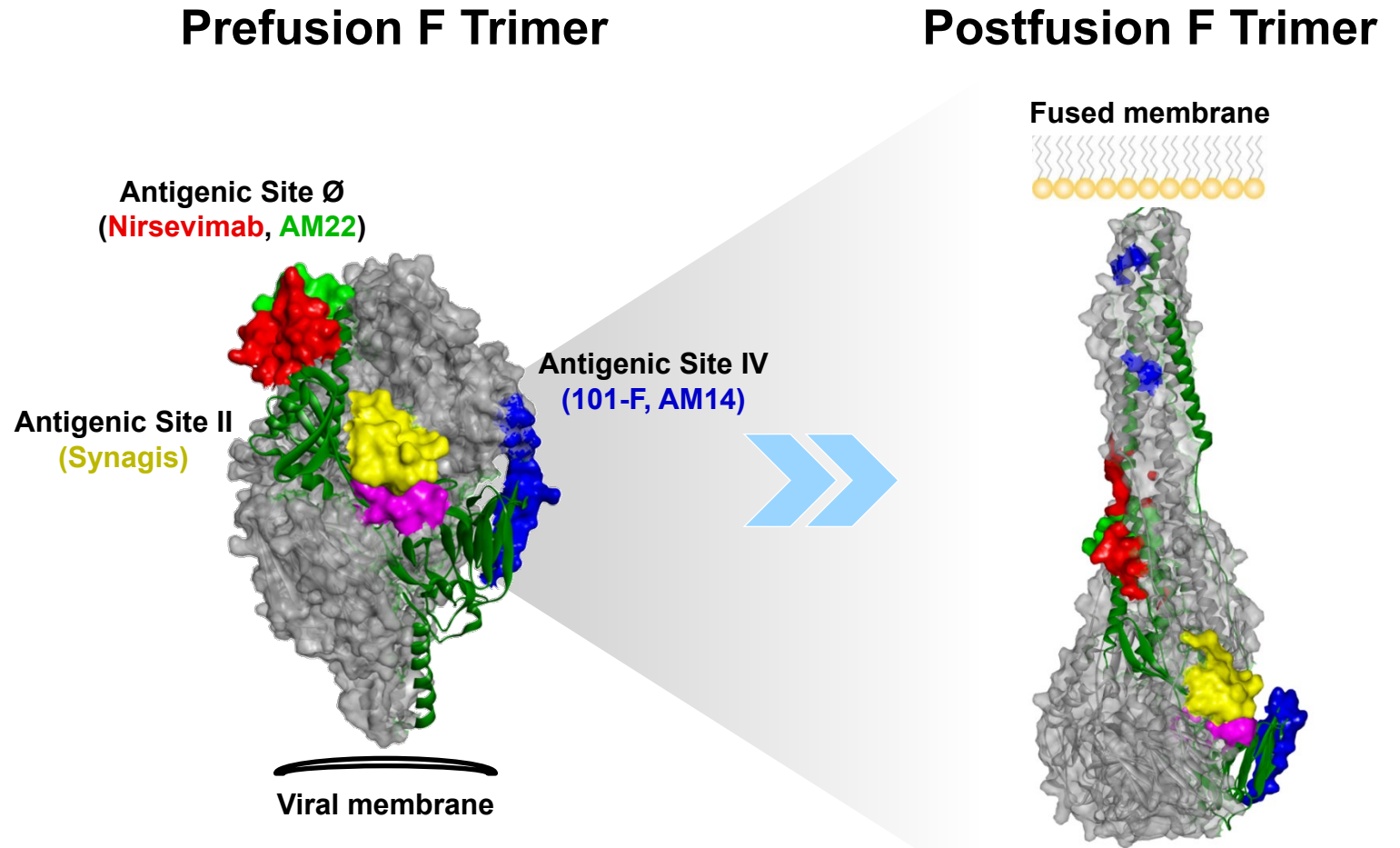
# Key Milestones in RSV Vaccine and Monoclonal Antibody Research and Development



# Structural Work by NIH Elucidated that RSV F on the Virus Exists as an Unstable Prefusion Form

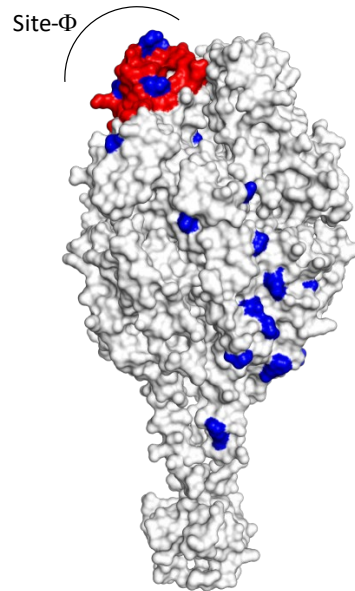
**ONLY Prefusion F can bind host cells for RSV to infect**

**Antibodies specific to the prefusion form are most effective at blocking virus infection**



# Rationale for Bivalent Stabilized RSV Prefusion F Vaccine

**RSV F subgroup A and B amino acid sequence differences (shown in blue) cluster in prefusion-specific sites**



Balanced neutralizing responses against both RSV A and RSV B observed with bivalent prefusion F-based vaccine in contrast with other monovalent investigational RSV prefusion F-based vaccines

**Ontario (RSV A) and Buenos Aires (RSV B) remain dominant genotypes and are the basis of Pfizer's RSVpreF bivalent vaccine**

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**RSV subgroup dominance can vary over time**

---

**Both subgroup viruses are associated with severe disease**

# RSVpreF to Address a Significant Unmet Medical Need



Leading cause  
of **LRTI** among  
infants globally

**50-80%**  
Hospitalizations for  
viral bronchiolitis<sup>1,2</sup>



## **MATISSE Study**

Highly Efficacious **against severe LRTI**

EFFICACY:

**82%**  
3 months

**69%**  
6 months

Efficacy also  
observed for less  
severe disease and  
against RSV A and B



**Well tolerated** in the pregnant  
population and in their infants with  
a **satisfactory safety profile**



# Bivalent RSV Prefusion F Vaccine

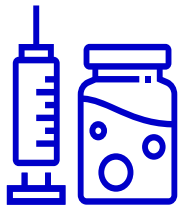
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## Proposed Indication

***Prevention of lower respiratory tract disease and severe lower respiratory tract disease caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age by active immunization of pregnant individuals.***

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- 120 µg without an adjuvant
- Stored at 2-8 °C
- Single dose vial + Pre-filled syringe
- 0.5 mL injection

# Burden of RSV in US Infants

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**Eric A.F. Simões, MB,BS, DCH, MD**

Professor of Pediatrics and Epidemiology,  
University of Colorado, Denver  
Colorado School of Public Health

# Conflicts of Interest

## Last 36 Months

Entity	Grant Support	Consultant		Travel	Other
	To Institution	Gratis	Fees Paid to Institution		DSMB, Study Section, etc.
<b>Nonpharmaceutical</b>					
Bill & Melinda Gates Foundation	X	X		X	X
US Centers for Disease Control and Prevention		X		X	
National Institutes of Health	X			X	X
United States Agency for International Development	X	X		X	
World Health Organization		X		X	
<b>Pharmaceutical</b>					
AbbVie Inc			X		X
Abbott Diagnostics			X		
AstraZeneca	X			X	
GSK plc			X		X
Johnson & Johnson	X		X		
Merck & Co, Inc	X				
Novavax	X				
Pfizer	X		X	X	
Regeneron	X				
Roche	X			X	
Sanofi		X			

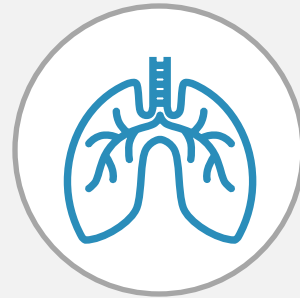
# RSV Burden of Disease in Children



**Leading cause of  
LRTI among infants  
globally<sup>1</sup>**  
**(50-80% of all  
hospitalizations for  
viral bronchiolitis)<sup>2</sup>**



**Historically,  
temperate climates  
have experienced  
seasonal  
outbreaks<sup>3</sup>**



**Infection  
can lead to  
respiratory distress  
and death<sup>4</sup>**

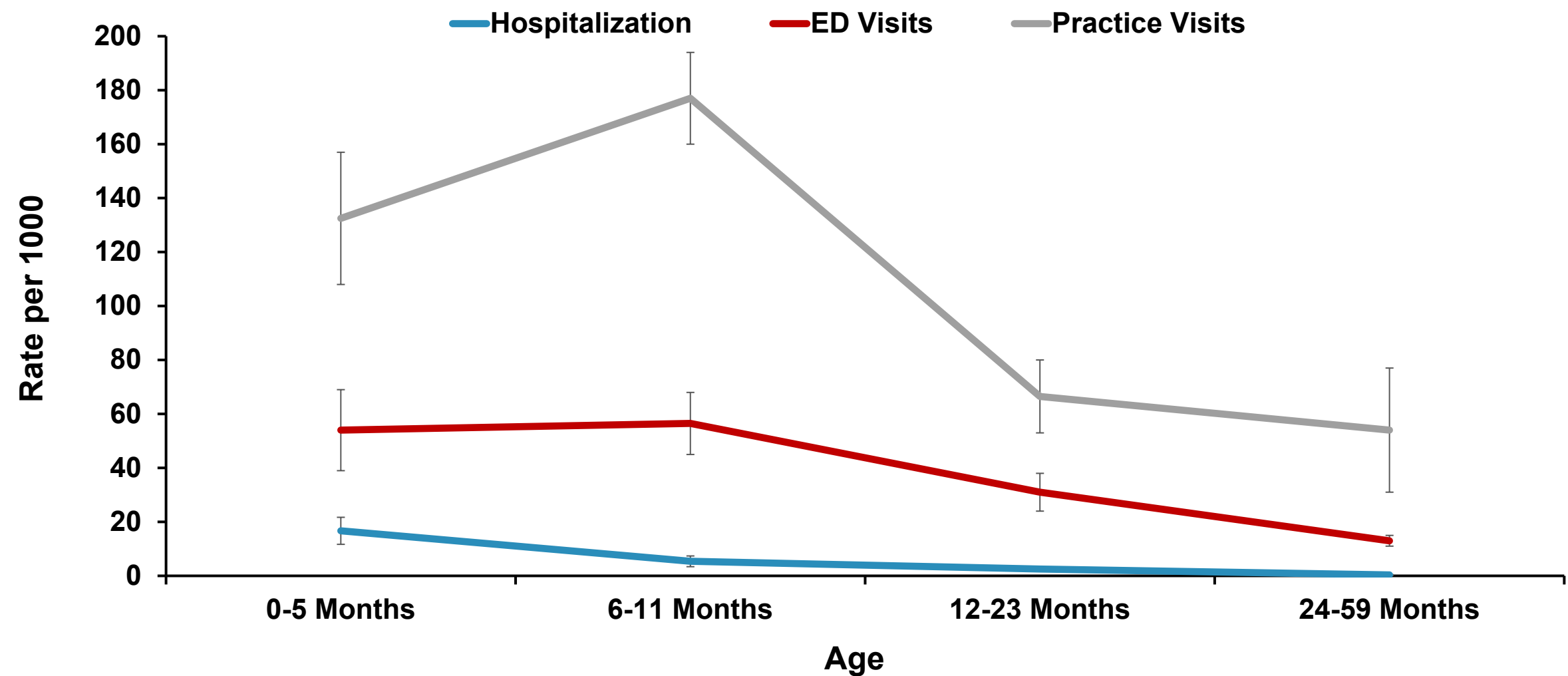


**Globally,  
RSV sickens  
33 million children  
<5 years and  
6.6 million infants  
<6 months each  
year<sup>5</sup>**



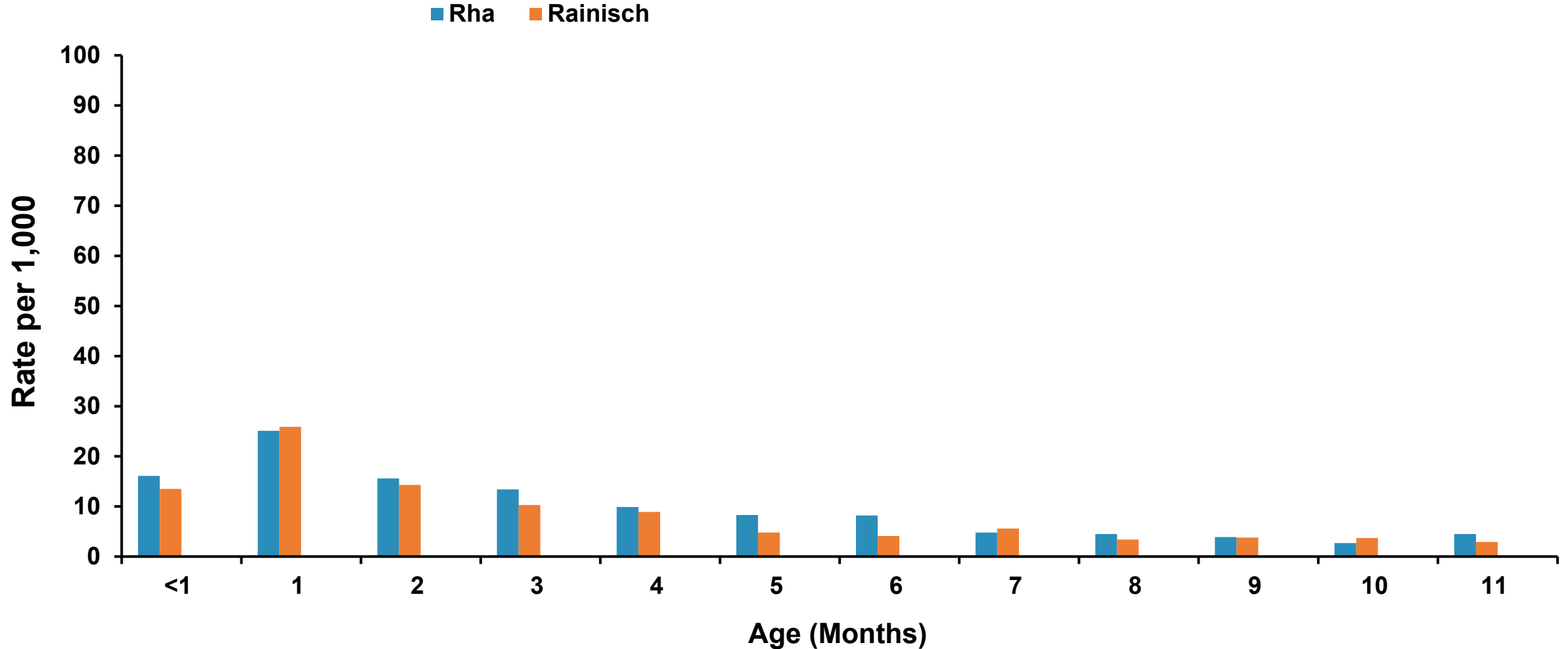
**Associated with  
longer term  
sequelae  
such as  
wheeze/asthma<sup>6-8</sup>**

# Burden of RSV Disease in Children Peaks in the First 6 Months



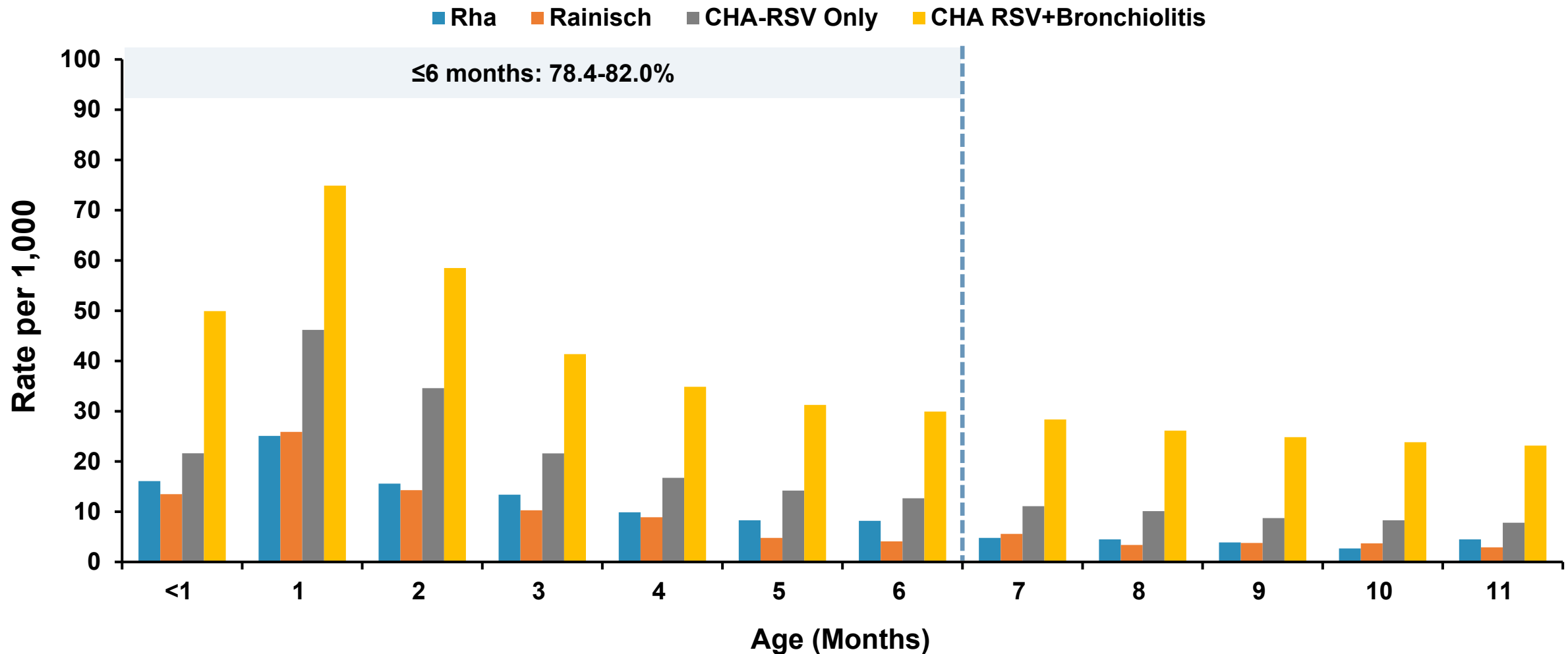
# RSV Hospitalization Rates Active Surveillance Studies

