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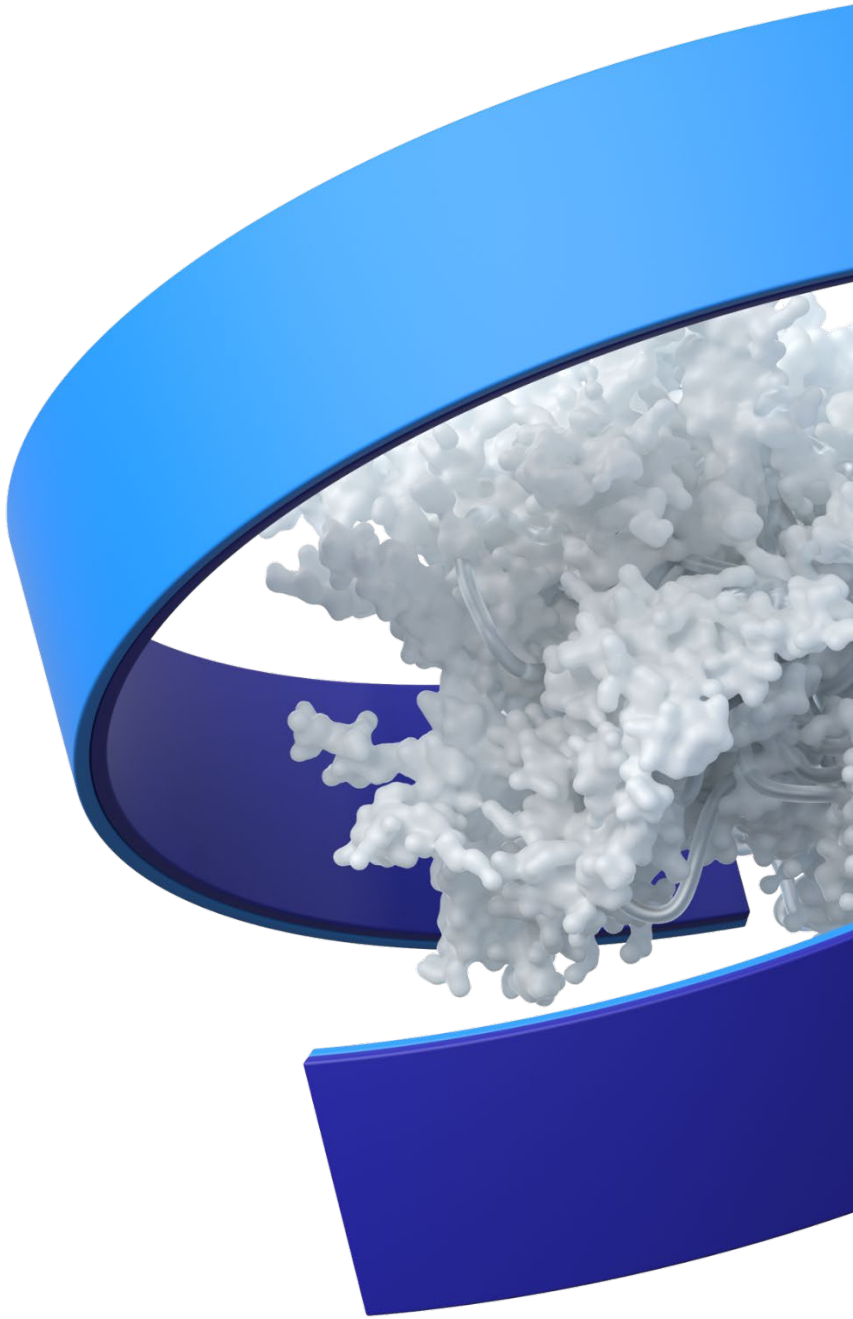
Bivalent RSV Prefusion F Vaccine for Maternal Immunization to Protect Infants



Vaccines and Related Biological Products Advisory Committee

May 18, 2023

Pfizer

RSV Disease and Pfizer's RSVpreF Vaccine

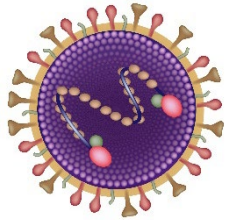
Bill Gruber, MD, FAAP, FIDSA, FPIDS

Senior Vice President Vaccine Clinical R&D
Pfizer

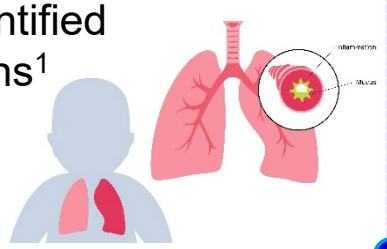
Presentation Agenda

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



1957
RSV identified in humans[1]



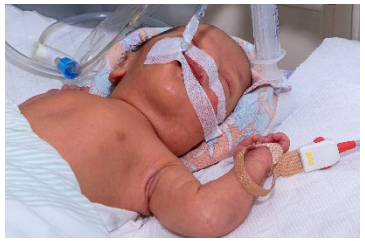
1970s
Glezen et al.
Neutralizing antibody titers in cord sera

1985-2003
Purified F protein[3]

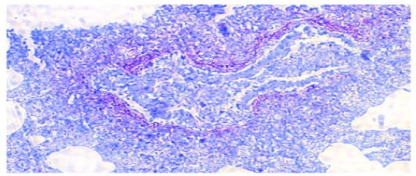
1996
RespiGam FDA approval

2003-2010
Vectored RSV vaccine

1950's | 1960's | 1970's | 1980's | 1990's | 2000's | 2010's



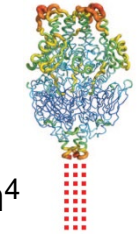
1966-69
Formalin-inactivated RSV[2]



1987-2003
Live attenuated RSV viruses

1998
Palivizumab/ Synagis FDA approval

2013
RSVpreF structure/ stabilization[4]

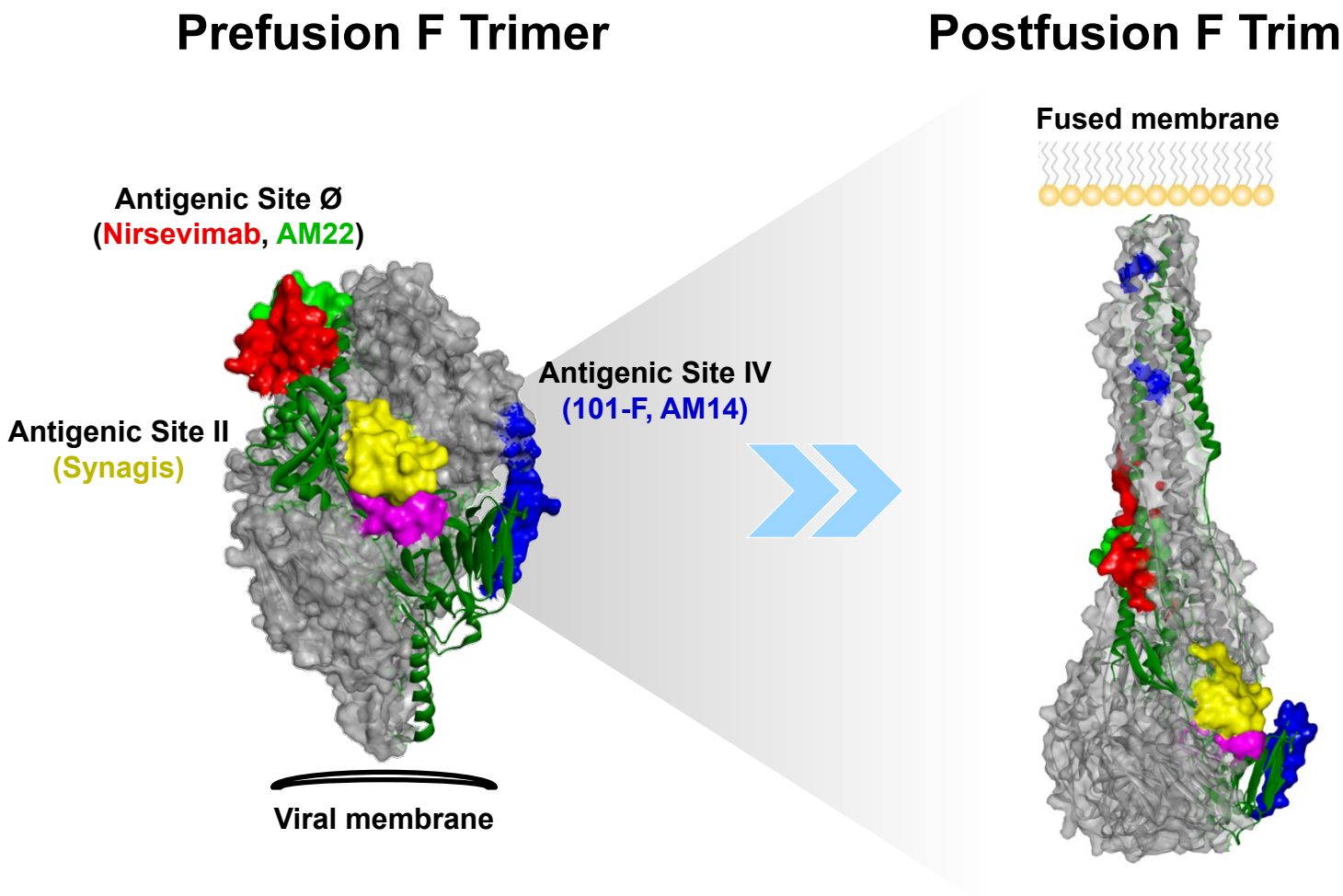


1. Gonik B. *Health Sci Pract*. 2019 Dec 23;7(4):515-520. doi: 10.9745/GHSP-D-19-00121. PMID: 31791975; PMCID: PMC6927832. 2. Fernando P. Polack et al. *J Exp Med* 2002;196:859-865.
3. Walsh., *J Gen Virol* 66:409; 1985. 4. McLellan., *Science* 342: 592; 2013

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

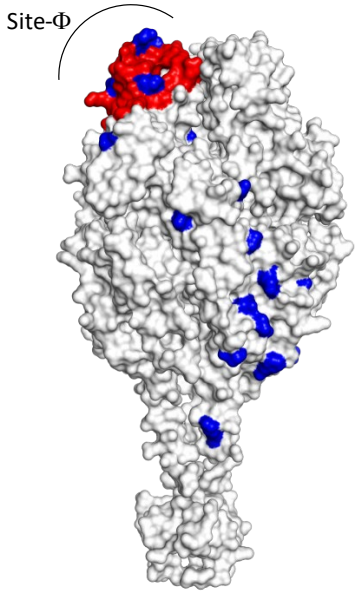
Antibodies specific to the prefusion form are most effective at blocking virus infection



NIH=National Institutes of Health
McLellan et al. Science, Nov 2013

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

RSV subgroup dominance can vary over time

Both subgroup viruses are associated with severe disease

Crank et al, Science 2019, 365:505-9; Hall et al,. J Infect Dis 1990; 162:1283-90 Langedijk et al., Rev Med Virol. 2021;e2284. https://doi.org/10.1002/rmv.2284

RSVpreF to Address a Significant Unmet Medical Need

Leading cause of LRTI among infants globally

50-80%
Hospitalizations for viral bronchiolitis[1,2]

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

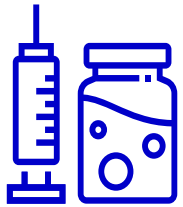
Well tolerated in the pregnant population and in their infants with a satisfactory safety profile

LRTI=Lower Respiratory Tract Infection
1. Meissner HC. *N Engl J Med.* 2016; 2. Shi T et al., *Lancet.* 2017.

Bivalent RSV Prefusion F Vaccine

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.



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

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Burden of RSV in US Infants

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

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Entity	Grant Support	Consultant		Travel	Other
	To Institution	Gratis	Fees Paid to Institution		DSMB, Study Section, etc.
Nonpharmaceutical					
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	
Pharmaceutical					
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			

DSMB, Data Safety Monitoring Board.

RSV Burden of Disease in Children

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Leading cause of LRTI among infants globally[1]

(50-80% of all hospitalizations for viral bronchiolitis)[2]

Historically, temperate climates have experienced seasonal outbreaks[3]

Infection can lead to respiratory distress and death[4]

Globally, RSV sickens 33 million children <5 years and 6.6 million infants <6 months each year[5]

Associated with longer term sequelae such as wheeze/asthma[6-8]

1. Shi et al., *Lancet*. 2017; 2. Meissner et al. *N Engl J Med.* 2016; 3. Li et al., *Lancet Global Health*. 2019; 4. Byington, et al., *Pediatrics*. 2015; 5. Li et al. *Lancet.* 2022; 6. Fauroux et al., *Infect Dis Ther.* 2017; 7. Blanken et al., *NEJM*. 2013; 8. Homaira et al., *JID*. 2018.