## Annual RSV Hospitalization by Age <1y (Rate/1000 Children)<sup>1-2</sup>

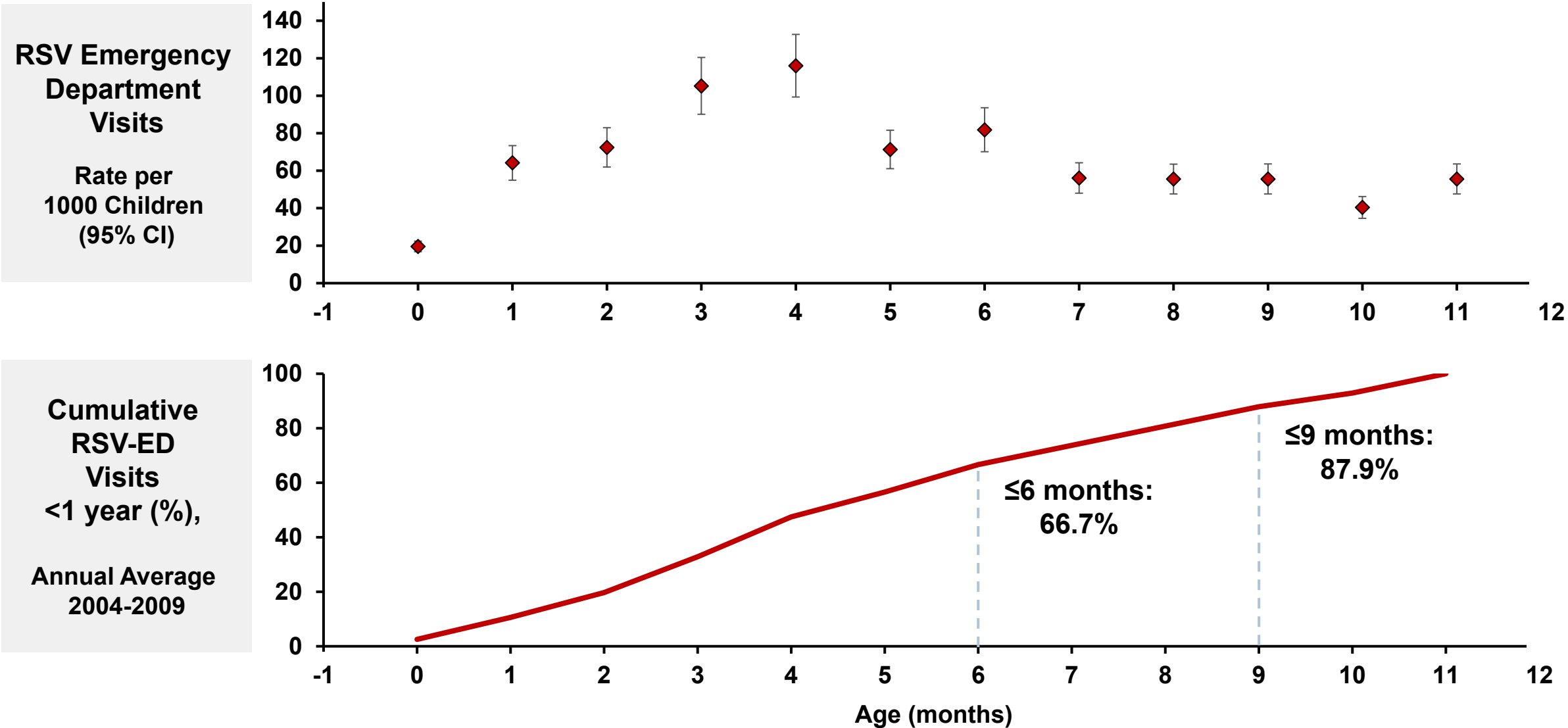


# Active Surveillance Underestimates Hospitalization Rates Majority of Cases Occur <3 Months

## Annual RSV Hospitalization by Age <1y (Rate/1000 Children)<sup>1-3</sup>



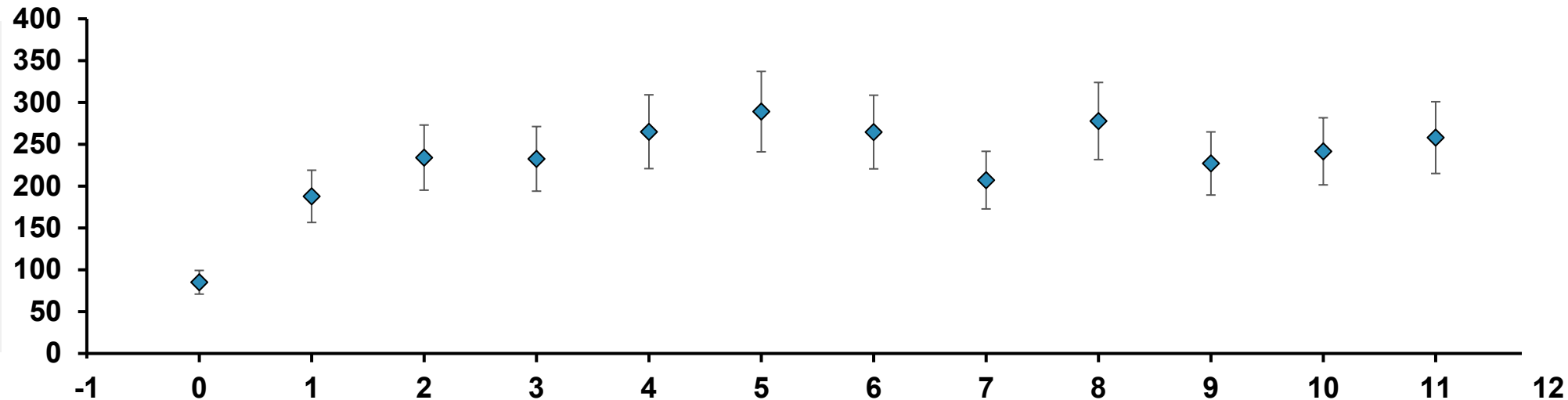
# Emergency Departments (ED) Also Have a Significant Burden Under 6 Months



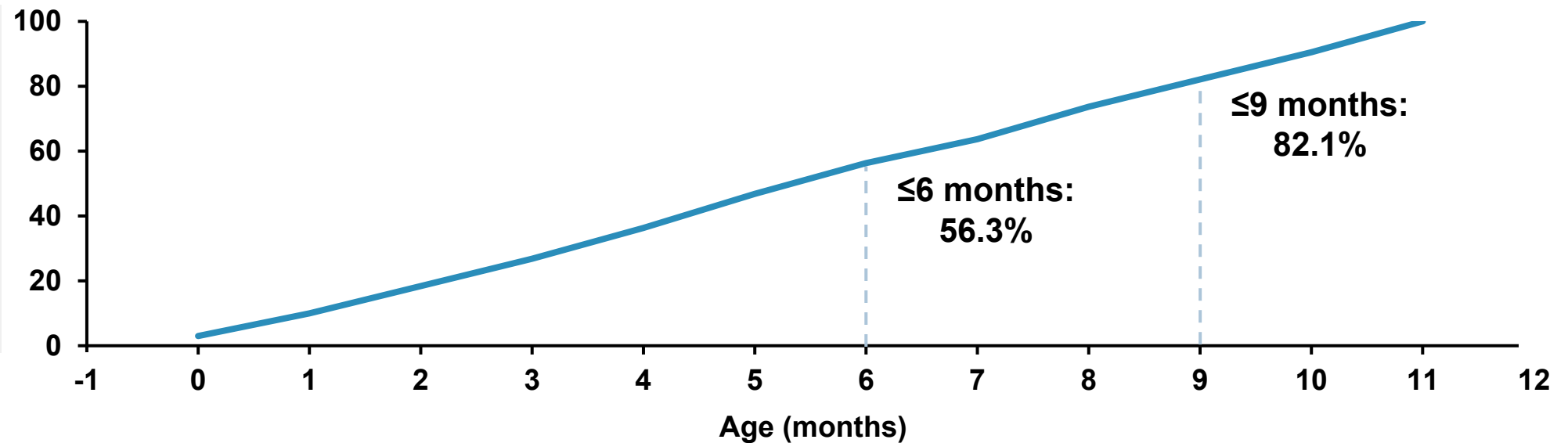


# Outpatient Visits Also Have a Significant Burden Under 6 Months

**RSV  
Outpatient  
Visits**  
  
Rate per  
1000 Children  
(95% CI)



**Cumulative  
RSV-Outpatient  
Visits  
<1 year (%),  
Annual Average  
2004-2009**



# Medicaid Recipients Constitute a Major Burden of Infant RSV Hospitalizations and ED Visits

- Medicaid recipients in the US, are hospitalized for RSV at twice the rate of private payers accounting for
  - 56% of ED visits
  - And almost 2/3 each of the total US burden of RSV hospitalizations, their aggregate costs and RSV deaths
- Medicaid recipients miss or cancel a substantial proportion of their well child visits (WCC) in the first 6 months of life – only 25% attend all recommended WCC; but >90% of Medicaid mothers attend at least 1 ANC visit prior to delivery

# Conclusions

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- RSV is the single most important cause of hospitalization in infancy outside of birth hospitalization in the USA and globally
- RSV causes between 56,000 and >70,000 hospitalizations in the US, annually if one accounts for undiagnosed bronchiolitis cases within the RSV season
- RSV overwhelms the pediatric practices and emergency departments throughout the country during the winter months, especially the last 2 seasons post pandemic
- Between 50 and 80% of this burden occur in the first 6 months of life
- Medicaid recipients form a disproportionate burden of disease



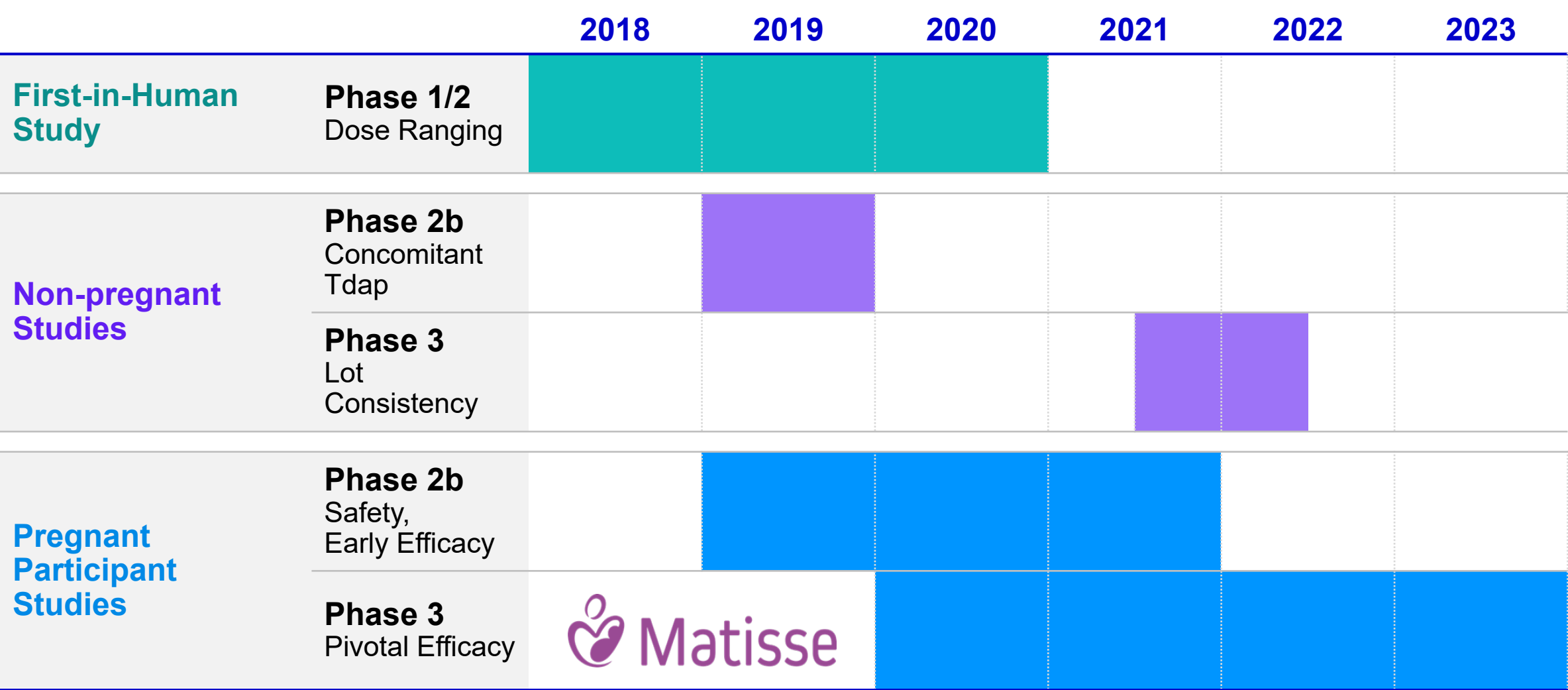
# Maternal RSV Program

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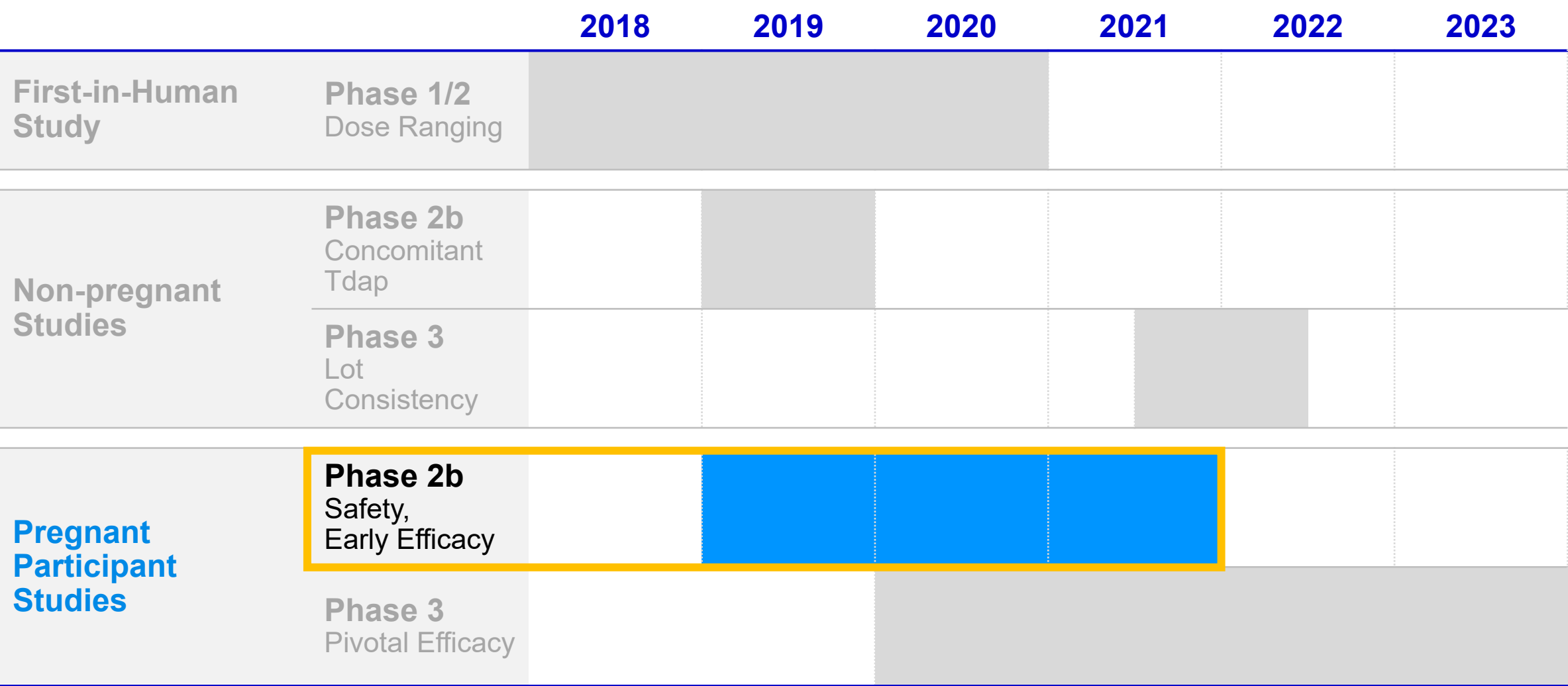
**Iona Munjal, MD, FAAP**

Senior Director,  
Vaccine Research and Development  
Maternal RSV Global Clinical Lead

# RSVpreF Maternal Immunization Clinical Development Program



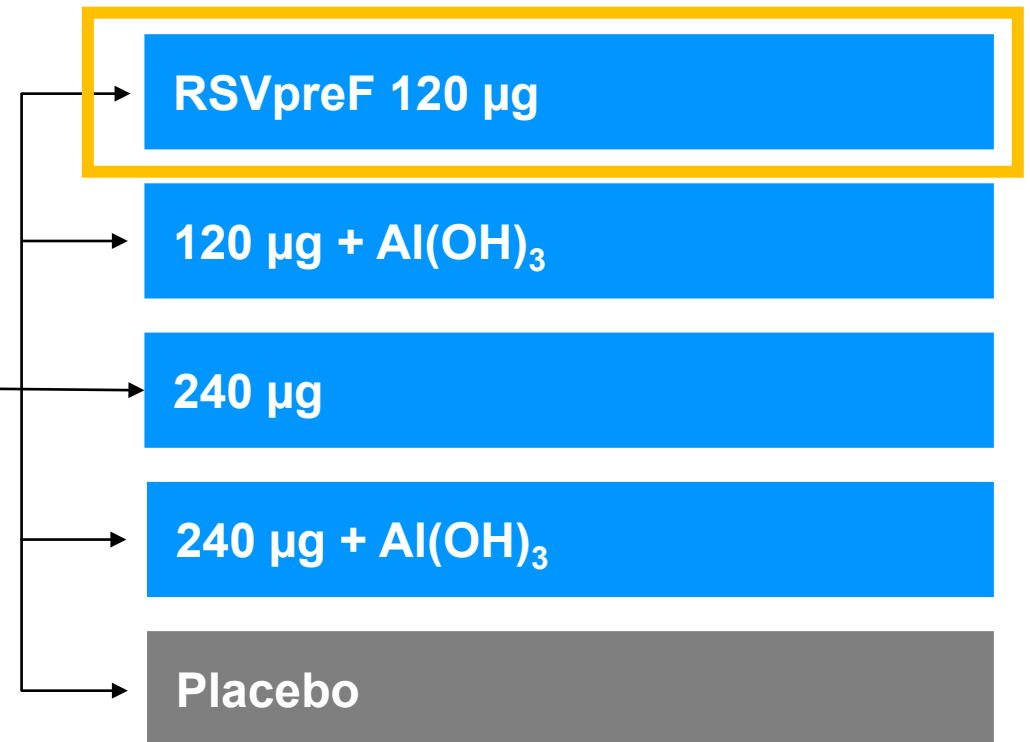
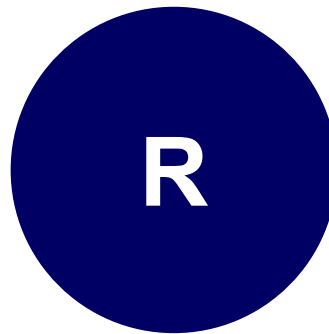
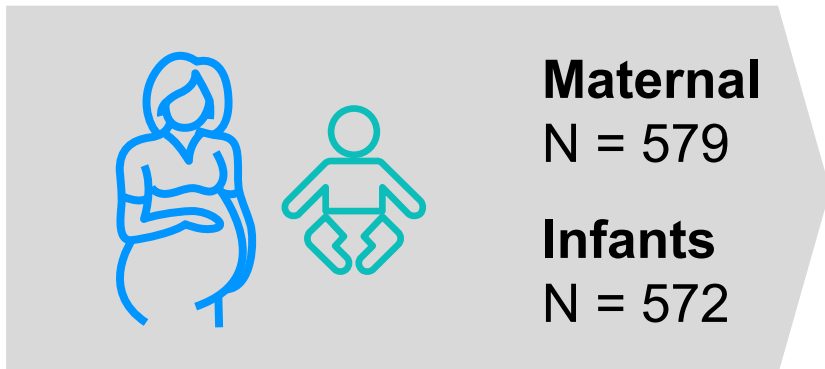
# RSVpreF Maternal Immunization Clinical Development Program