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

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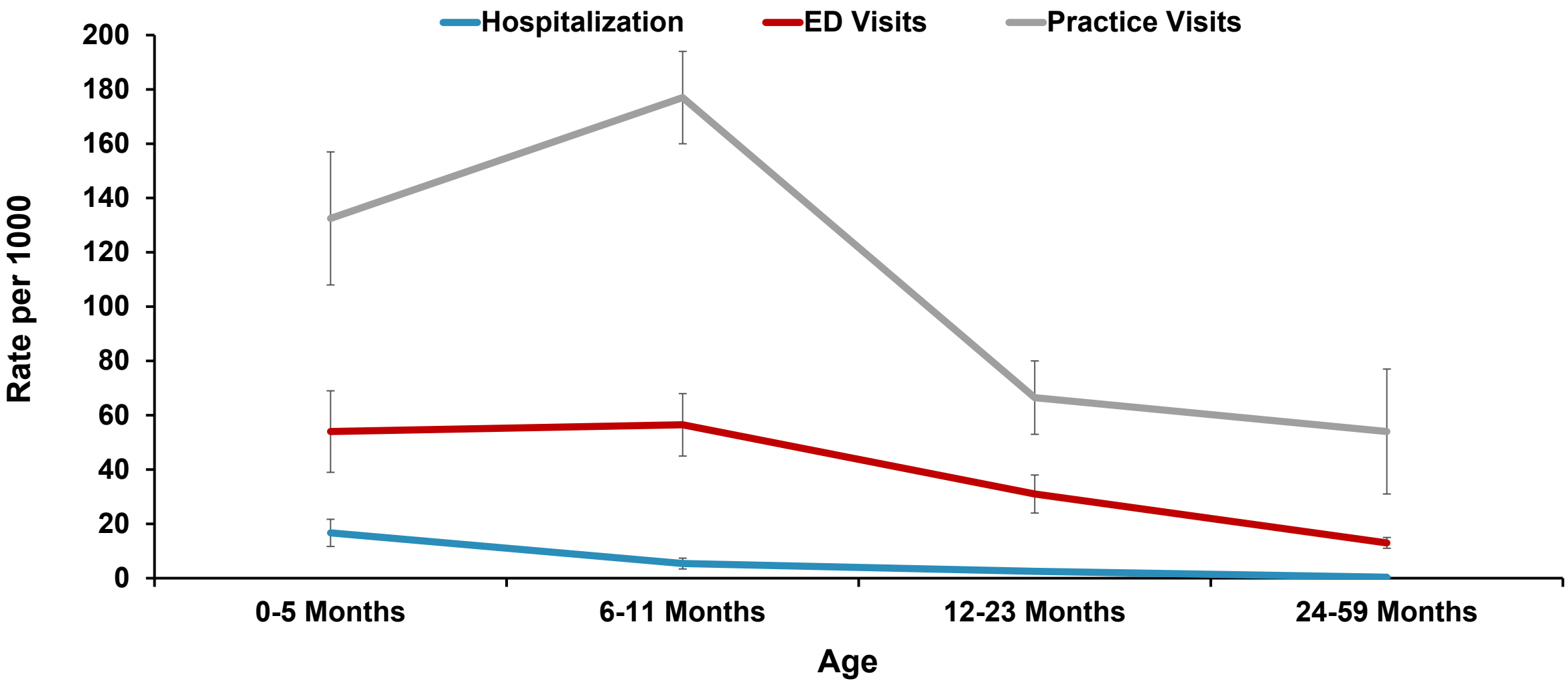

ED=Emergency department
Hall CB et al. *NEJM*. 2009;360:588-598

RSV Hospitalization Rates
Active Surveillance Studies

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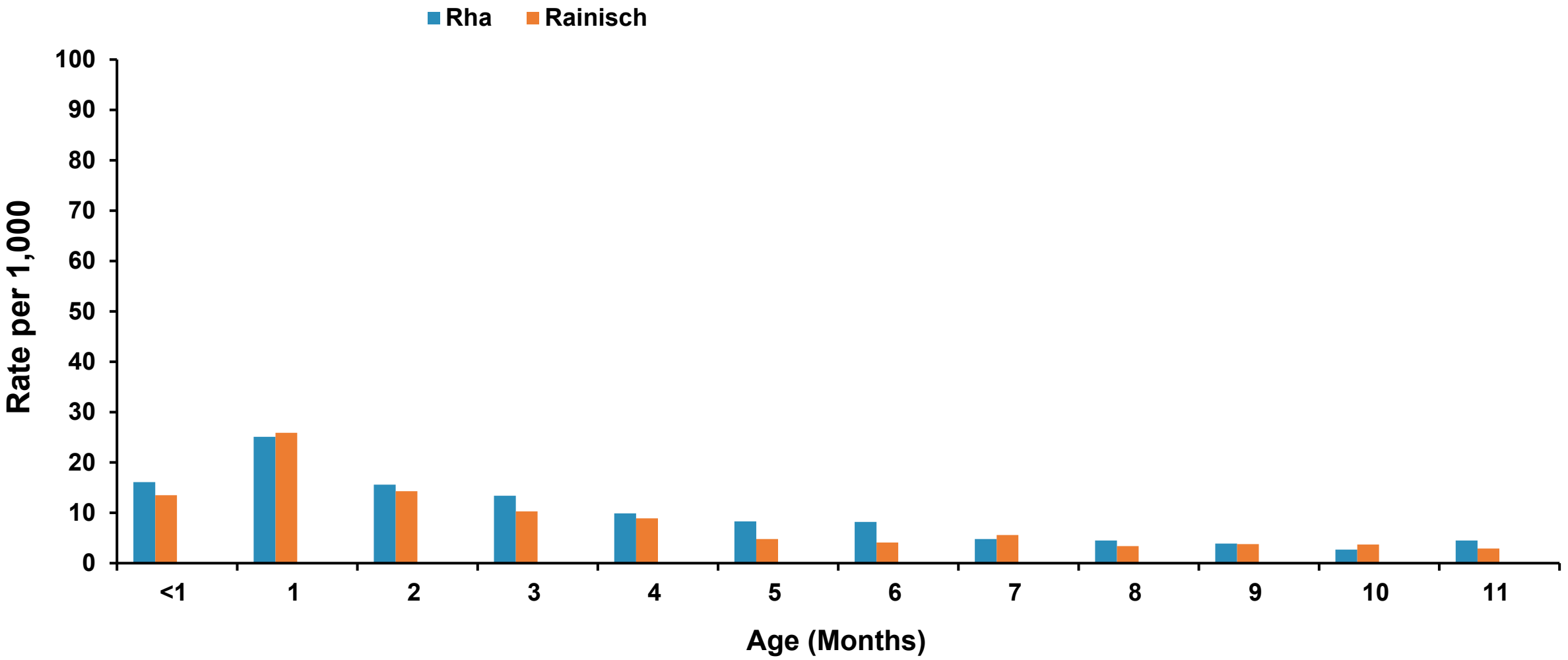
Annual RSV Hospitalization by Age <1y (Rate/1000 Children)[1-2]