# Phase 2b Maternal Immunization Study

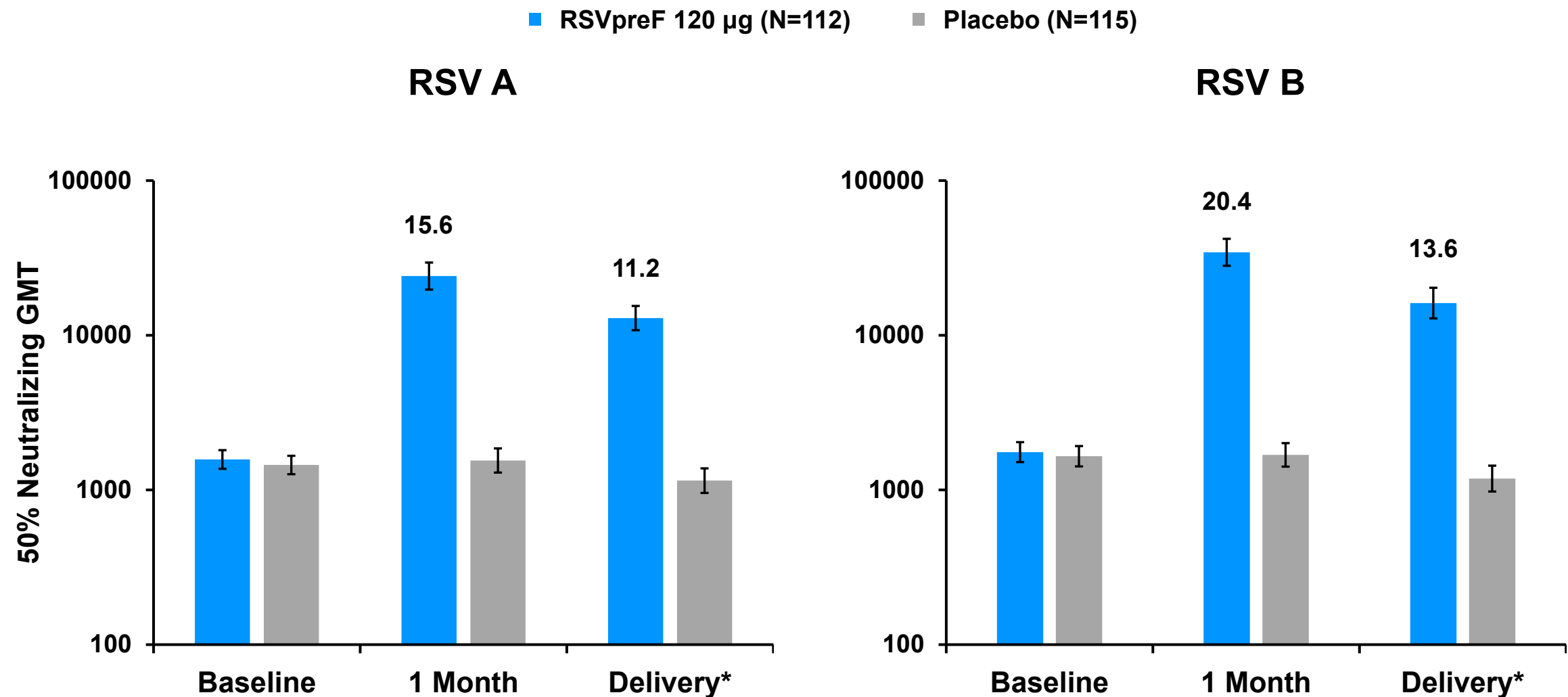
## Safety, Dose Finding, & Immunogenicity throughout Pregnancy and Infancy

Healthy Pregnant Women  
24 to 36 weeks gestation



# RSVpreF Elicits High **Maternal** Neutralizing Titers at Delivery

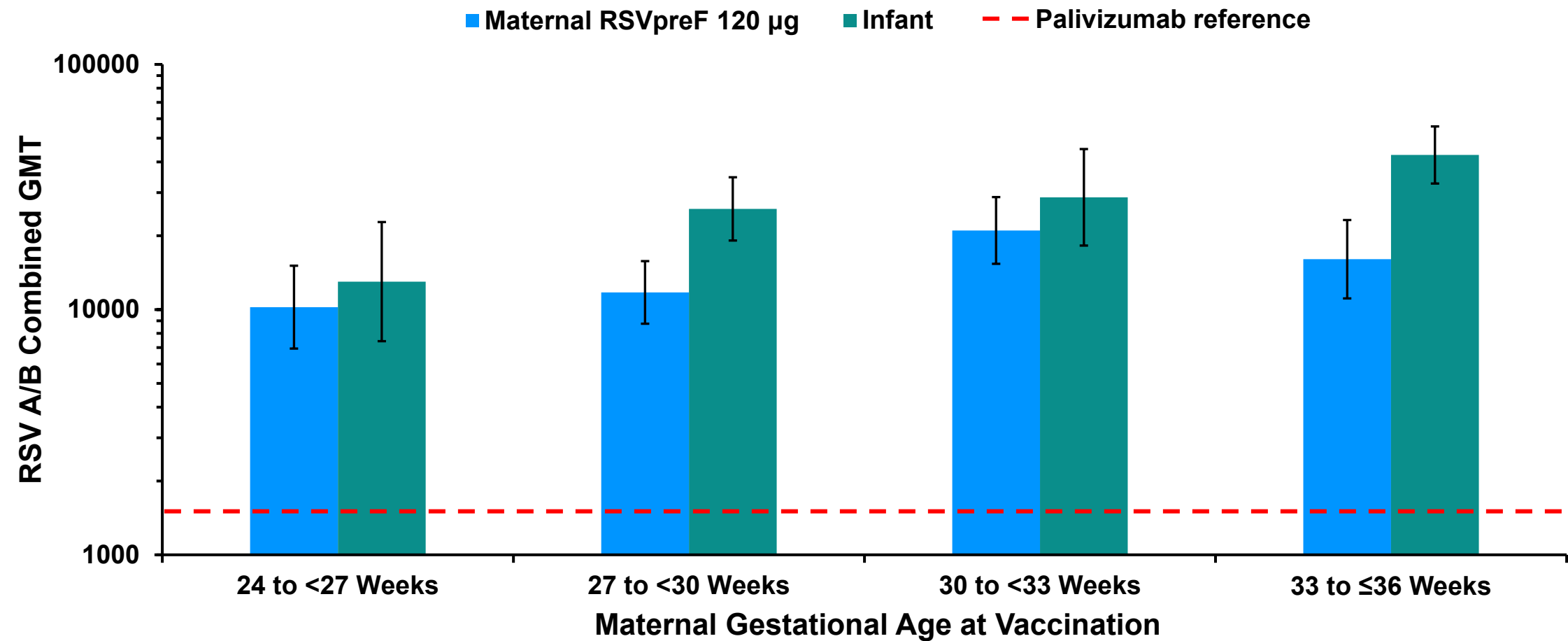
50% Neutralization GMTs & GMRs



\*Mean time from vaccination to delivery, 62.1 days for RSVpreF and placebo groups displayed  
GMR=Geometric Mean Ratio; GMT=Geometric Mean Titer, Lower Limit of Quantitation (LLOQ) for RSV A=50 and LLOQ for RSV B=70



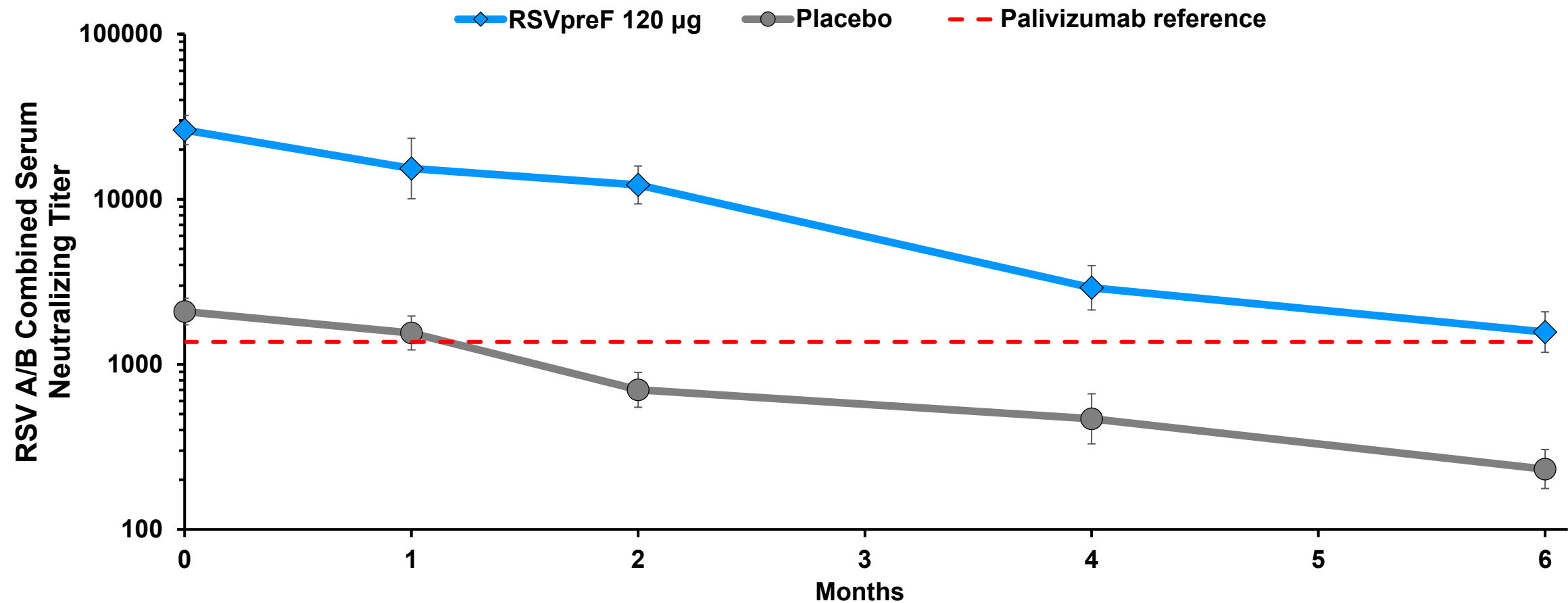
# Neutralizing GMTs at Birth Higher in Infants at All Maternal Gestational Ages at Vaccination



Transplacental Transfer Ratio	1.18	2.21	1.46	2.69
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# Infant Neutralizing Titers Persist, Remaining High Through 6 Months of Age

RSV A/B Combined 50% Geometric Mean Neutralizing Titers by Month



Palivizumab reference line = 50% A/B neutralizing titer of a 100ug/mL palivizumab dose, demonstrated to be efficacious in preventing infant RSV-associated ICU admission (Forbes ML, Kumar VR, Yogeve R, et al. *Hum Vaccin Immunother* 2014;10:2789-94.)

# RSVpreF **Maternal** Immunization Clinical Development Program

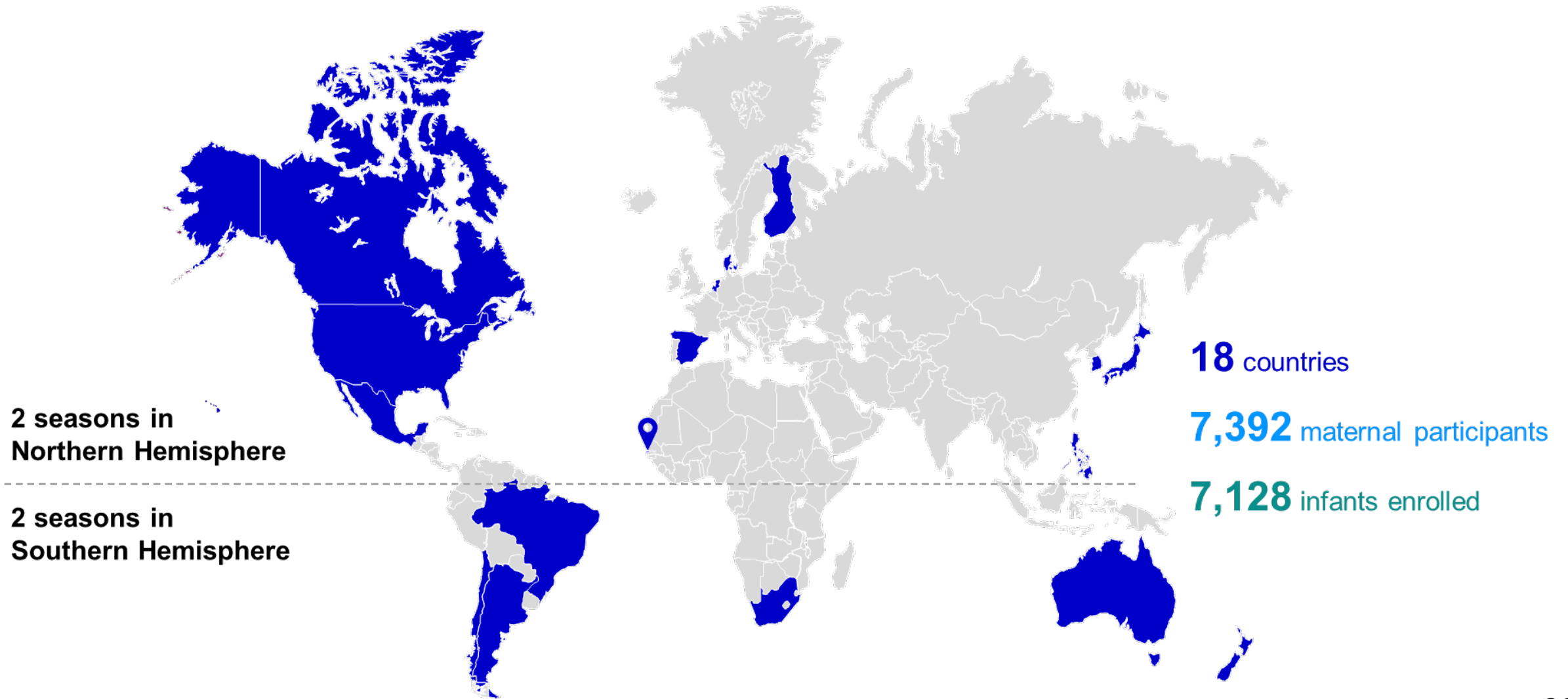
		2018	2019	2020	2021	2022	2023
First-in-Human Study	Phase 1/2 Dose Ranging						
Non-pregnant Studies	Phase 2b Concomitant Tdap						
	Phase 3 Lot Consistency						
Pregnant Participant Studies	Phase 2b Safety, Early Efficacy						
	Phase 3 Pivotal Efficacy						



- **FDA agreement on all study endpoints and safety criteria for licensure**
  - Vaccine efficacy in either primary endpoint with a lower bound of >20% for the CI would be sufficient
  - 3000 mother-infant pairs exposed was sufficient for the safety database

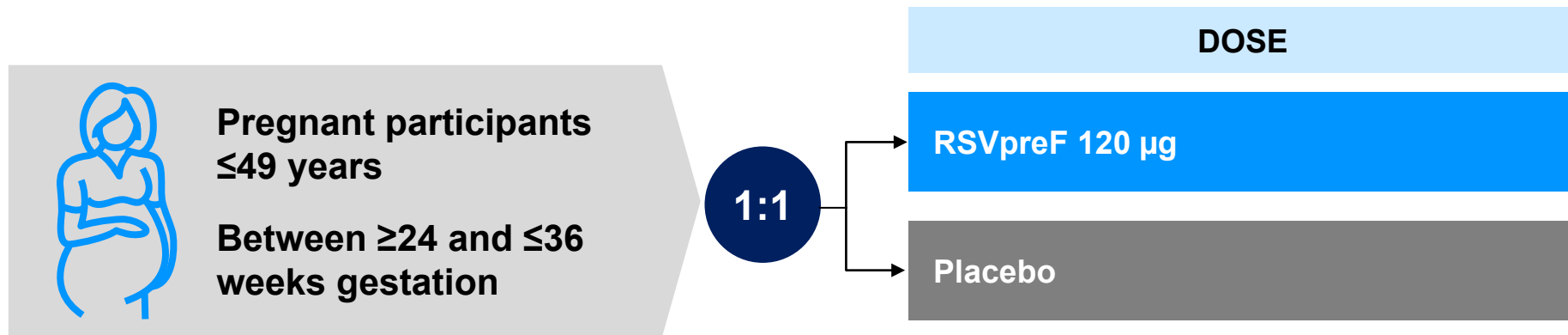
- **Additional key stakeholders informed the trial including:**
  - RSV experts
  - Clinical providers
  - Nurses who conduct trials in maternal populations
  - Pregnant persons and their partners

# MATISSE: Global Footprint

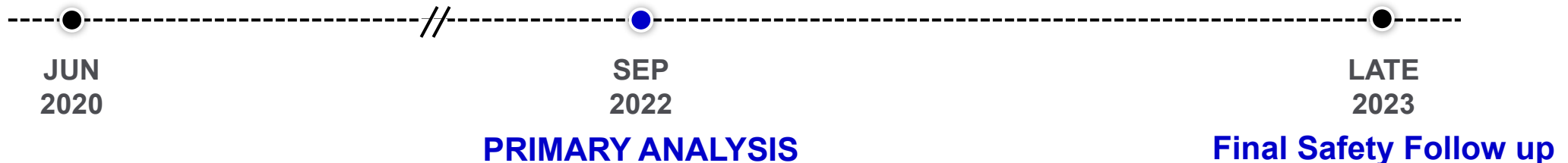


# MATISSE: Phase 3 Pivotal **Maternal** Vaccination Trial

**Maternal Participants: Safety 6 Months after Delivery**  
**Infants: Safety and Respiratory Surveillance up to 2 years**



**Analysis Included June 2020-September 2022**



# Demographics Were Balanced Between Vaccine and Placebo Recipients (Maternal Safety Population)

	RSVpreF 120 µg N=3682 n (%)	Placebo N=3675 n (%)	Total N=7357 n (%)
Race			
White	2383 (64.7)	2365 (64.4)	4748 (64.5)
Black or African American	720 (19.6)	723 (19.7)	1443 (19.6)
Asian	454 (12.3)	464 (12.6)	918 (12.5)
American Indian or Alaskan Native	38 (1.0)	37 (1.0)	75 (1.0)
Native Hawaiian or Other Pacific Islander	9 (0.2)	12 (0.3)	21 (0.3)
Multiracial	30 (0.8)	21 (0.6)	51 (0.7)
Ethnicity			
Hispanic/Latino	1049 (28.5)	1075 (29.3)	2124 (28.9)



# Demographics Were Balanced Between Vaccine and Placebo Recipients (Maternal Safety Population)

	RSVpreF 120 µg N=3682 n (%)	Placebo N=3675 n (%)	Total N=7357 n (%)
<b>Age at Vaccination* (years)</b>			
Mean (SD)	29.1 (5.64)	29.0 (5.74)	29.0 (5.69)
Range	16 – 45	14 – 47	14 – 47
<b>Gestational Age (GA) at Vaccination**</b>			
≥24 weeks to <28 weeks	941 (25.6)	909 (24.7)	1850 (25.1)
≥28 weeks to <32 weeks	1085 (29.5)	1128 (30.7)	2213 (30.1)
≥32 weeks to ≤36 weeks	1653 (44.9)	1632 (44.4)	3285 (44.7)

\*Average age at vaccination: 29 years  
\*\*Average GA at vaccination: 31 weeks  
One participant is counted under ≥24 weeks to <28 weeks however actual age was 23 weeks 6 days. Nine participants were enrolled with GA >36 weeks

# Demographics Were Balanced Between Vaccine and Placebo Recipients (Infant Safety Population)

	RSVpreF 120 µg N=3568 n (%)	Placebo N=3558 n (%)	Total N=7126 n (%)
<b>Sex</b>			
Male	1816 (50.9)	1793 (50.4)	3609 (50.6)
Female	1752 (49.1)	1765 (49.6)	3517 (49.4)
<b>Race</b>			
White	2294 (64.3)	2284 (64.2)	4578 (64.2)
Black or African American	687 (19.3)	688 (19.3)	1375 (19.3)
Asian	420 (11.8)	430 (12.1)	850 (11.9)
American Indian or Alaskan Native	42 (1.2)	36 (1.0)	78 (1.1)
Native Hawaiian or other Pacific Islander	13 (0.4)	11 (0.3)	24 (0.3)
Multiracial	65 (1.8)	59 (1.7)	124 (1.7)
<b>Ethnicity</b>			
Hispanic/Latino	1033 (29.0)	1039 (29.2)	2072 (29.1)



# **MATISSE**

(**MAT**ernal Immunization **S**tudy for **S**afety and **E**fficacy)

## **Safety**

# Phase 3 Safety Objectives

## Safety

- **Describe the safety & tolerability profile of RSVpreF**
  - Local reactions and systemic events within 7 days post-vaccination (Maternal)
  - Adverse Events through 1-month post-vaccination (Maternal)
  - Adverse Events through 1-month after birth (Infant)
  - AESI, SAEs (Maternal and Infant) and NDCMCs (Infant) throughout study

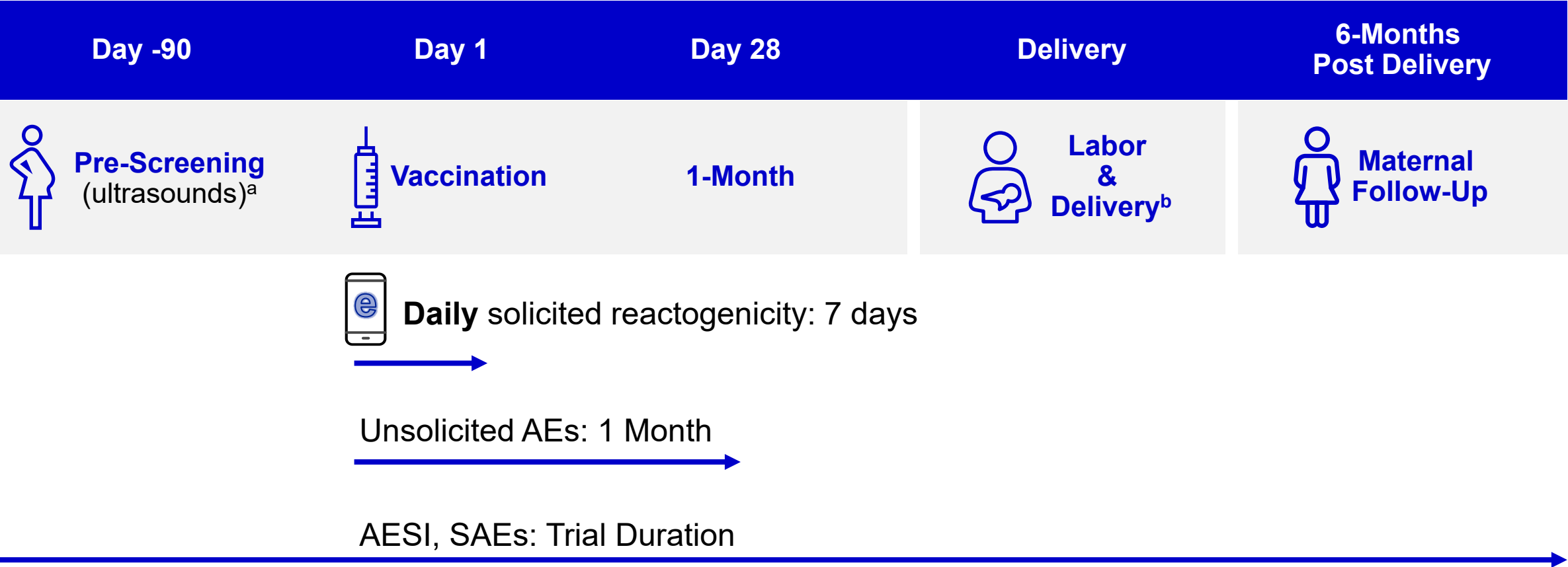
### Adverse Events of Special Interest (AESI)

Preterm birth (infant) preterm delivery (mother)  
Low birth weight  
Developmental delay  
SARS-CoV-2 (infant and mother)\*



**DMC**

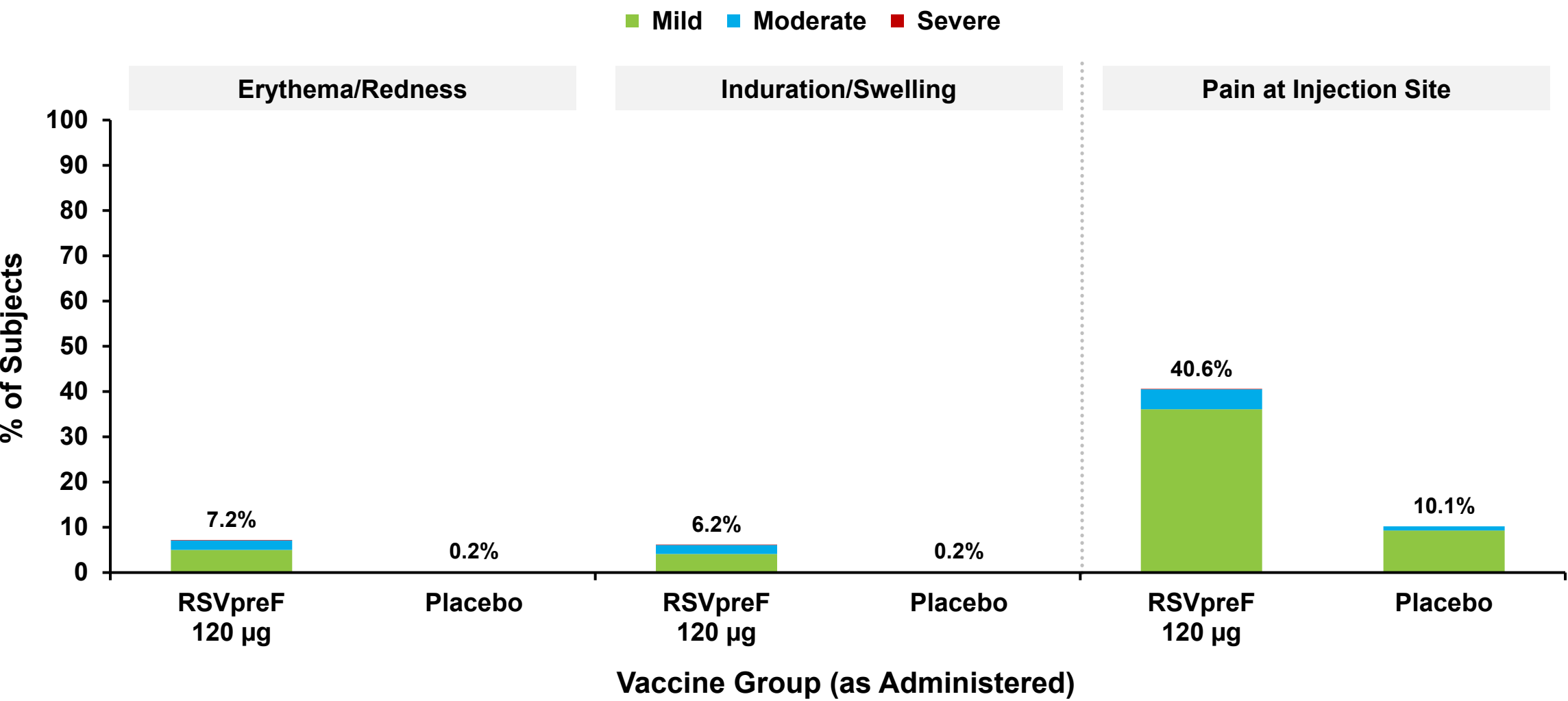
# Maternal Safety Assessments



a. Where applicable by country b. Mean time from vaccination to delivery, 58 days (Range 1 to 132)  
AESI=AE of Special Interest including preterm delivery and SARS-CoV-2 test positive; SAE=serious adverse event

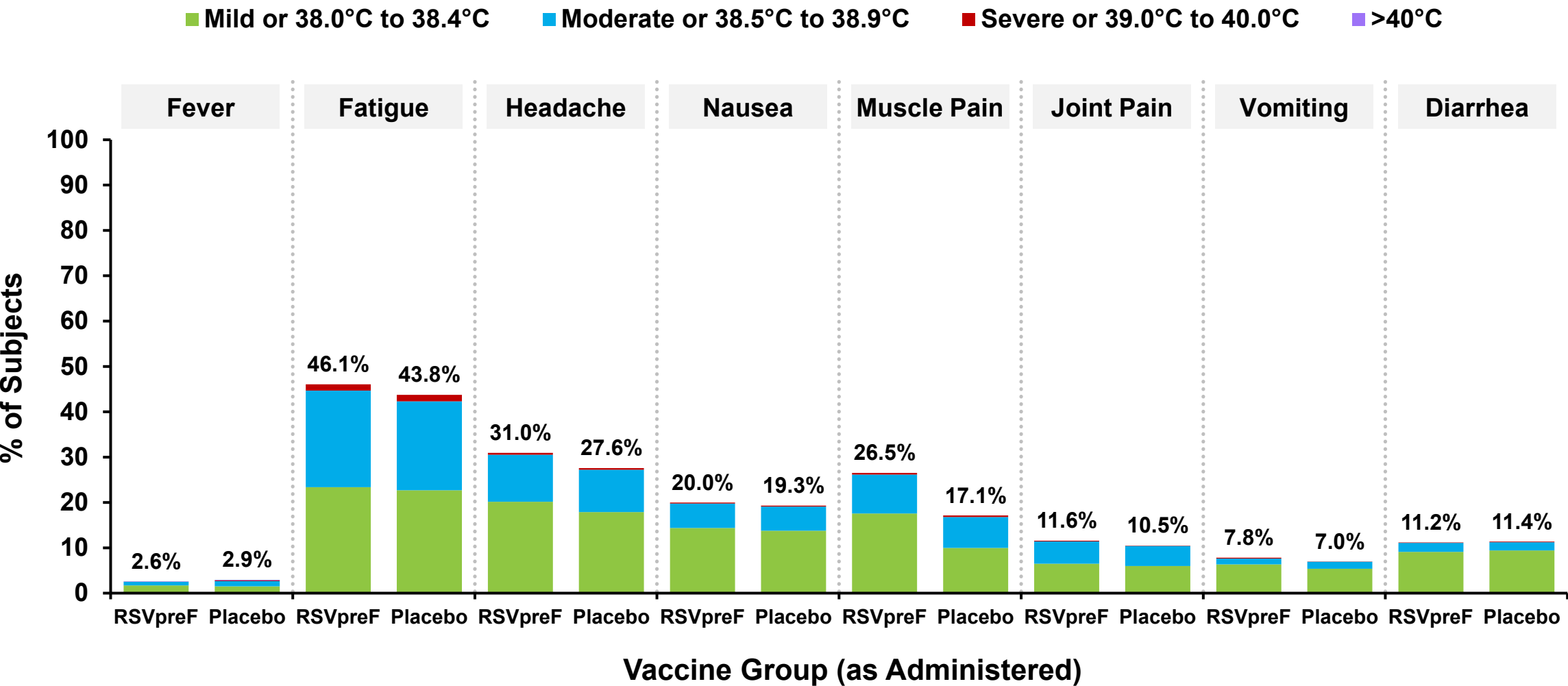
# Solicited Local Reactions were Mild to Moderate and Resolved Quickly

Maternal Participants



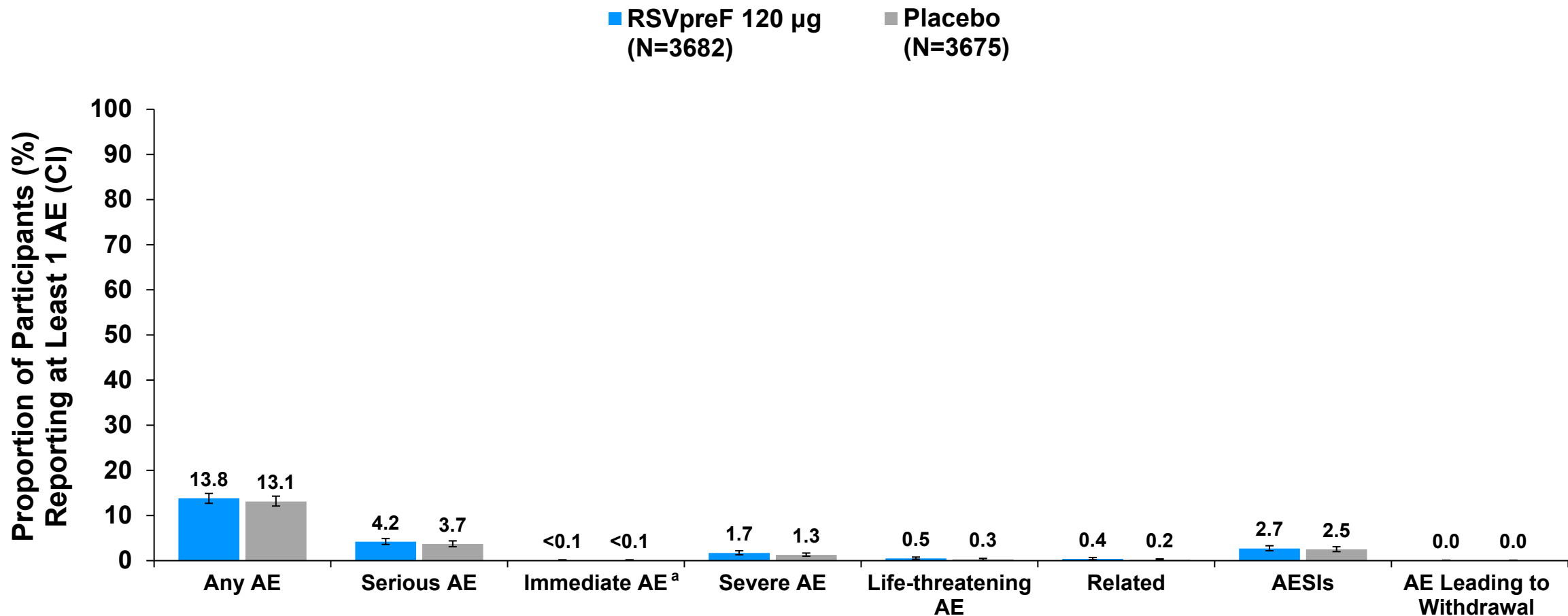
# Solicited Systemic Events were Mild to Moderate and Resolved Quickly

## Maternal Participants



# Adverse Events Comparable Between RSVpreF and Placebo

Maternal Participants within 1 Month After Vaccination

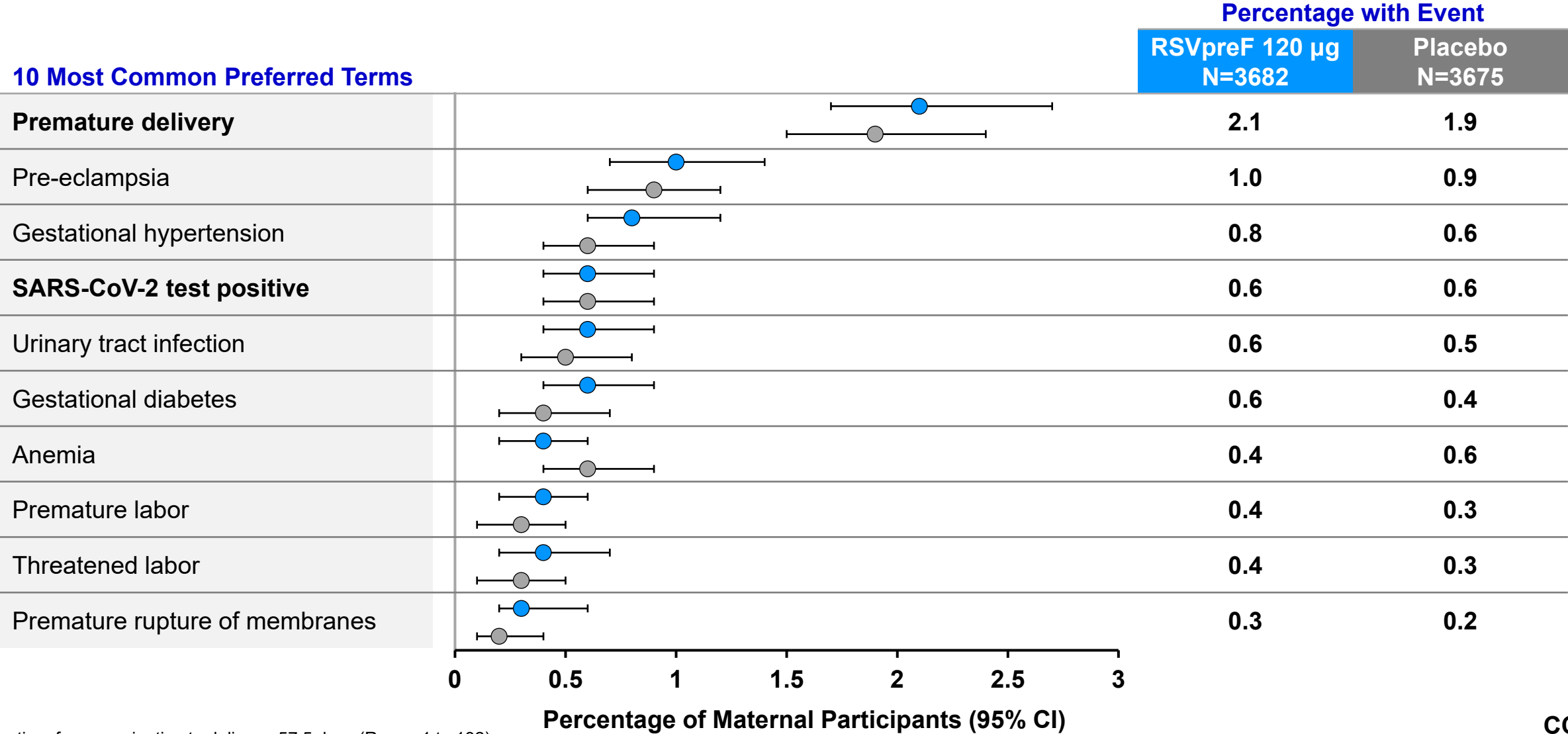


The severity of the event is in the determination of the investigator.  
a. An immediate AE is defined as any AE that occurred within the first 30 minutes of vaccination.  
AE=Adverse Event; AESI=Adverse Events of Special Interest





# Common AEs Comparable Between RSVpreF & Placebo within 1 Month After Vaccination

Maternal Participants: Terms Consistent with Conditions Associated with Pregnancy<sup>a</sup>



# Infant Safety Assessments

Birth Day 1	1-Mo	6-Mo	12-Mo	18-Mo	24-Mo
Delivery & Endpoint Surveillance			 12-Mo Follow-up (45% infants)	 24-mo Follow-up (55% infants)	