1. Rha B et al *Pediatrics* 2020;146:e20193611 2. Rainisch G et al *Vaccine* 2020;38:251-257

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

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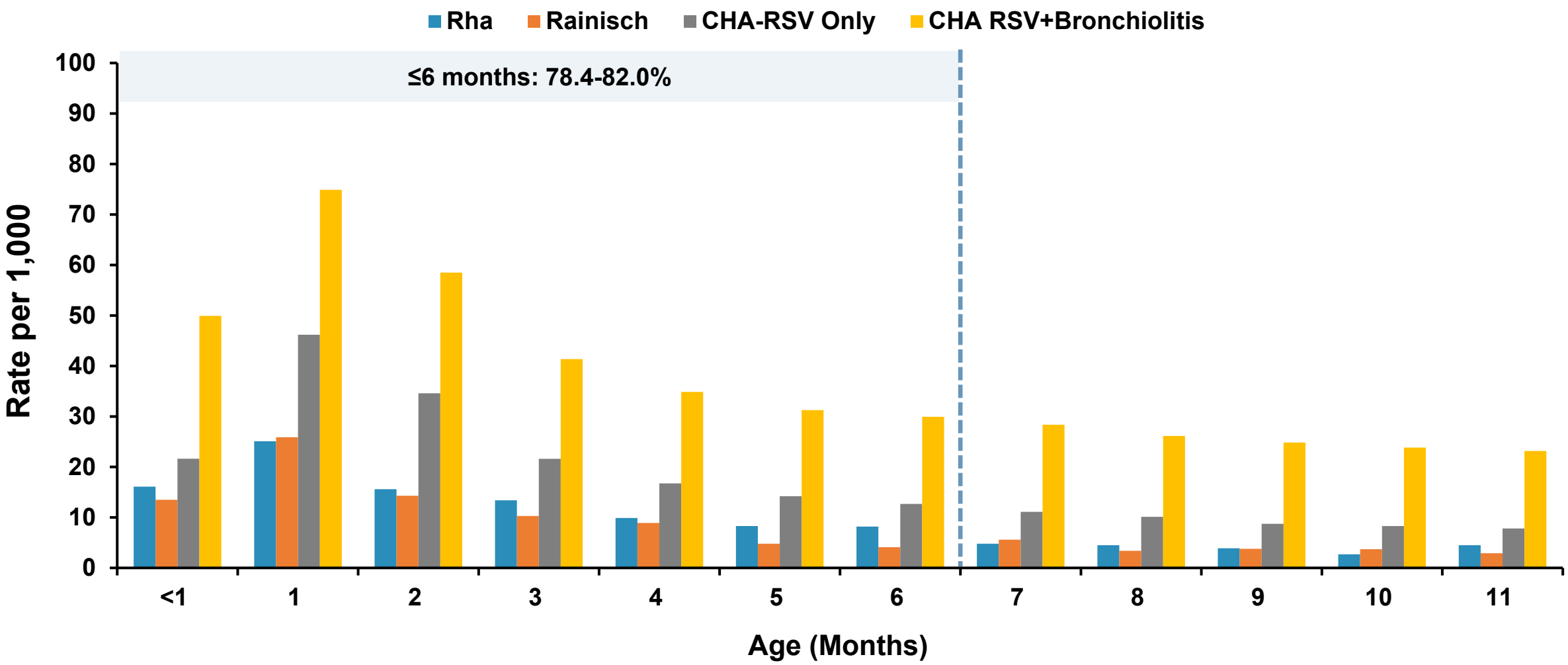
Annual RSV Hospitalization by Age <1y (Rate/1000 Children)[1-3]



CHA=Colorado Hospital Association

1. Rha B et al *Pediatrics* 2020;146:e20193611 2. Rainisch G et al *Vaccine* 2020;38:251-257. 3. Suss RJ et al (CHA data) Poster No ARNI0213 presented at RSVV2022 Belfast 29 Sept-2 Oct 2022.

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

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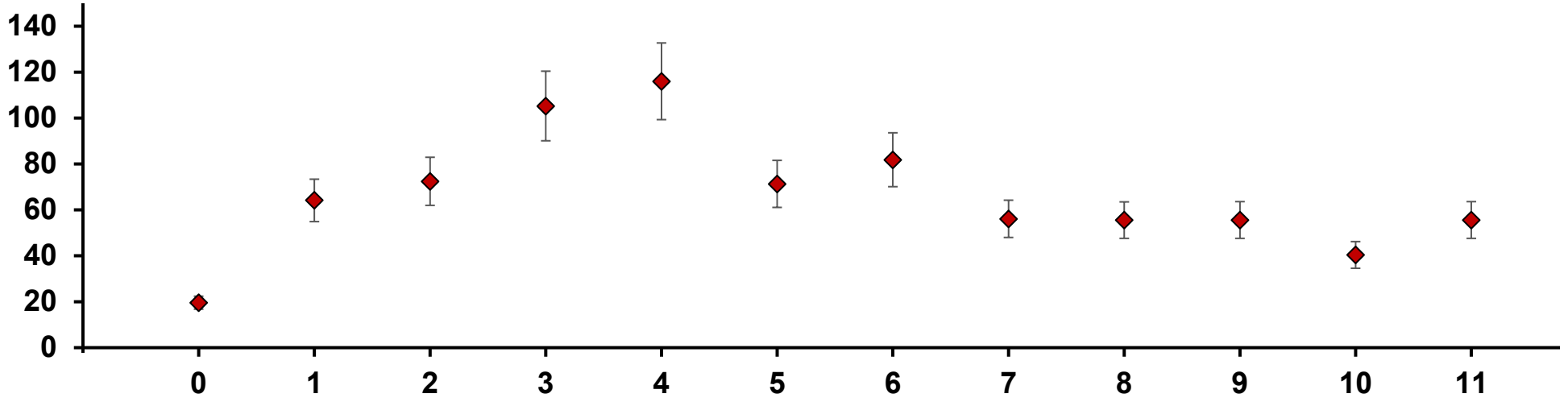
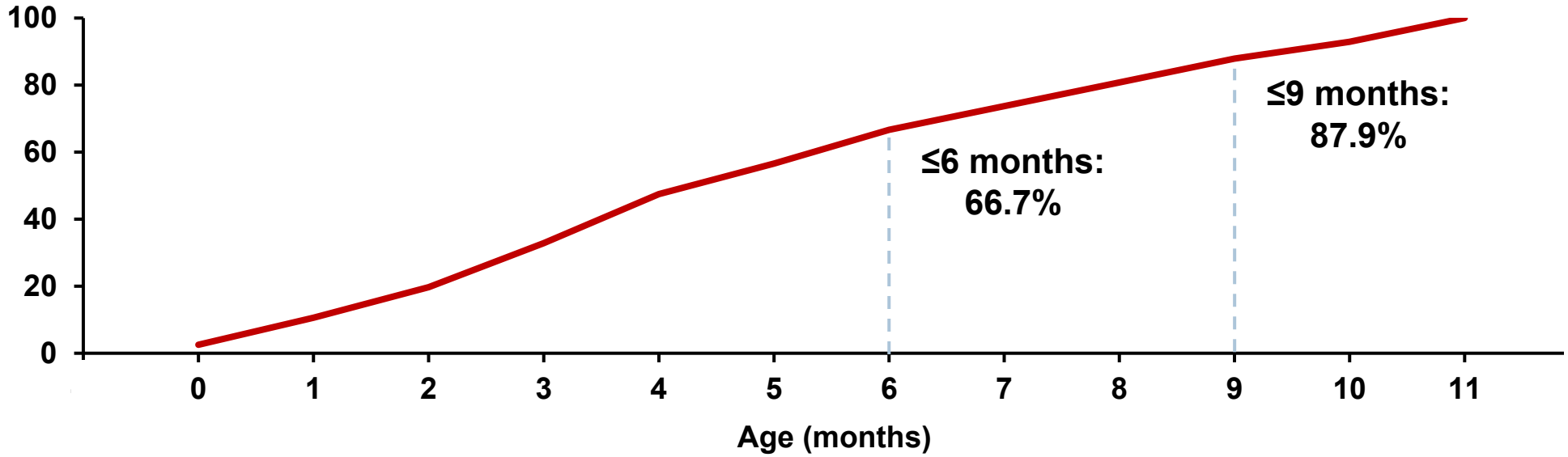
RSV Emergency Department Visits

Rate per 1000 Children (95% CI)



Cumulative RSV-ED Visits <1 year (%),

Annual Average 2004-2009



Hall CB et al. *NEJM*. 2009;360:588-598; Lively JY et al. *J Pediatr Infect Dis Soc* 2019; 8:284-286

Outpatient Visits Also Have a Significant Burden Under 6 Months

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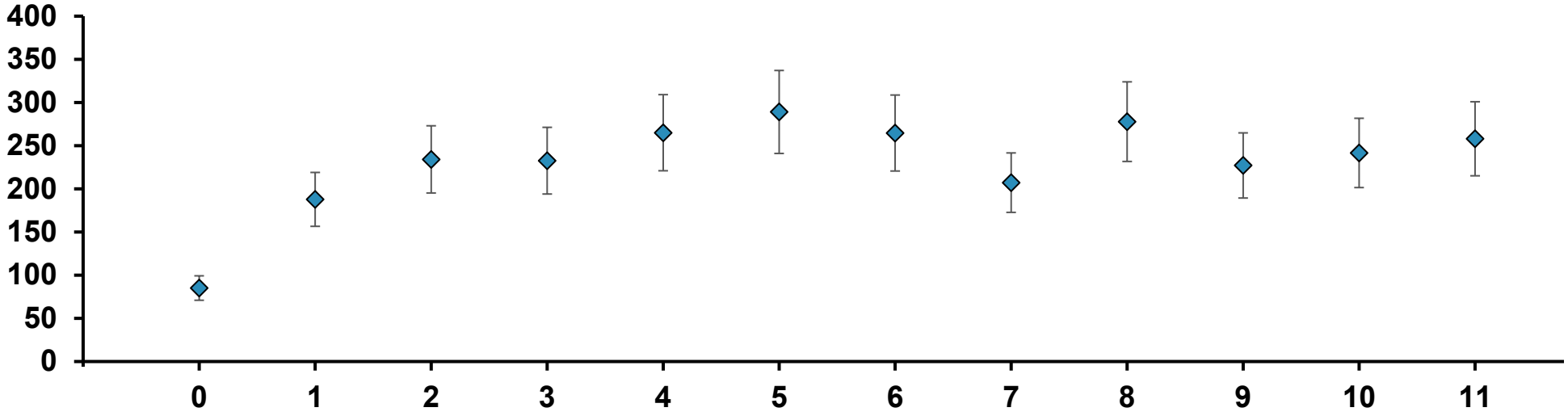
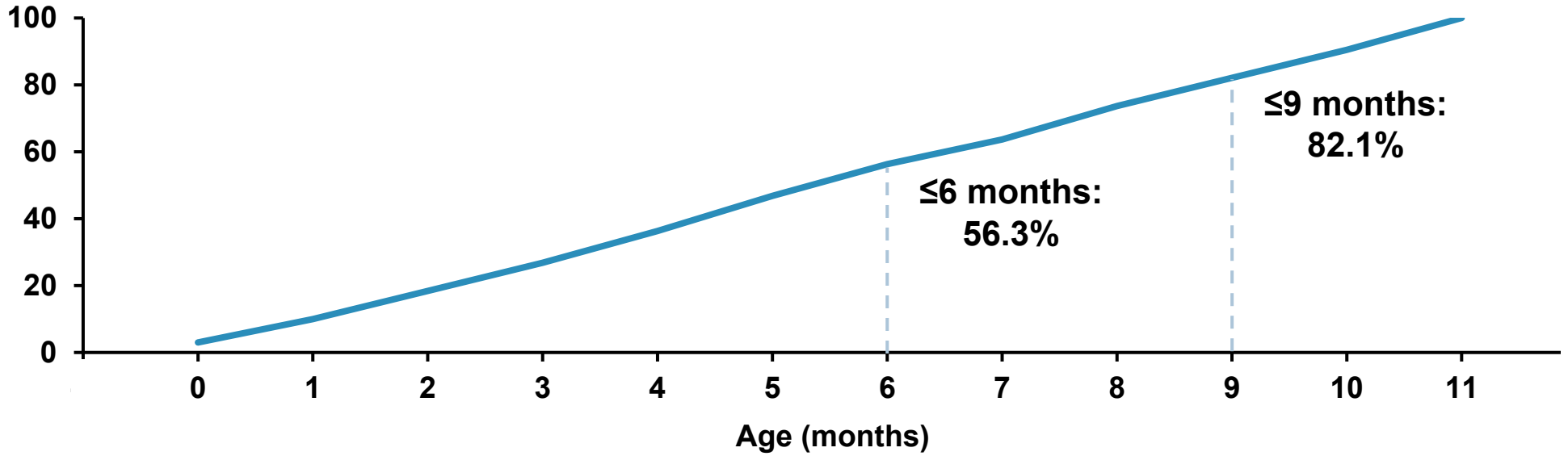
RSV Outpatient Visits

Rate per 1000 Children (95% CI)



Cumulative RSV-Outpatient Visits <1 year (%),

Annual Average 2004-2009



Hall CB et al. *NEJM*. 2009;360:588-598; Lively JY et al. *J Pediatr Infect Dis Soc* 2019; 8:284-286

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

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- 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

Simoes EA. *JID*. 2022;226(s2):s143-s147; Lefchak B et al. *Health Equity* 2022:6.1;40-48. Osterman MJ et al. *National Center for Health Statistics* 2018.