Unsolicited AEs: 1 Month

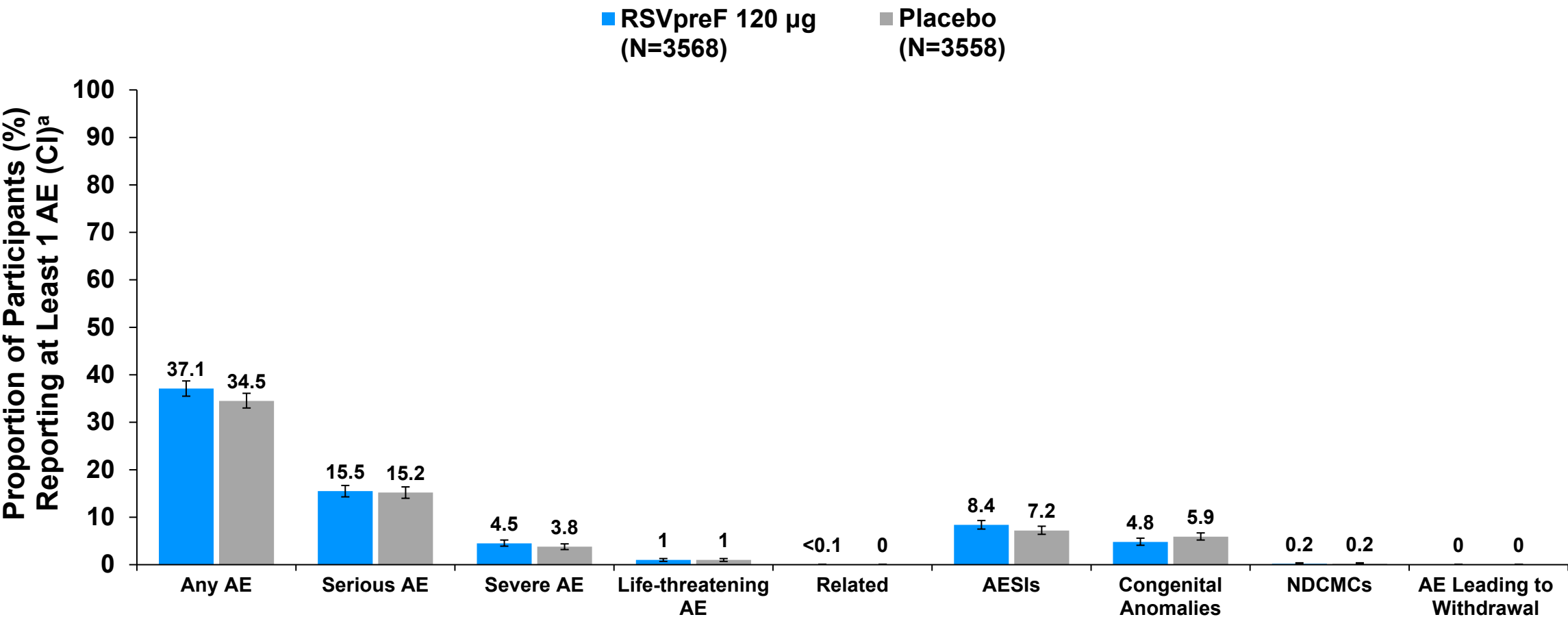


AESI, SAEs, and NDCMCs: Trial Duration



# Adverse Events Comparable Between RSVpreF and Placebo

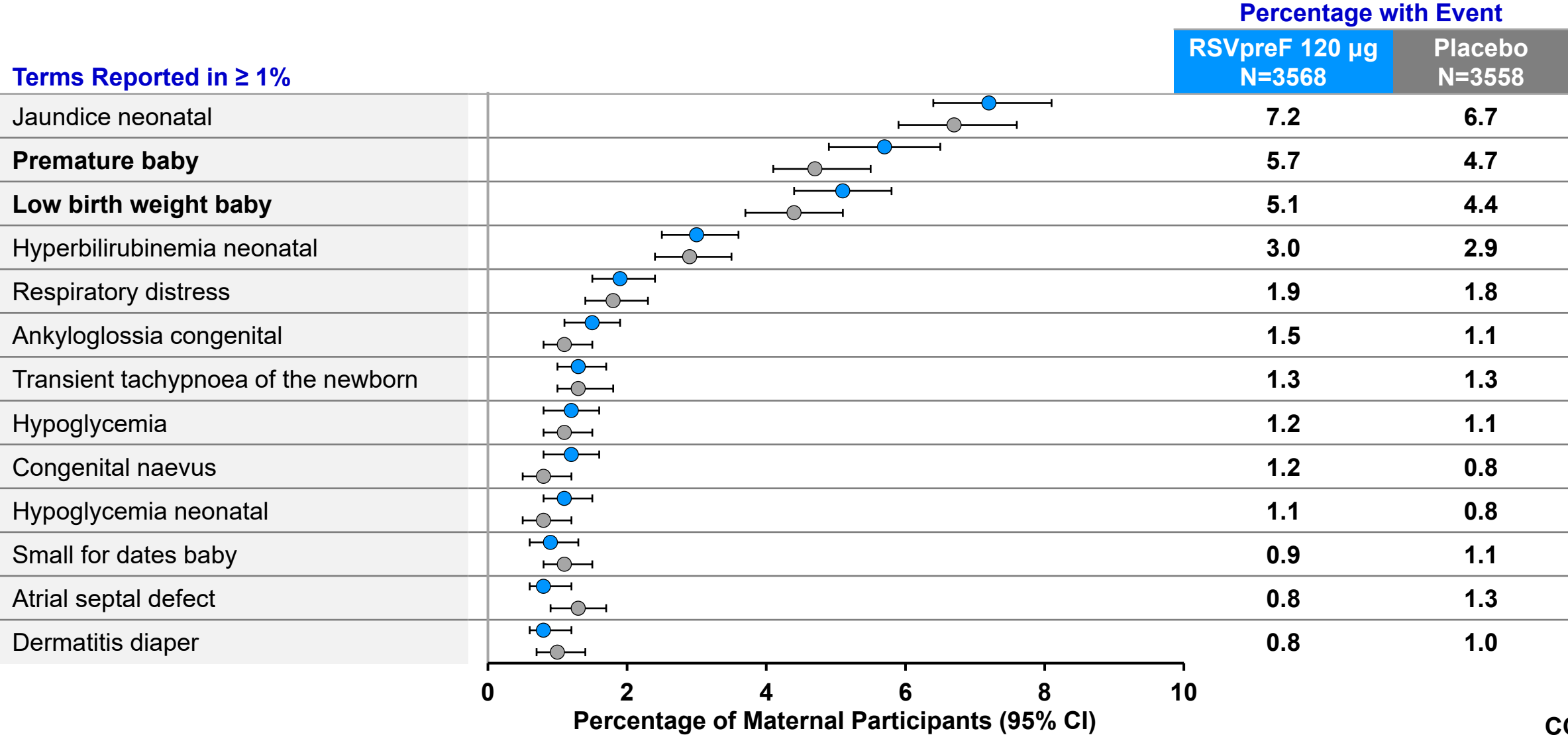
Infant Participants Within 1 Month After Birth



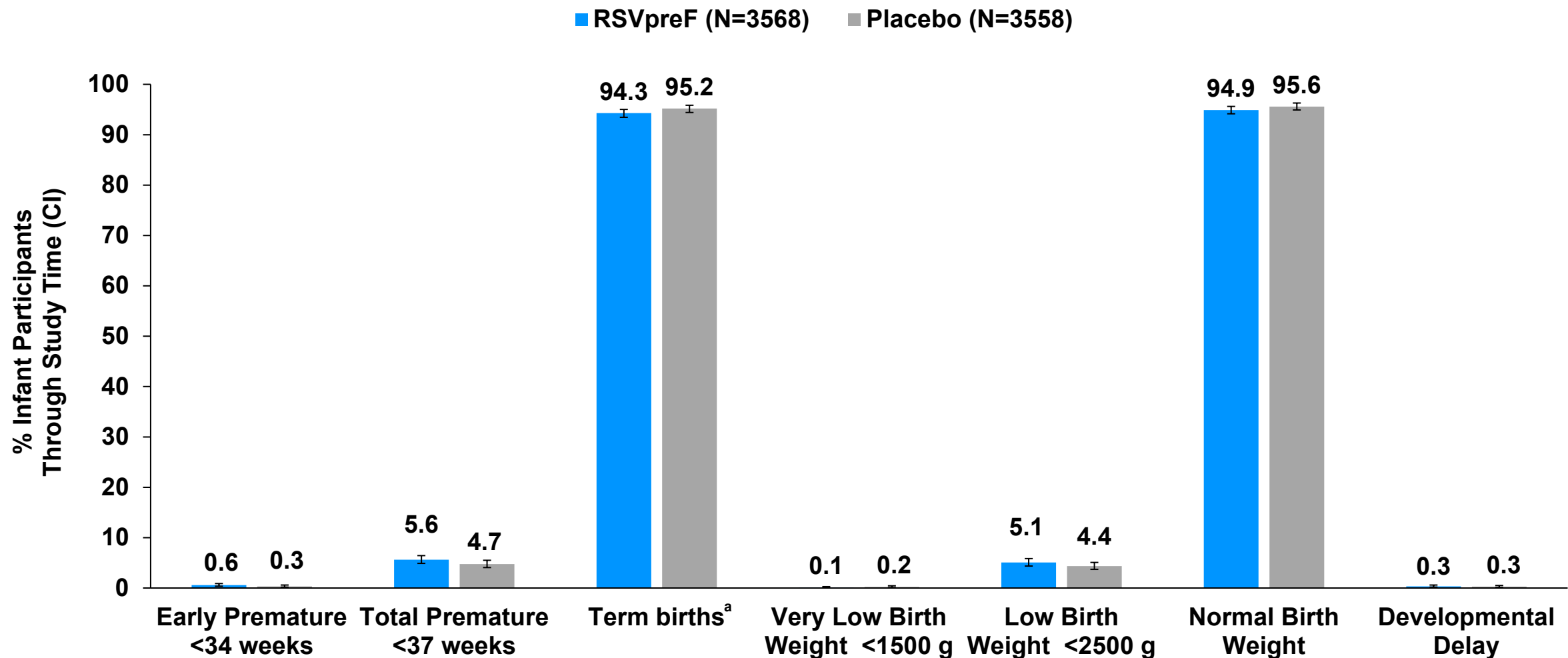
The severity of the event is in the determination of the investigator. a. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.  
AE=Adverse Event; AESI=Adverse Events of Special Interest; NDCMCs=Newly Diagnosed Chronic Medical Conditions

# AEs ≥1.0% Comparable Between RSVpreF & Placebo Within 1 Month After Birth

Infant Participants: Terms Consistent with Neonatal Conditions

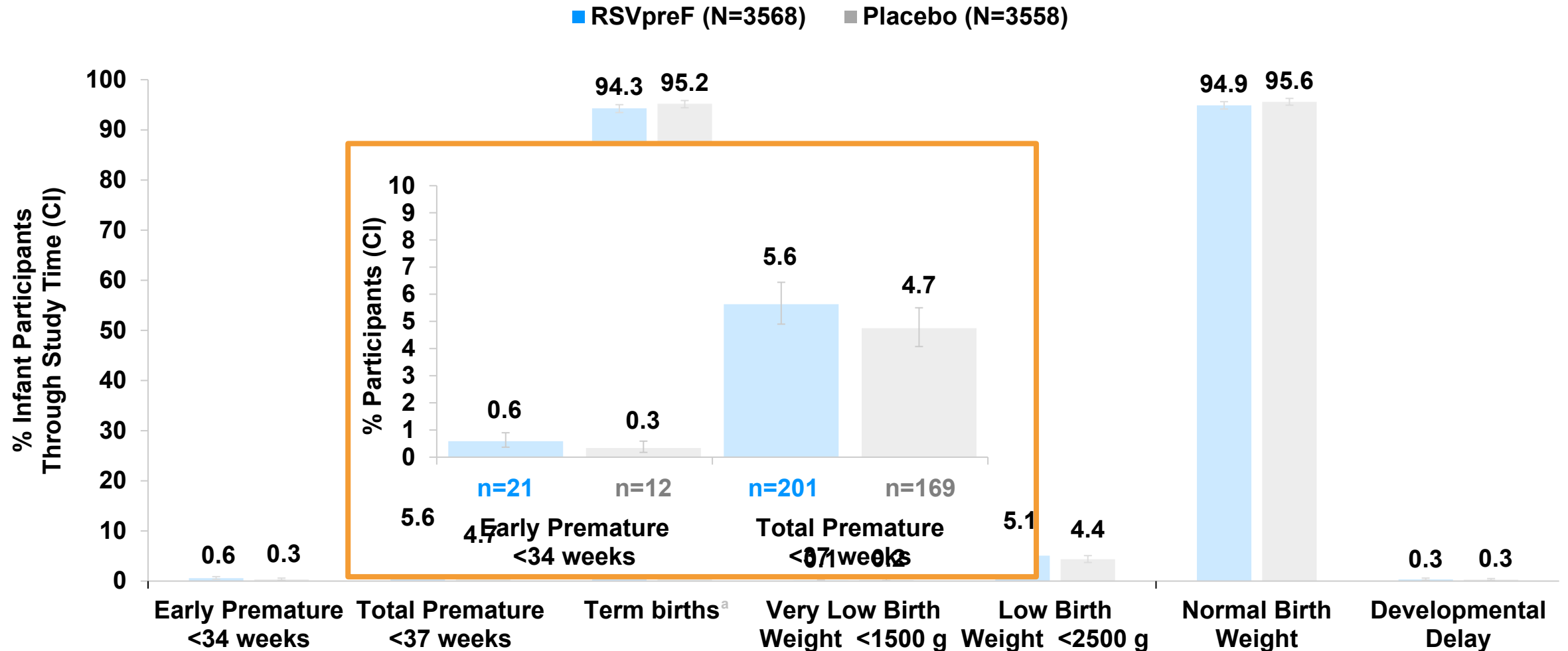


# Birth Outcomes and Developmental Delay Comparable Between RSVpreF and Placebo

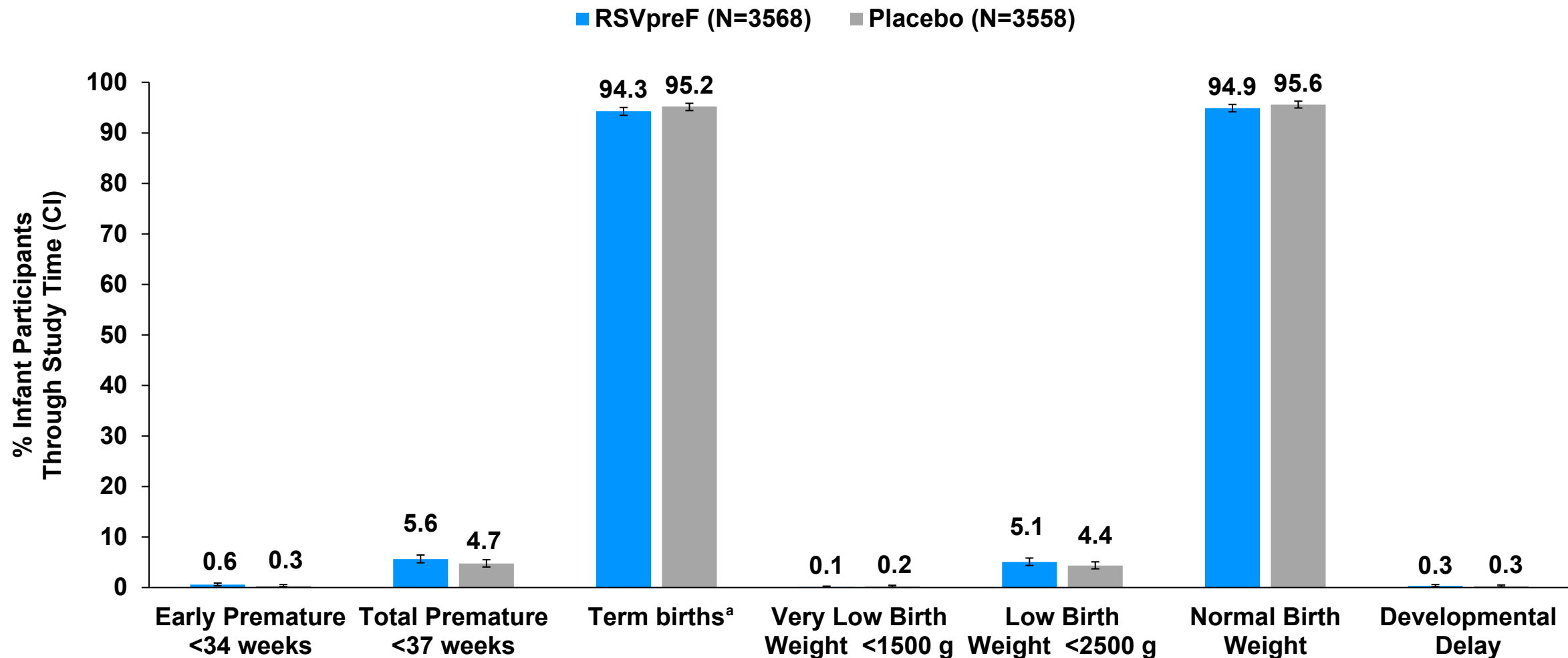


a. Term births: infants born ≥37 weeks

# Birth Outcomes: Prematurity and Extreme Prematurity Rates



# Birth Outcomes and Developmental Delay Comparable Between RSVpreF and Placebo



a. Term births: infants born ≥37 weeks

# Maternal and Fetal Deaths Reported in the Trial

(All not related)

Event Type	RSVpreF 120 µg N=3682 n (%)	Placebo N=3675 n (%)	RR (95% CI)
Maternal death (n=1)	1 (<0.1)	0	-
Fetal demise (n=18) (before birth)	10 (0.3)	8 (0.2)	1.25 (0.49, 3.16)



# Infant Deaths Overall and by Subcategory

Event Type	RSVpreF 120 µg N=3568 n	Placebo N=3558 n	RR (CI)
Total Infant death due to any cause (n=17)	5	12	0.42 (0.15, 1.18)
Infant death due to RSV	0	1	-
Preterm deaths (<37 weeks at birth)	1*	2	0.50 (0.05, 5.50)
Neonatal deaths (<30 days after birth)	2*	5	0.40 (0.08, 2.05)

\*A single preterm infant died in the neonatal (<30 days) period. The infant was in the RSVpreF group and from South Africa. The infant is represented in both subcategories: preterm and neonatal.