Conclusions

- 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

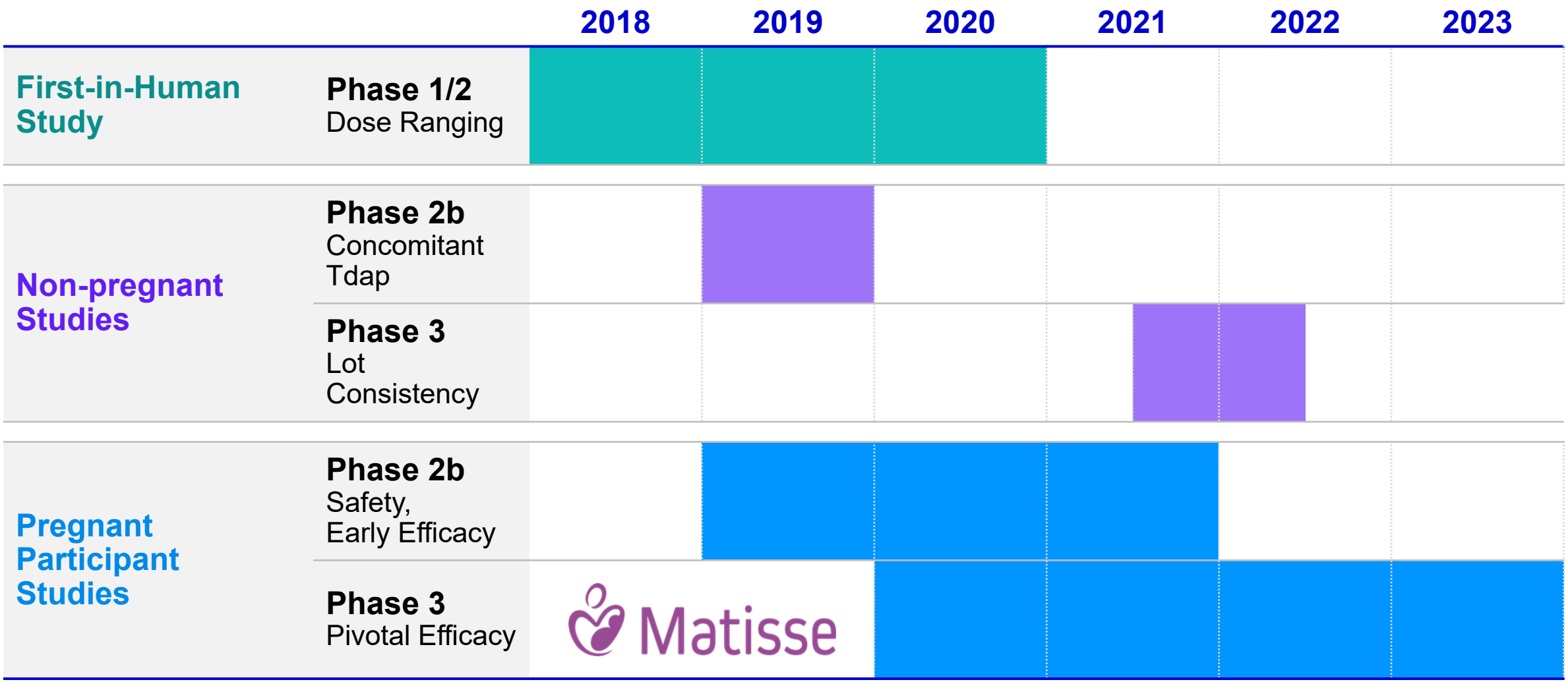
Shi et al., *Lancet*. 2017; Meissner et al. *N Engl J Med.* 2016; Li et al. *Lancet*. 2022, Hall CB et al. *NEJM*. 2009;360:588-598, Rha B et al *Pediatrics* 2020;146:e20193611; Rainisch G et al *Vaccine* 2020;38:251-257; Suss RJ et al (CHA data) Poster No ARNI0213 presented at RSVV2022 Belfast 29 Sept-2 Oct 2022; Lively JY et al. *J Pediatr Infect Dis Soc* 2019; 8:284-286; https://www.npr.org/2022/10/24/1130764314/childrens-hospitals-rsv-surge; Simões EA. *JID*. 2022;226(s2):s143-s147