# **Favorable Safety Profile and Well Tolerated**

---

- **Local and systemic events were mostly mild to moderate and short in duration**
- **AE profile did not suggest any safety concerns**
- **There was a numerical imbalance in late preterms, in UMICs, and most preterms were near term**
- **Mortality data favorable for the vaccine group**
- **Pharmacovigilance studies will continue to monitor outcomes in both maternal and infant populations**



**MATISSE**

(**MAT**ernal Immunization **S**tudy for **S**afety and **E**fficacy)

## **Infant Efficacy Endpoints**

# Phase 3 Study Efficacy Objectives

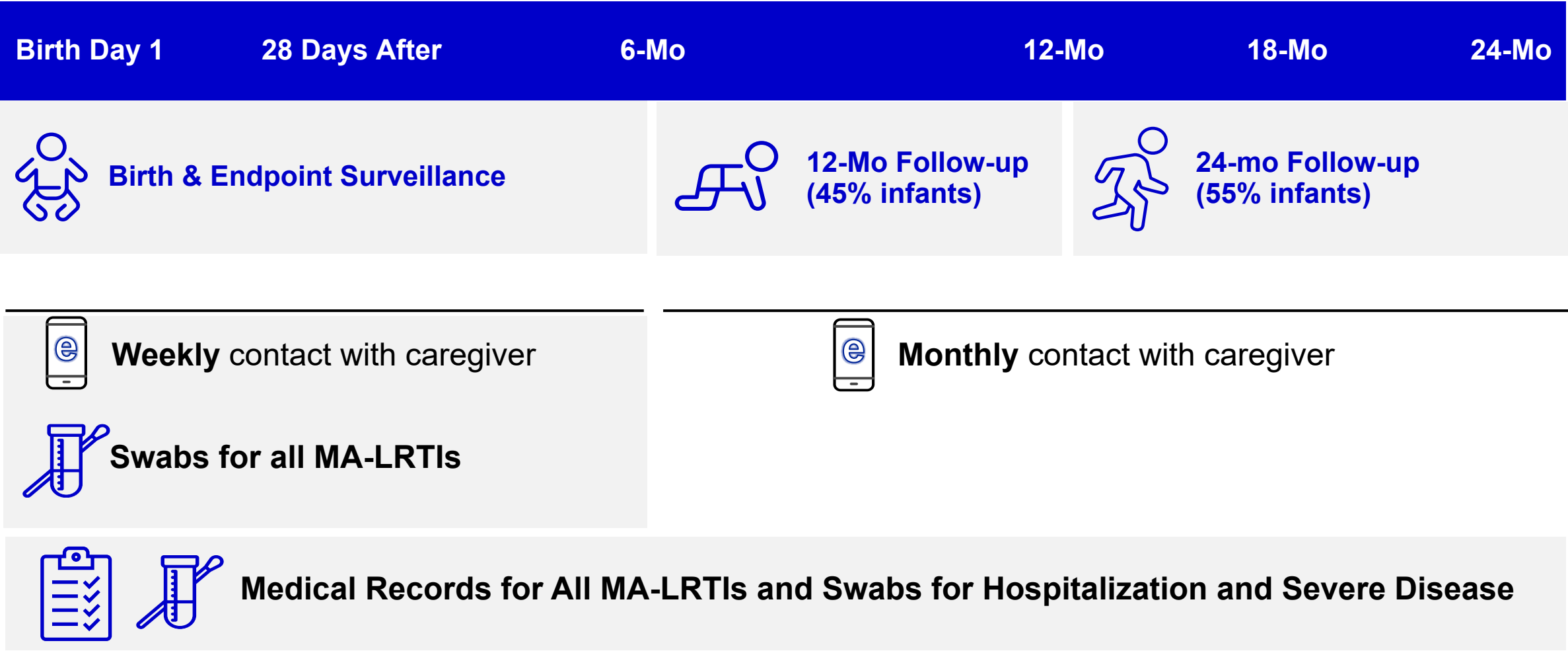
## Primary Efficacy

- **Prevention of RSV MA-LRTI within 90-180 days after birth**
- **Prevention of RSV severe MA-LRTI within 90-180 days after birth**

## Secondary Efficacy

- **Prevention of RSV MA-LRTIs within 360 days after birth**
- **Prevention of RSV hospitalization within 360 days after birth**
- **Prevention of MA-LRTIs due to any cause within 360 days after birth**

# Infant Efficacy Surveillance



# Phase 3 Efficacy Endpoints Defined



**Weekly active surveillance for MA visit + RTI symptoms**  
Symptoms trigger nasal swab and visit



Primary Endpoints	Criteria used by the Adjudication Committee
<b>RSV LRTI</b> Medically attended visit and ≥1:	<ul style="list-style-type: none"><li>• Tachypnea (RR <b>≥60</b> (&lt;2 M [60 days]) or <b>≥50</b> (≥2 to &lt;12 M))</li><li>• SpO2 measured <b>&lt;95%</b></li><li>• Chest wall indrawing</li></ul>
<b>Severe RSV LRTI</b> Medically attended visit and ≥1:	<ul style="list-style-type: none"><li>• Tachypnea (RR <b>≥70</b> (&lt;2 M [60 days]) or <b>≥60</b> (≥2 to &lt;12 M))</li><li>• SpO2 measured <b>&lt;93%</b></li><li>• High-flow nasal cannula or mechanical ventilation</li><li>• ICU admission for &gt;4 hours</li><li>• Unresponsive/unconscious</li></ul>



**Positive validated RT-PCR**

# Successful 90 Day Analysis

Primary Endpoint	Time Period	Vaccine Efficacy % (99.5% CI)
Severe MA-LRTI	First 90 days of life	81.8 (40.6, 96.3)
MA-LRTI	First 90 days of life	57.1 (14.7, 79.8)

Met Lower Bound CI Criteria of >20% to Trigger a Primary Analysis

# Primary Endpoint: RSV-Positive Severe MA-LRTI

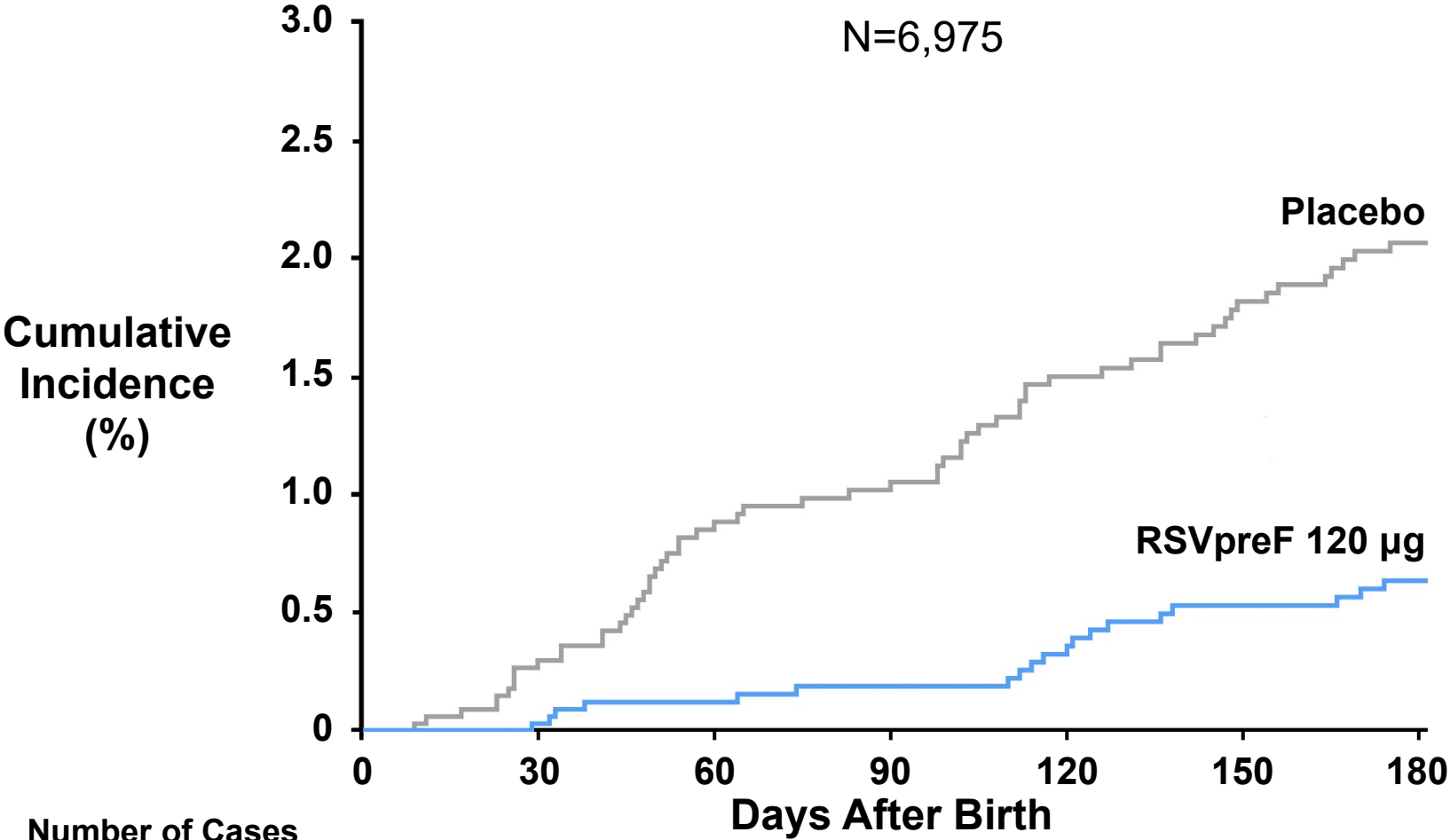
Time Interval	Maternal Vaccine Group (as Randomized)		Vaccine Efficacy (97.58-99.5% CI*)
	RSVpreF 120 µg N = 3495 n	Placebo N = 3480 n	
0-90 Days after birth	6	33	81.8% (40.6, 96.3)
0-120 Days after birth	12	46	73.9% (45.6, 88.8)
0-150 Days after birth	16	55	70.9% (44.5, 85.9)
0-180 Days after birth	19	62	69.4 (44.3, 84.1)

**Primary efficacy endpoint met licensure criteria of Lower Bound >20%\*\***

\*99.5% CI for 90 days, 97.58% CI for 120/150/180 days. CI LB >20% for all time points.  
Bonferroni procedure and accounting for the primary endpoints results.  
\*\*Kampmann et al. N Engl J Med 2023; 388:1451-1464  
MA-LRTI=Medically Attended Lower Respiratory Tract Illness



# Efficacy Maintained Against Severe MA-LRTIs Through 6 Months



Number of Cases						
RSVpreF	1	4	6	12	16	19
Placebo	10	28	33	46	55	62

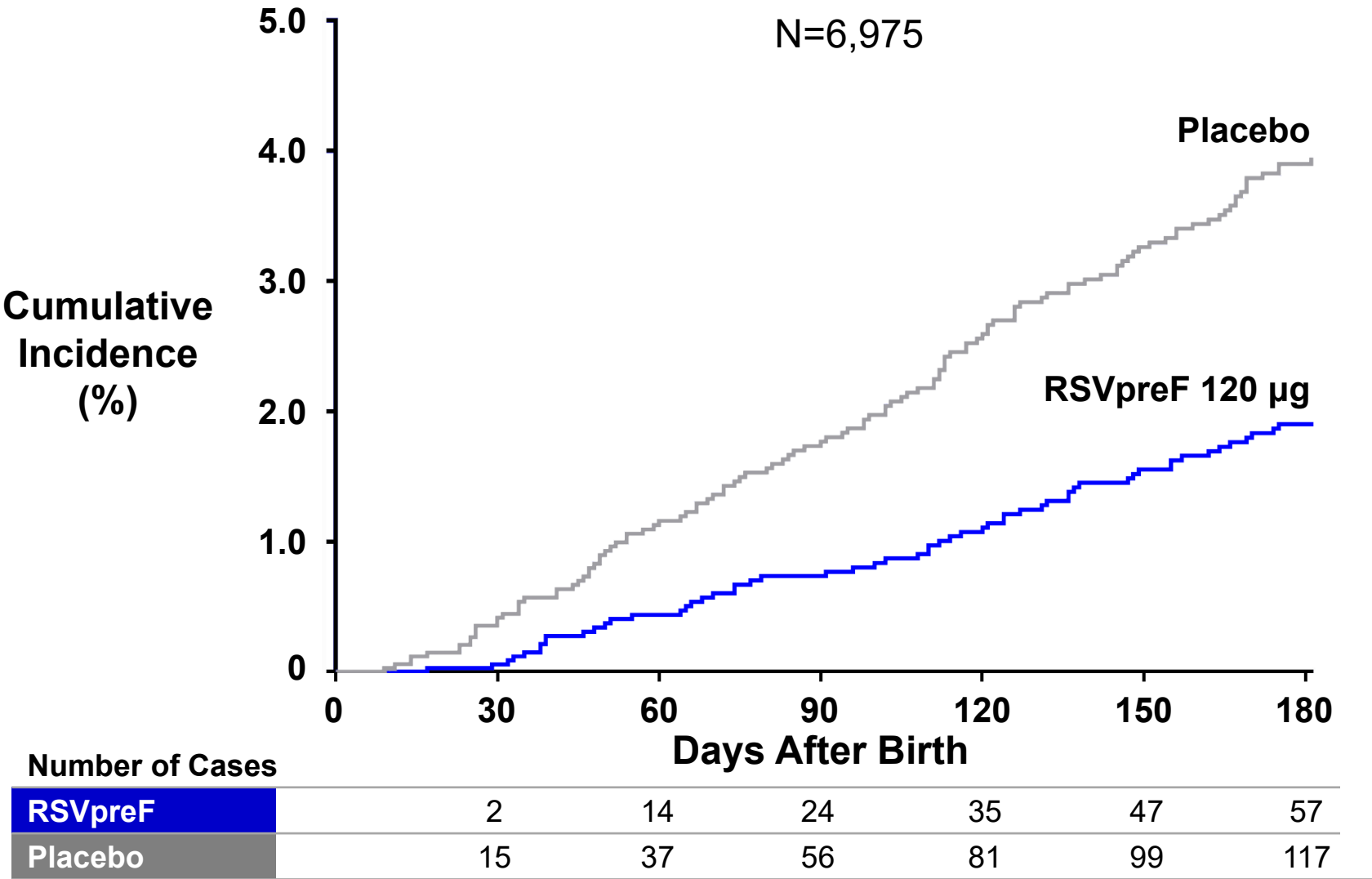
# Primary Endpoint: RSV-Positive MA-LRTI

## Maternal Vaccine Group (as Randomized)

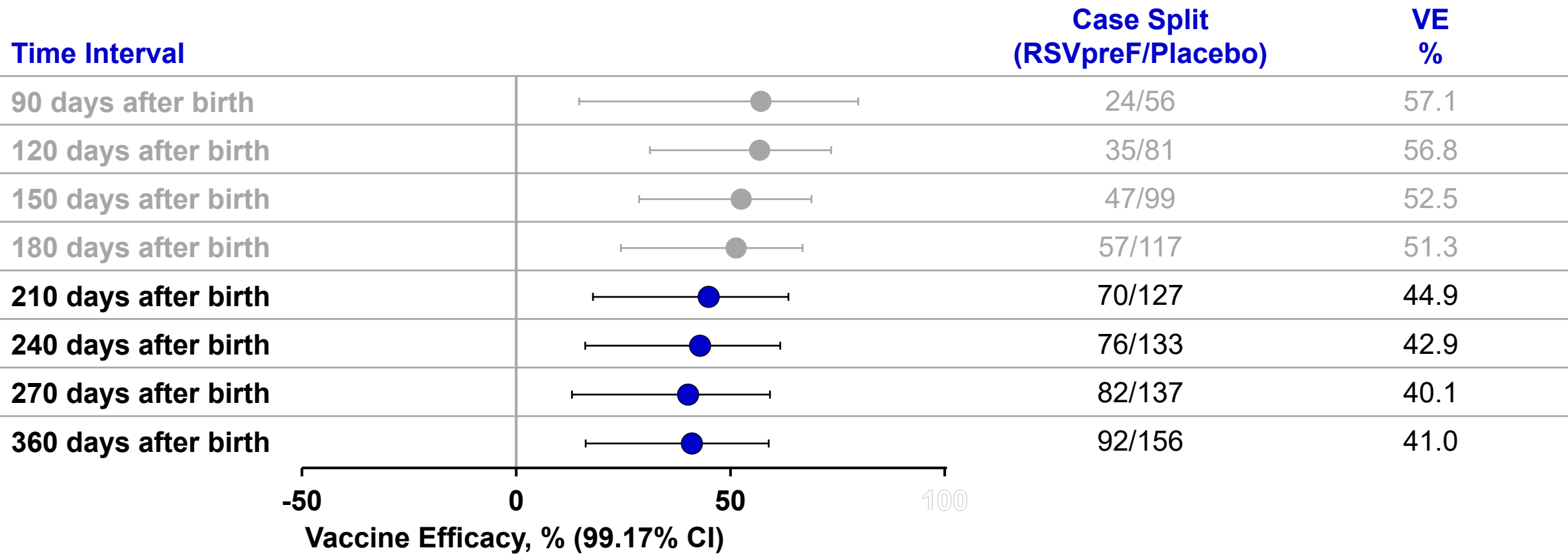
Time Interval	RSVpreF 120 µg N = 3495 n	Placebo N = 3480 n	Vaccine Efficacy (97.58-99.5% CI*)
0-90 Days after birth	24	56	57.1% (14.7, 79.8)
0-120 Days after birth	35	81	56.8% (31.2, 73.5)
0-150 Days after birth	47	99	52.5% (28.7, 68.9)
0-180 Days after birth	57	117	51.3% (29.4, 66.8)

\*99.5% CI for 90 days, 97.58% CI for 120/150/180 days. CI LB >20% for all time points.  
Bonferroni procedure and accounting for the primary endpoints results.  
MA-LRTI=Medically Attended Lower Respiratory Tract Illness

# Efficacy Maintained Against MA-LRTIs Through 6 Months



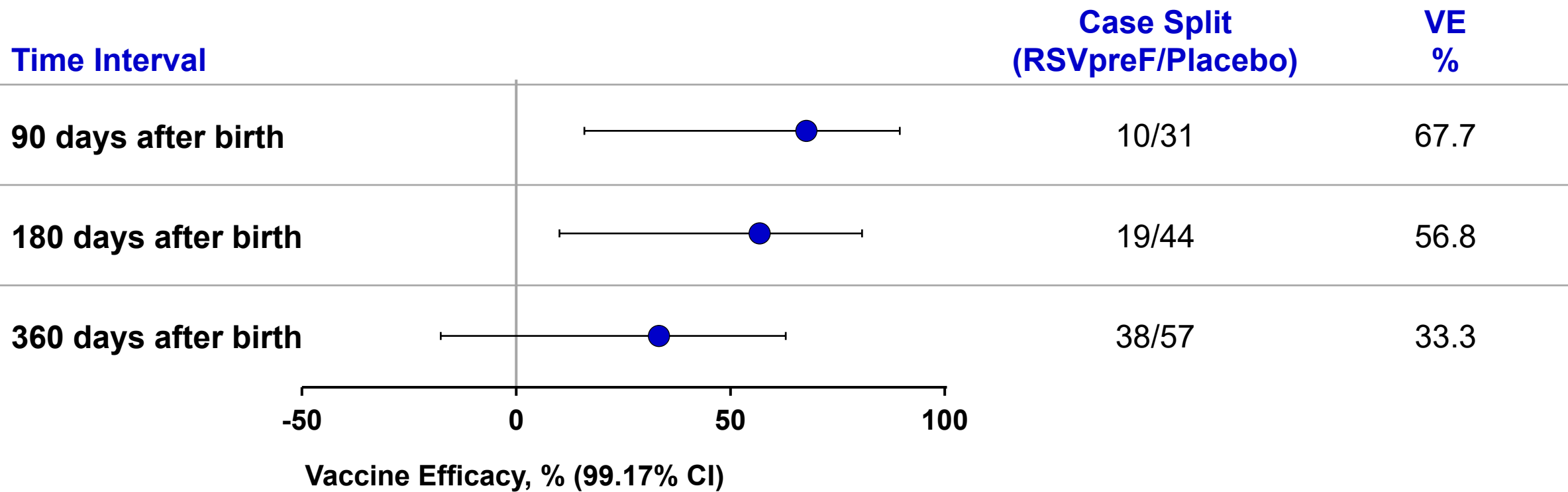
# Secondary Endpoint: Continued Efficacy Against RSV MA-LRTIs Through One Year



Met Statistical Criteria for Success (CI LB>0%)

# Secondary Endpoint: Hospitalizations Due to RSV

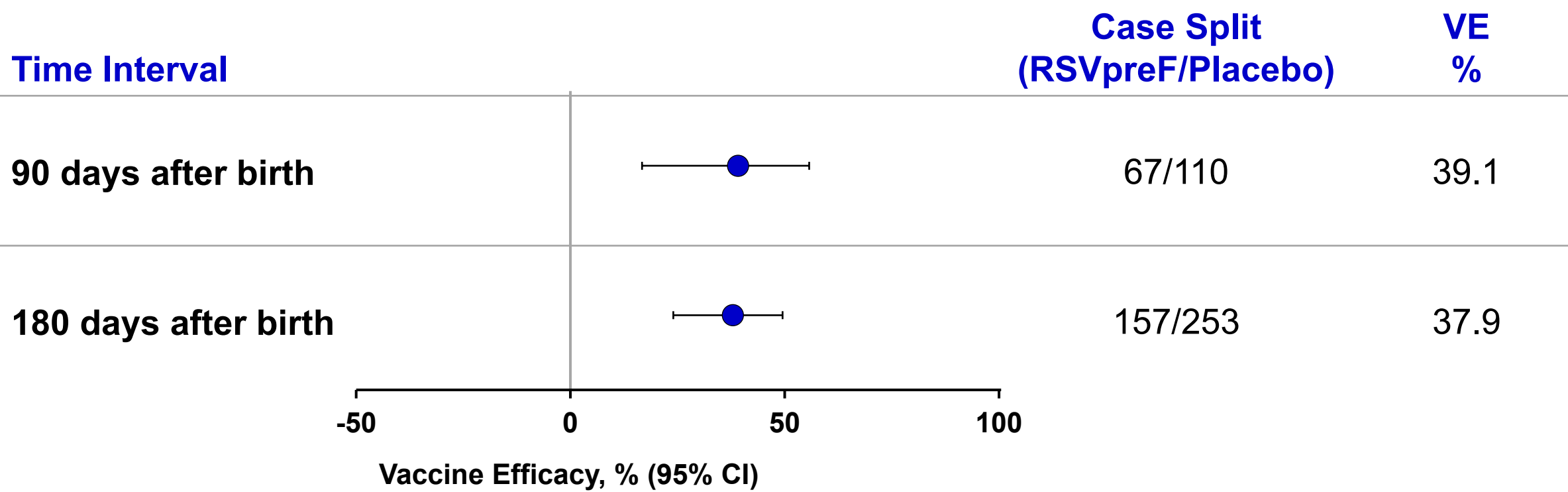
## Demonstrate Efficacy Through 6 Months



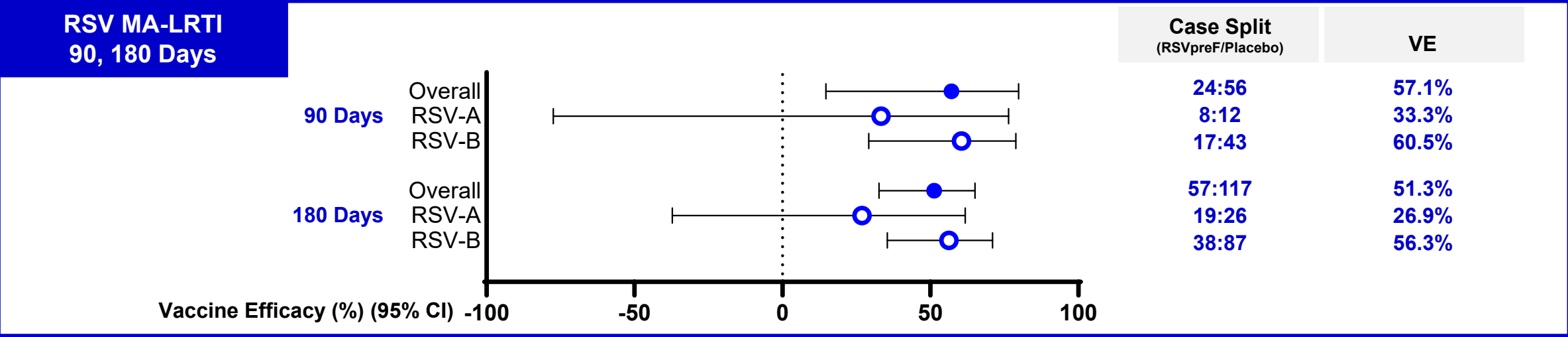
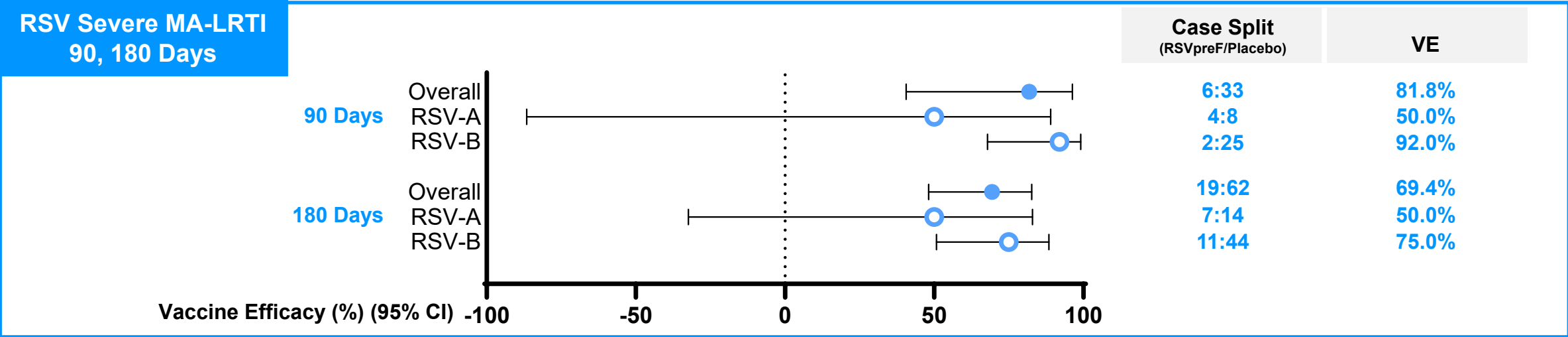
Met Statistical Criteria for Success Through 180 Days (CI LB>0%)

The confidence interval was adjusted using Bonferroni procedure and accounting for the primary endpoints results.

# Exploratory Endpoint: Efficacious Against RSV MA-RTI



# Consistent Efficacy Was Observed Across RSV Subgroups A and B



# RSVpreF Efficacious Against Severe MA-LRTI & MA-LRTI

	Time Period	Vaccine Efficacy % (CI*)
Severe MA-LRTI	First 90 days of life	81.8 (40.6, 96.3)
	Six-month follow-up	69.4 (44.3, 84.1)
MA-LRTI	One-year	41.0 (16.2, 58.9)

Met Statistical Criteria for Success





# Pharmacovigilance Plan

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**Jamie Wilkins, PharmD**

Senior Director,  
Head-Risk Management Center of Excellence  
Worldwide Safety

# Pharmacovigilance

## Pharmacovigilance



- Detect unexpected safety events rapidly
- Spontaneous report collection
- Active follow-up
- Frequent signal detection and evaluation

## Proactive Risk Mitigation

- Labeling
- Post-marketing safety study

# Proposed Post-Marketing Safety Study to Continue to Monitor the Safety of RSVpreF in Real-World Pregnant Populations



## STUDY OBJECTIVE

**Estimate the prevalence of adverse pregnancy and neonatal safety outcomes at or after birth in women who are exposed to RSVpreF during pregnancy**

- compared to women who are not exposed to RSVpreF during pregnancy, overall
- and among women who are immunocompromised

## STUDY DESIGN

Non-interventional cohort study

## MATERNAL & INFANT ENDPOINTS<sup>a</sup>

- Stillbirth
- Preterm birth
- Small for gestational age
- Low birth weight
- Guillain Barre Syndrome (GBS) and other immune-mediated demyelinating conditions

## DATA SOURCE

Large healthcare claims data source in the United States

- Including both commercial and Medicaid data

## GENERALIZABILITY

Inclusion of Medicaid data will allow for surveillance of demographically diverse populations overburdened by RSV disease

# Conclusions and Benefit Risk Assessment

**Bill Gruber, MD**

# Conclusions

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- **Significant RSV disease burden in infants <6m of age**
- RSVpreF maternal immunization demonstrated a **satisfactory safety profile** in mothers and their infants
- Phase 3 pivotal study demonstrated **high and consistent efficacy** across the spectrum of RSV disease
- Pharmacovigilance activities will **continue to monitor safety outcomes of interest** to further inform benefit:risk

# Favorable Benefit: Global

## RSVpreF has the Potential to Annually Prevent

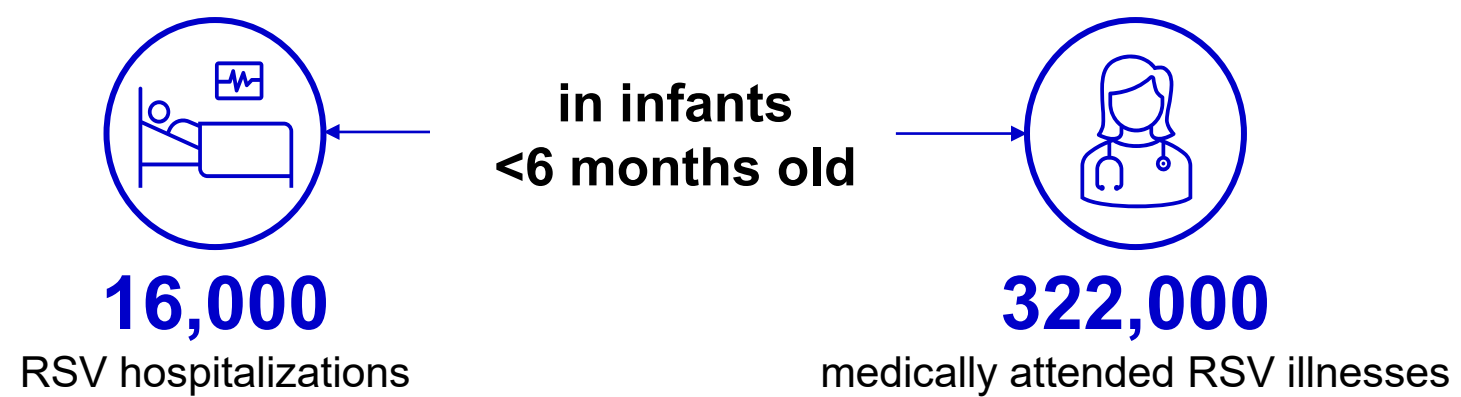
	Developing Countries	Industrialized Countries	Global
RSV-associated ALRI hospitalizations 0-6 mo olds (n)*	1,188,000	194,000	1,376,000
<b>Estimated RSV hospitalizations averted (n)**</b>	<b>824,472</b>	<b>134,636</b>	<b>954,944</b>

\*ALRI=acute lower respiratory infection. Modeled estimates are taken from Table 2 of Li et al, Lancet. 2022. Estimates of associated ALRI hospitalizations in 'developing' and 'industrialized' settings do not add up exactly to the 'Global' estimates as Global estimates were obtained by summing the numbers of developing and industrialized countries for each of the 1000 samples in the Monte Carlo simulation, see Li et al for details.

\*\*Assumes 100% uptake of vaccine.VE 69.4% for severe RSV LRTI 0-180 days (Kampmann et al, NEJM 2023)

# Favorable Benefit: US

In the US, RSVpreF has the Potential to Annually Prevent<sup>a</sup>:



BENEFITS		
	3 Months	6 Months
Severe MA-LRTI	81.8%	69.4%
MA-LRTI	57.1%	51.3%

Estimation of hospitalizations and medically-attended illness averted: Assumes 100% vaccine coverage, vaccine efficacy of 69.4% against severe MA-LRTI due to RSV and 51.3% against medically attended RSV LRTI (Kampmann et al, *NEJM* 2023): applied against estimated 29,000 RSV LRTI hospitalizations and 628,000 outpatient visits due to RSV that occur each year in children <6 mo old informed by Rha et al, *Pediatrics*, 2020, and Lively et al, *J. Pediatric Infect. Dis. Soc.*, 2019, respectively.

CC-70

# Bivalent RSV Prefusion F Vaccine

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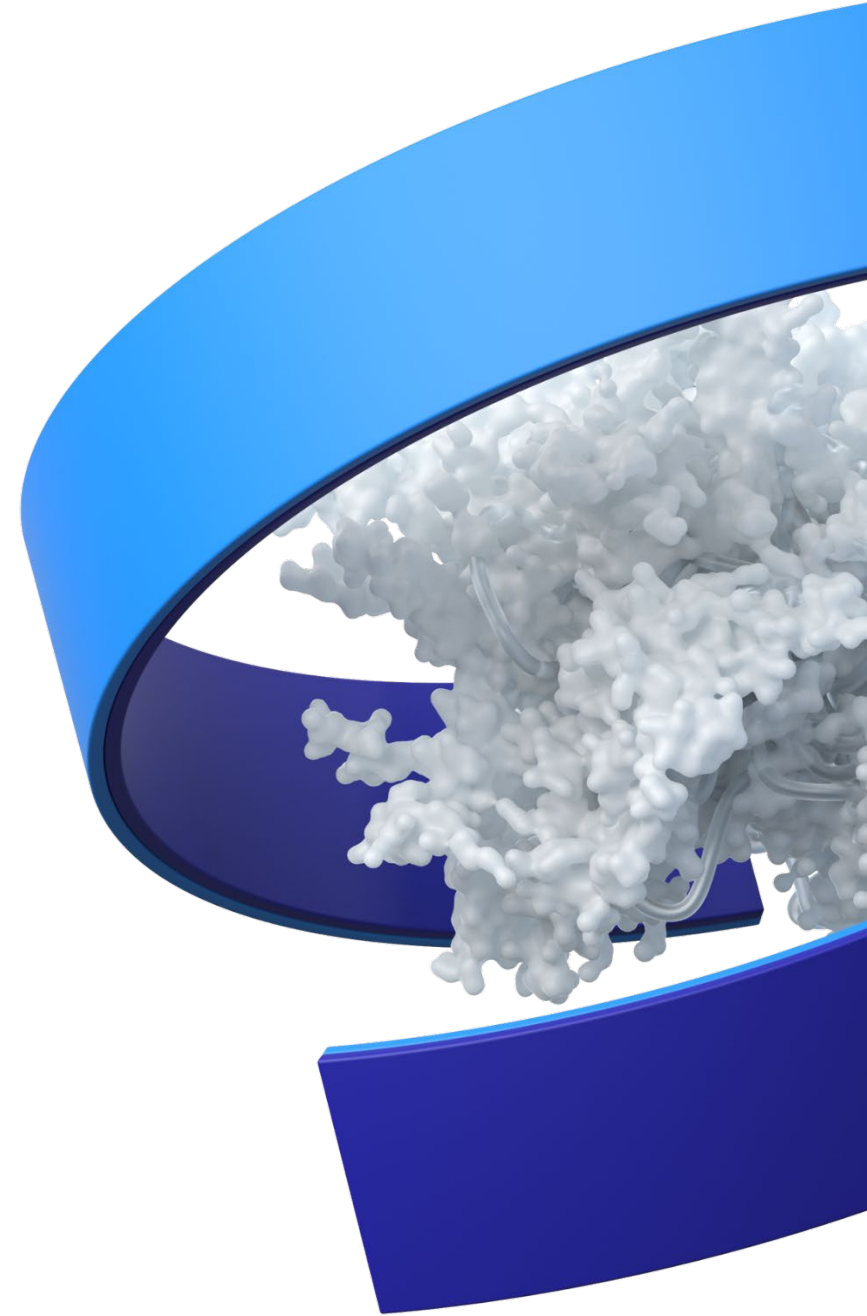
## Proposed Indication

***Prevention of lower respiratory tract disease and severe lower respiratory tract disease caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age by active immunization of pregnant individuals.***



# Bivalent RSV Prefusion F Vaccine for Maternal Immunization to Protect Infants

Vaccines and Related Biological  
Products Advisory Committee





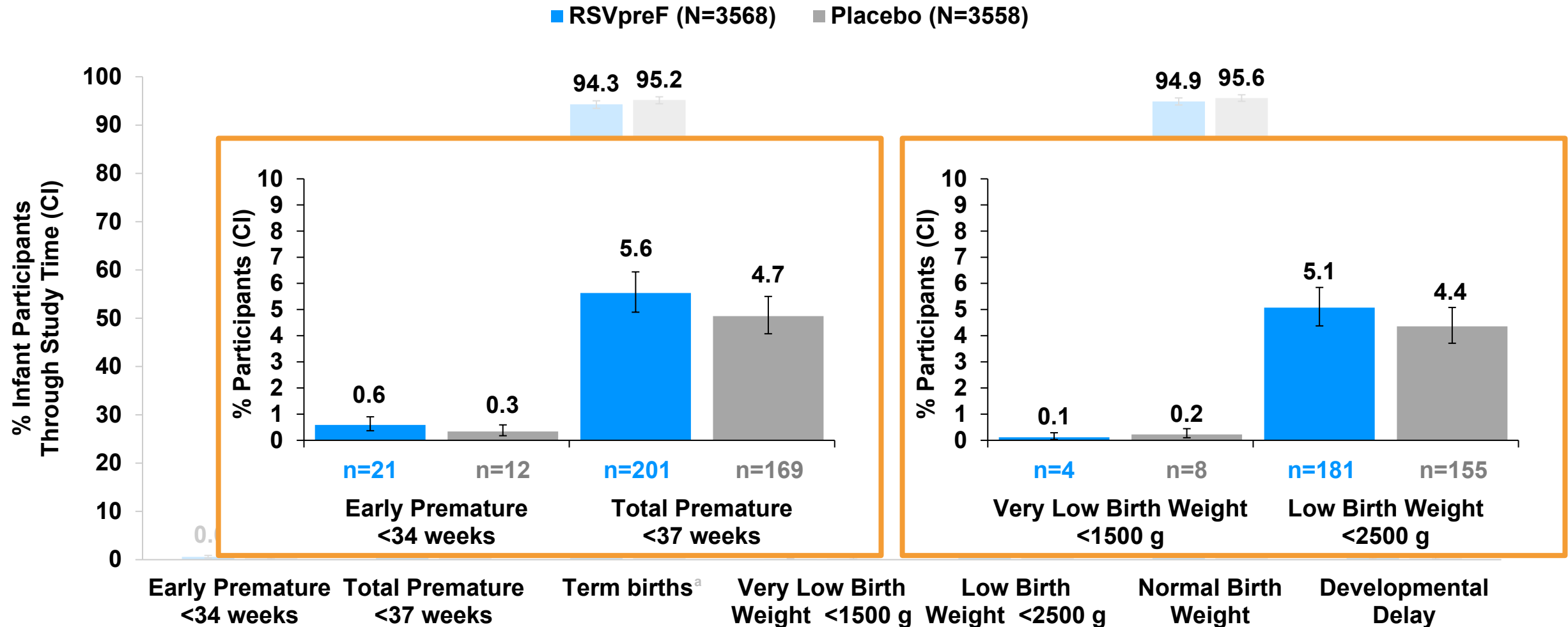
# Sponsor Backup Slides Presented to VRBPAC

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Bivalent RSV Prefusion F Vaccine  
for Maternal Immunization to Protect Infants