Maternal RSV Program

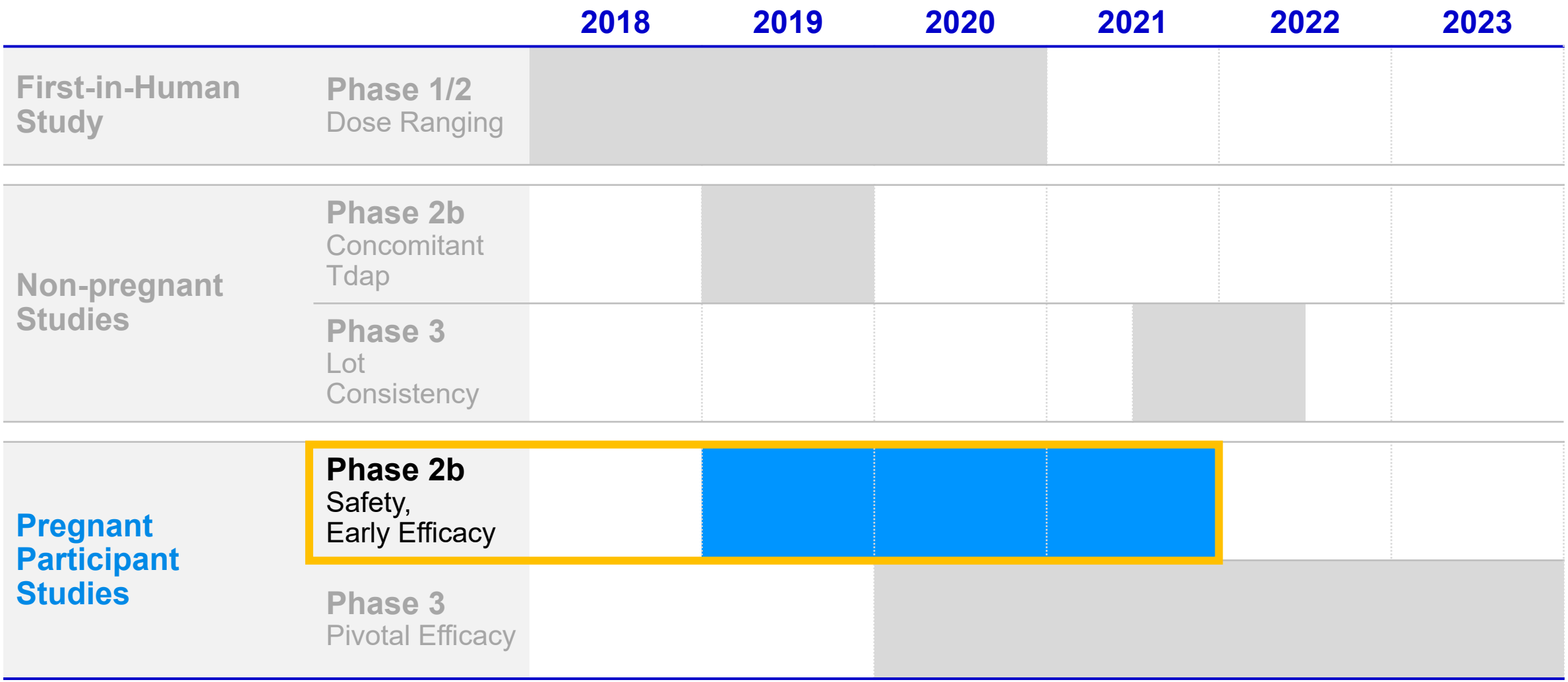
Iona Munjal, MD, FAAP

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

RSVpreF Maternal Immunization Clinical Development Program



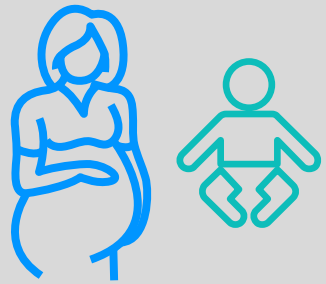
RSVpreF Maternal Immunization Clinical Development Program