May 18, 2023

# Birth Outcomes: Prematurity and Extreme Prematurity Rates



a. Term births: infants born  $\geq 37$  weeks

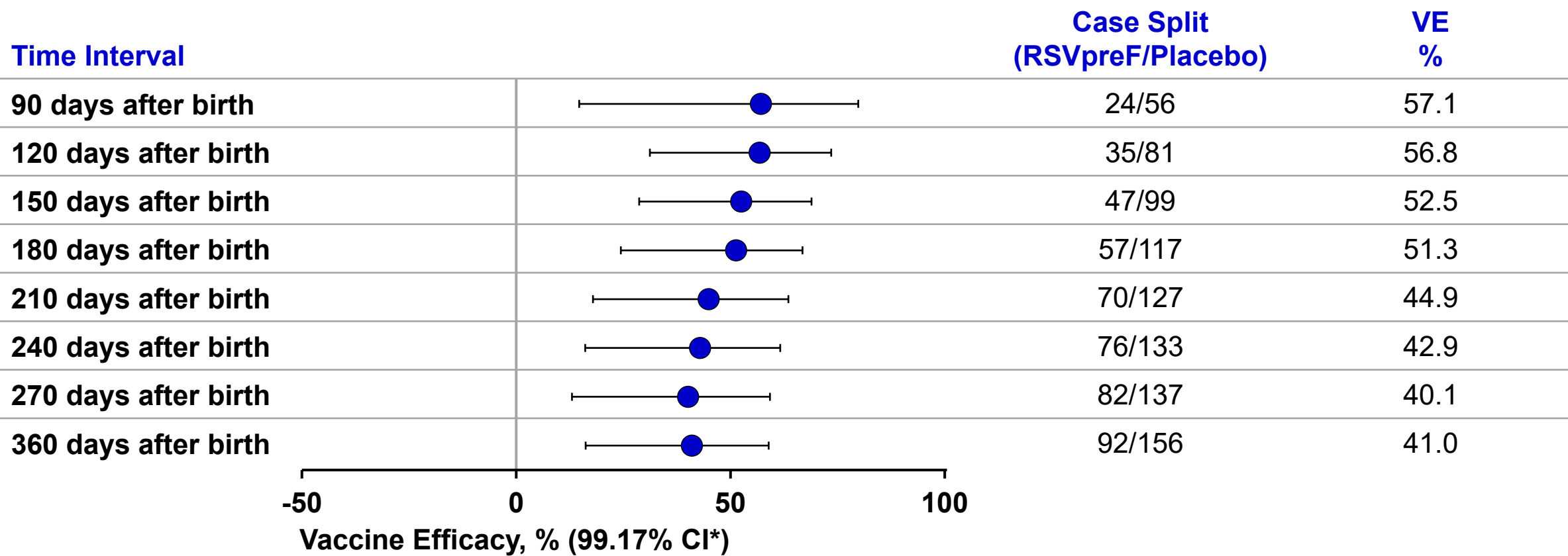
# Vaccine Efficacy by Interval Months

MA-LRTI	Time Interval (months)	RSVpreF 120 µg # Cases	Placebo # Cases	Total # Cases	Vaccine Efficacy %
	0-1	2	15	17	86.7
	1-2	12	22	34	45.5
	2-3	10	19	29	47.4
	3-4	11	25	36	56.0
	4-5	12	18	30	33.3
	5-6	10	18	28	44.4

# Vaccine Efficacy by Interval Months

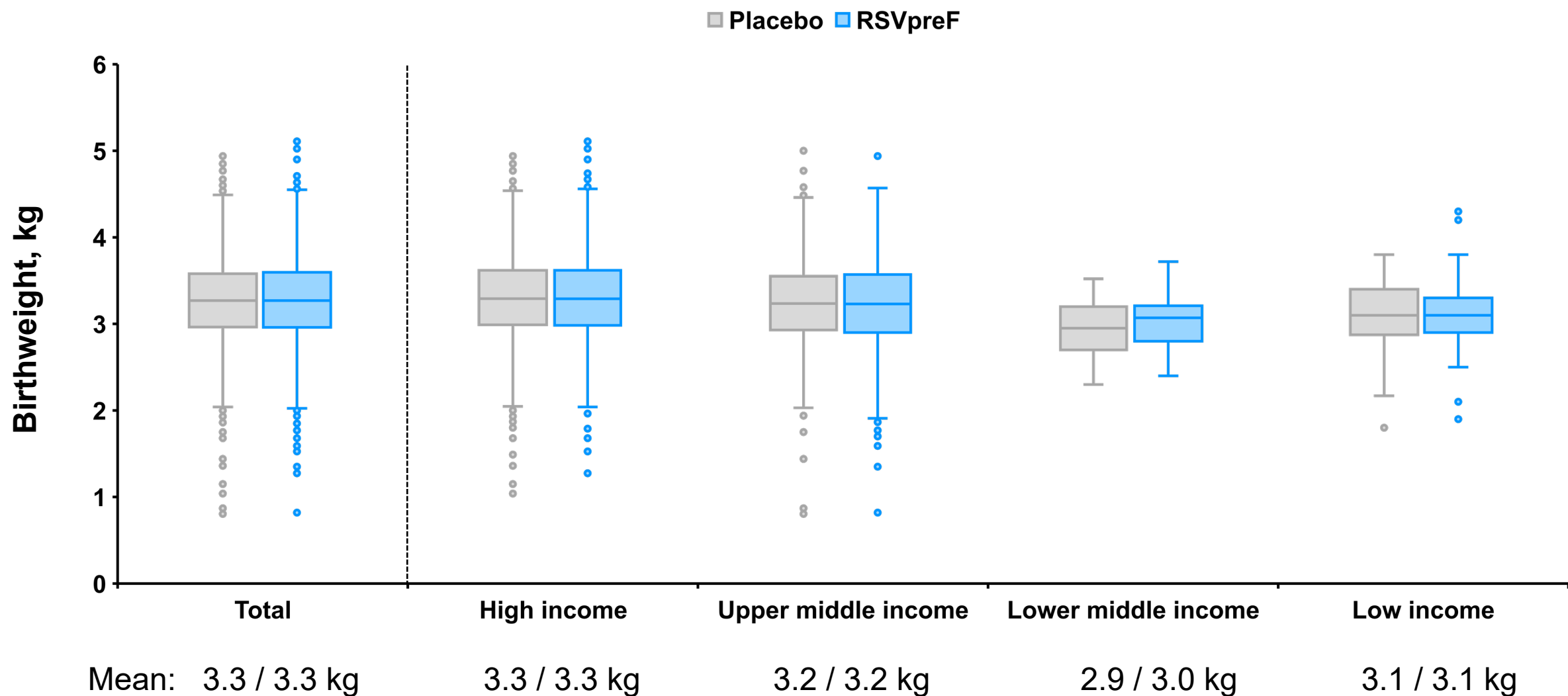
	Time Interval (months)	RSVpreF 120 µg # Cases	Placebo # Cases	Total # Cases	Vaccine Efficacy %
Severe MA-LRTI	0-1	1	10	11	90.0
	1-2	3	18	21	83.3
	2-3	2	5	7	60.0
	3-4	6	13	19	53.8
	4-5	4	9	13	55.6
	5-6	3	7	10	57.1

# Secondary Endpoint: Continued Efficacy Against RSV MA-LRTIs Through One Year



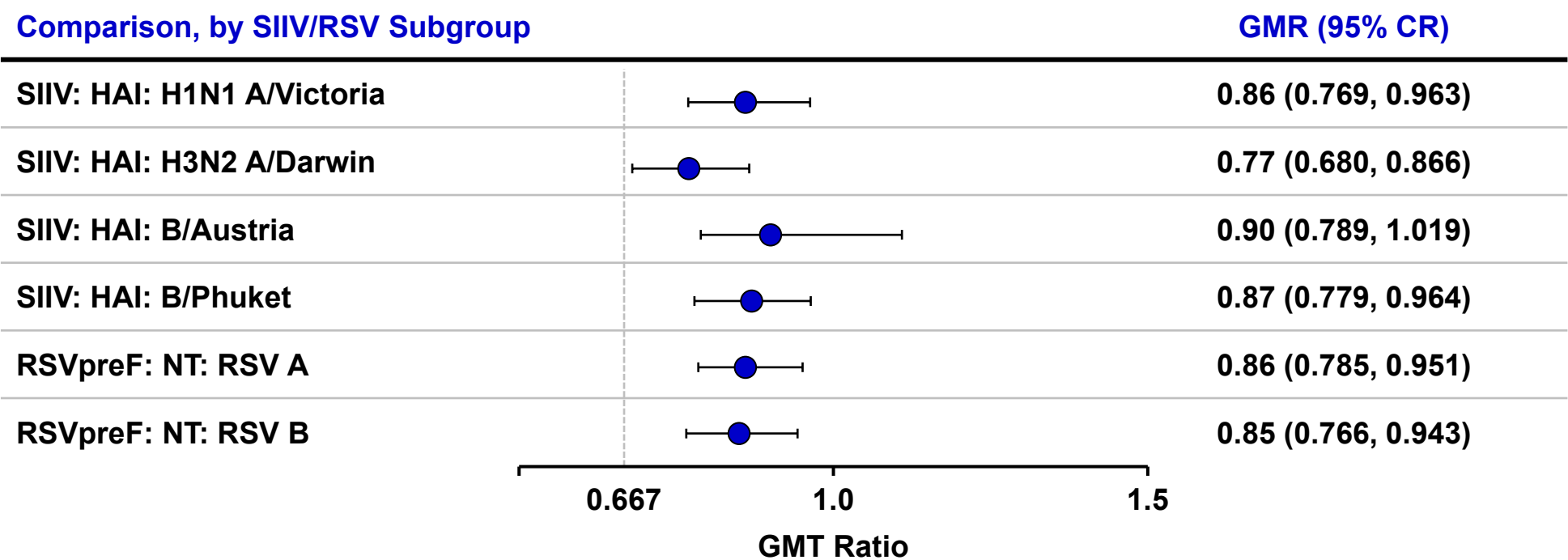
**Met Statistical Criteria for Success (CI LB>0%)**

# Mean Birthweight by Region Overall, and by Income Category



# C3671006 – Non-inferiority Demonstrated by SIIV HAI and RSV Neutralizing Titer GMRs

Forest Plot, Geometric Mean Ratios with 95% CIs – Evaluable RSV Immunogenicity Population and Evaluable SIIV Immunogenicity Population



Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; HAI = hemagglutination inhibition assay; NT = neutralizing titer; RSV = respiratory syncytial virus. GMRs and 2-sided confidence intervals (CIs) were calculated by exponentiating the mean difference of the logarithms of the titers (coadministration minus sequential-administration) and the corresponding confidence intervals (CIs) (based on Student's t distribution).



# Preterm Birth and Low Birth Weight by Income Group

	RSVpreF		Placebo	
	n/N	% (95% CI)	n/N	% (95% CI)
<b>Preterm &lt;37 weeks</b>				
All	201/3568	5.6 (4.9, 6.4)	169/3558	4.7 (4.1, 5.5)
HIC	126/2494	5.1 (4.2, 6.0)	126/2484	5.1 (4.2, 6.0)
UMIC	72/964	7.5 (5.9, 9.3)	39/961	4.1 (2.9, 5.5)
LMIC/LIC	3/110	2.7 (0.6, 7.8)	4/113	3.5 (1.0, 8.8)
<b>Low Birth Weight ≤2500g</b>				
All	181/3568	5.1 (4.4, 5.8)	155/3558	4.4 (3.7, 5.1)
HIC	108/2494	4.3 (3.6, 5.2)	102/2484	4.1 (3.4, 5.0)
UMIC	66/964	6.8 (5.3, 8.6)	42/961	4.4 (3.2, 5.9)
LMIC/LIC	7/110	6.4 (2.6, 12.7)	11/113	9.7 (5.0, 16.8)

# Live Birth Outcomes - Infant Participants from Combined Phase 2b and 3 Studies by Maternal Vaccine Group

	Pooled RSVpreF N=4024 n (%)	RSVpreF 120 µg N=3682 n (%)	Placebo N=3674 n (%)
Gestational age at birth <37 weeks	223 (5.5)	207 (5.6)	172 (4.7)

# Time from Vaccination to Birth Among Preterm and At Term Births

## Study C3671008, Infant Safety Population

Days from Vaccination to Birth	RSVpreF 120 µg N=3568 <sup>a</sup> n (%) <sup>b</sup>	Placebo N=3558 <sup>a</sup> n (%) <sup>b</sup>	Total N=7126 <sup>a</sup> n (%) <sup>b</sup>
Preterm Deliveries	201	169	370
≤7 days <sup>c</sup>	11 (5.5)	13 (7.7)	24 (6.5)
>7 days to ≤30 days <sup>c</sup>	69 (34.3)	58 (34.3)	127 (34.3)
>30 days <sup>c</sup>	121 (60.2)	98 (58.0)	219 (59.2)
At Term Deliveries	3364	3386	6750
≤7 days <sup>c</sup>	1 (<0.1)	2 (<0.1)	3 (<0.1)
>7 days to ≤30 days <sup>c</sup>	516 (15.3)	498 (14.7)	1014 (15.0)
>30 days <sup>c</sup>	2847 (84.6)	2886 (85.2)	5733 (84.9)

Note: Six participants have missing gestational age at birth in database, so are not included in counts above.

Note: Preterm/at term deliveries are determined based on gestational age at birth. Preterm = gestational age at birth less than 37 weeks. At term = gestational age at birth of 37 weeks or more.

Note: Number of days between vaccination and birth is calculated as birth date - vaccination date.

a. N = number of participants having birth date in the specified vaccine group. This value is the denominator for the percentage calculations.

b. n = Number of participants in the specified category.

c. Percentages for this row are based on the number of preterm/at term deliveries, respectively.

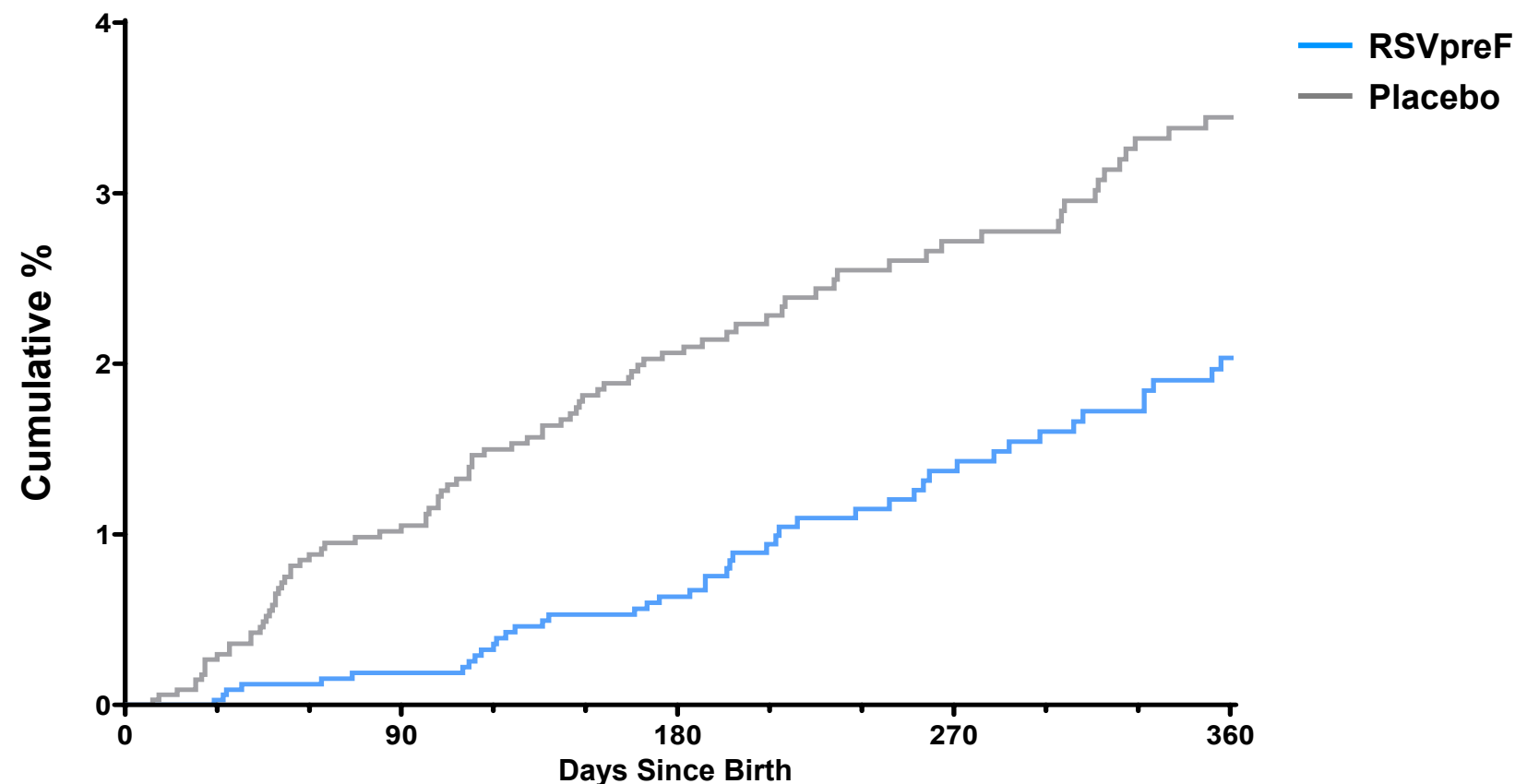
# Demographic and Baseline Characteristics US Safety Population

## All Maternal Participants

	RSVpreF N=1671 n (%)	Placebo N=1666 n (%)	Total N=3337 n (%)	US Census <sup>1</sup> %
Race				
American Indian or Alaska Native	10 (0.6)	12 (0.7)	22 (0.7)	1.3
Asian	39 (2.3)	44 (2.6)	83 (2.5)	6.1
Black or African American	167 (10.0)	171 (10.3)	338 (10.1)	13.6
Multiple	22 (1.3)	17 (1.0)	39 (1.2)	2.9
Native Hawaiian or other pacific islander	2 (0.1)	7 (0.4)	9 (0.3)	0.3
White	1397 (83.6)	1379 (82.8)	2776 (83.2)	75.8
Ethnicity				
Hispanic or Latino	357 (21.4)	375 (22.5)	732 (21.9)	18.9
Not Hispanic or Latino	1294 (77.4)	1265 (75.9)	2559 (76.7)	59.3

1. <https://www.census.gov/quickfacts/fact/table/US/LFE046221>. Note: US census data for “Not Hispanic or Latino” is reported as “White alone, not Hispanic or Latino”

# RSV-Positive Severe MA-LRTI Through 360 Days



Number at Risk						
RSVpreF	N	3495	2981	2820	1736	1378
	%	100%	85%	81%	50%	39%
Placebo	N	3480	2899	2749	1689	1361
	%	100%	83%	79%	49%	39%

# Infant Outcomes by Race and Ethnicity (US)

Race	Non-White US		White US		Total US	
	RSVpreF N=270 n (%)	Placebo N=262 n (%)	RSVpreF N=1352 n (%)	Placebo N=1350 n (%)	RSVpreF N=1654 n (%)	Placebo N=1644 n (%)
Infant Outcome						
Preterm Delivery <37 weeks	15 (5.6)	17 (6.5)	77 (5.7)	69 (5.1)	94 (5.7)	87 (5.3)
Low Birthweight	15 (5.6)	18 (6.9)	53 (3.9)	46 (3.4)	70 (4.2)	65 (4.0)

Ethnicity	Hispanic US		Non-Hispanic US		Total US	
	RSVpreF N=383 n (%)	Placebo N=389 n (%)	RSVpreF N=1234 n (%)	Placebo N=1224 n (%)	RSVpreF N=1654 n (%)	Placebo N=1644 n (%)
Infant Outcome						
Preterm Delivery <37 weeks	28 (7.3)	29 (7.5)	64 (5.2)	54 (4.4)	94 (5.7)	87 (5.3)
Low Birthweight	25 (6.5)	22 (5.7)	43 (3.5)	40 (3.3)	70 (4.2)	65 (4.0)

# Exploratory Analysis - Efficacy by Timing of Dosing During Pregnancy: RSV Severe MA-LRTI