Phase 2b Maternal Immunization Study

Safety, Dose Finding, & Immunogenicity throughout Pregnancy and Infancy

Healthy Pregnant Women
24 to 36 weeks gestation



Maternal
N = 579

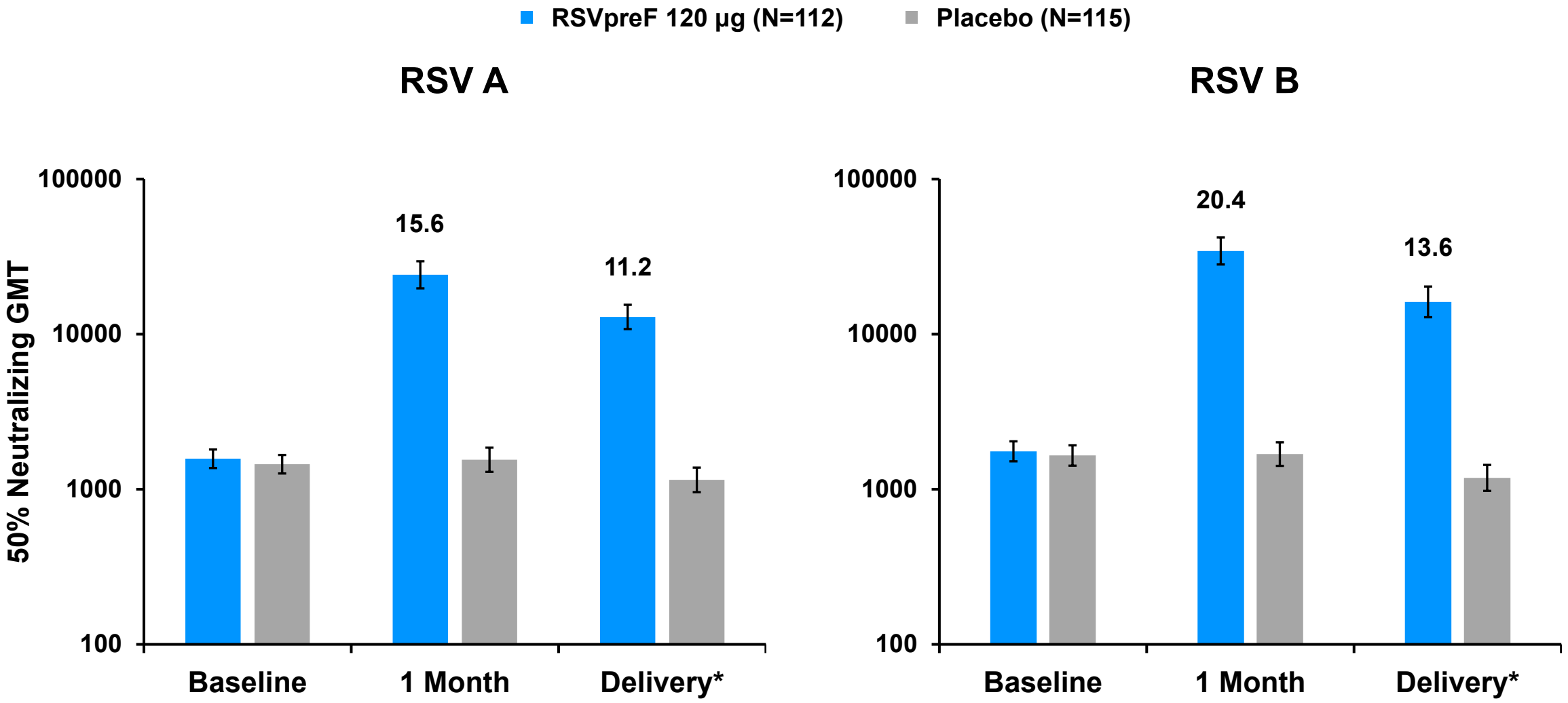
Infants
N = 572

R

- RSVpreF 120 µg
- 120 µg + $Al(OH)_3$
- 240 µg
- 240 µg + $Al(OH)_3$
- Placebo

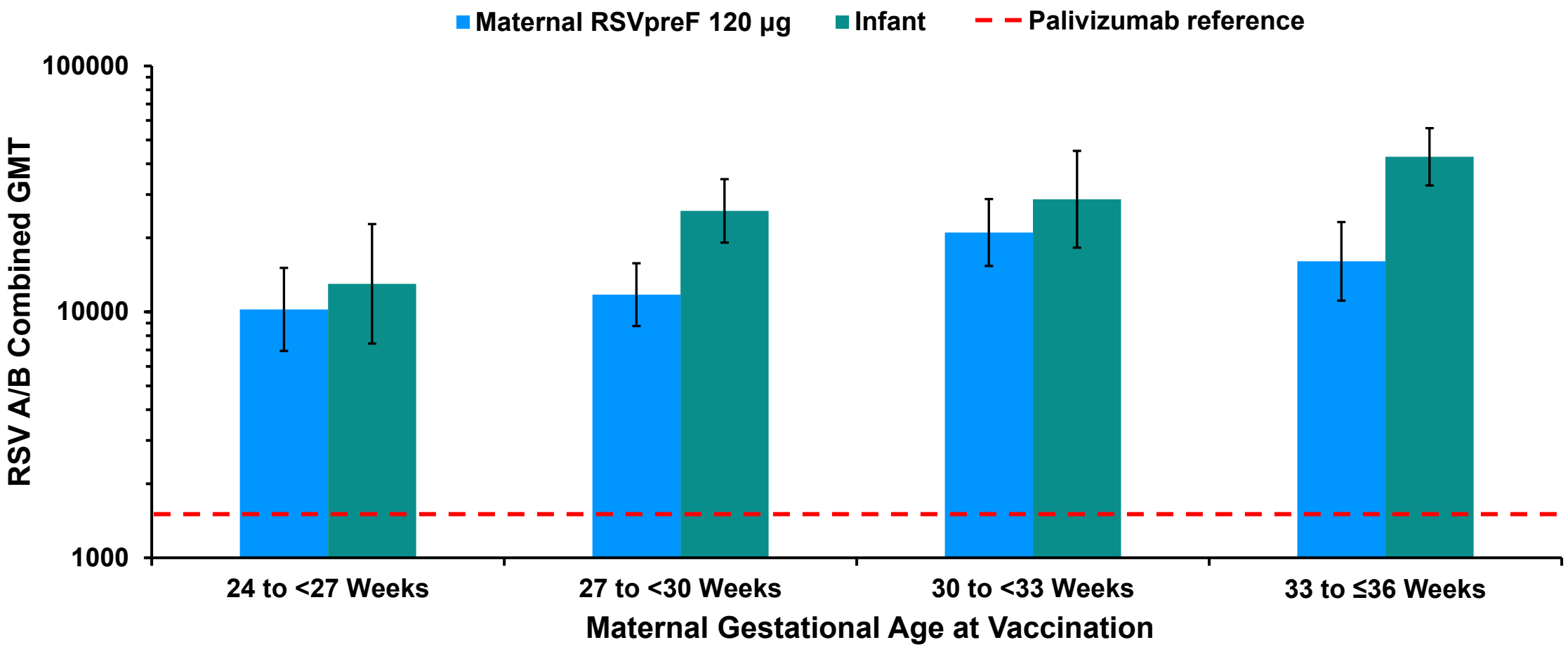
RSVpreF Elicits High Maternal Neutralizing Titers at Delivery

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

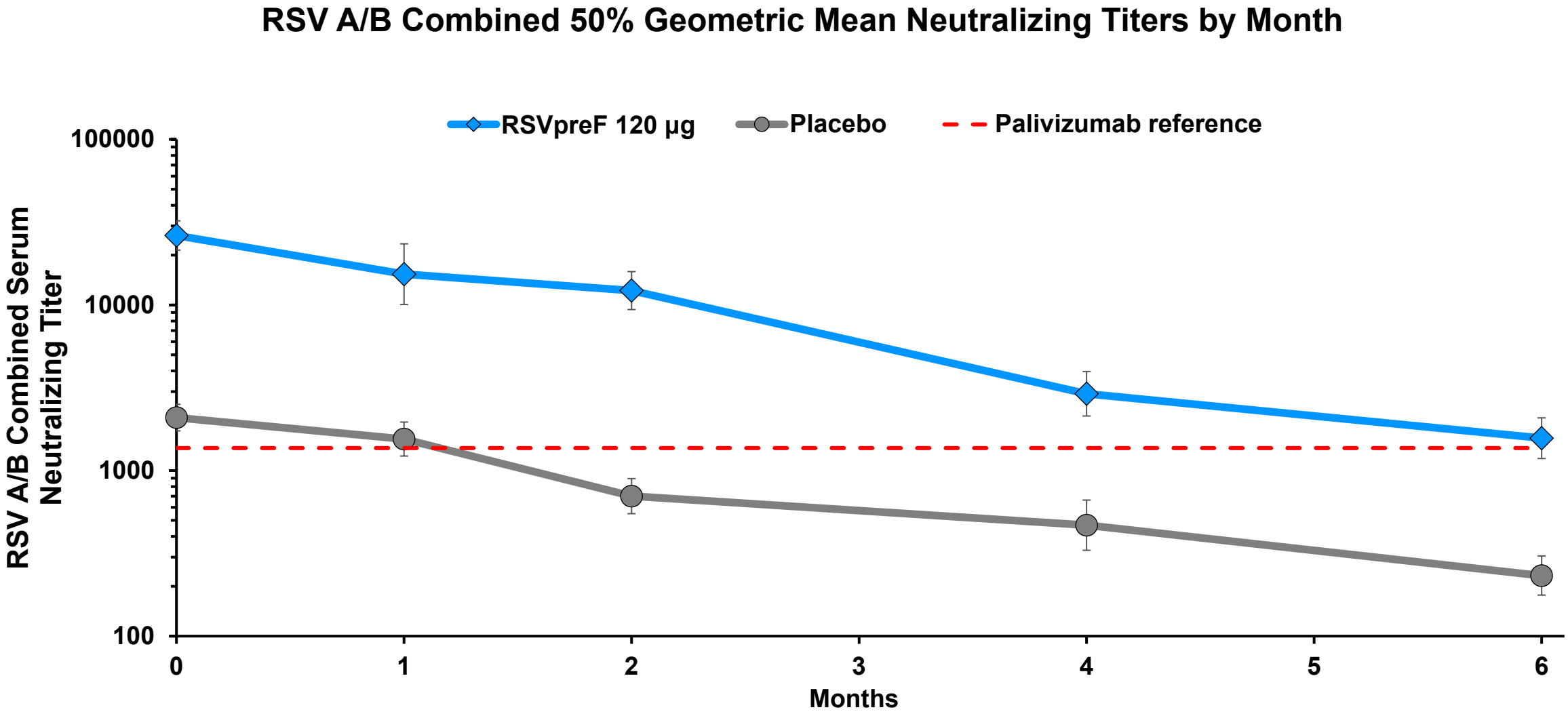
Neutralizing GMTs at Birth Higher in Infants at All Maternal Gestational Ages at Vaccination



Transplacental Transfer Ratio	**1.18**	**2.21**	**1.46**	**2.69**

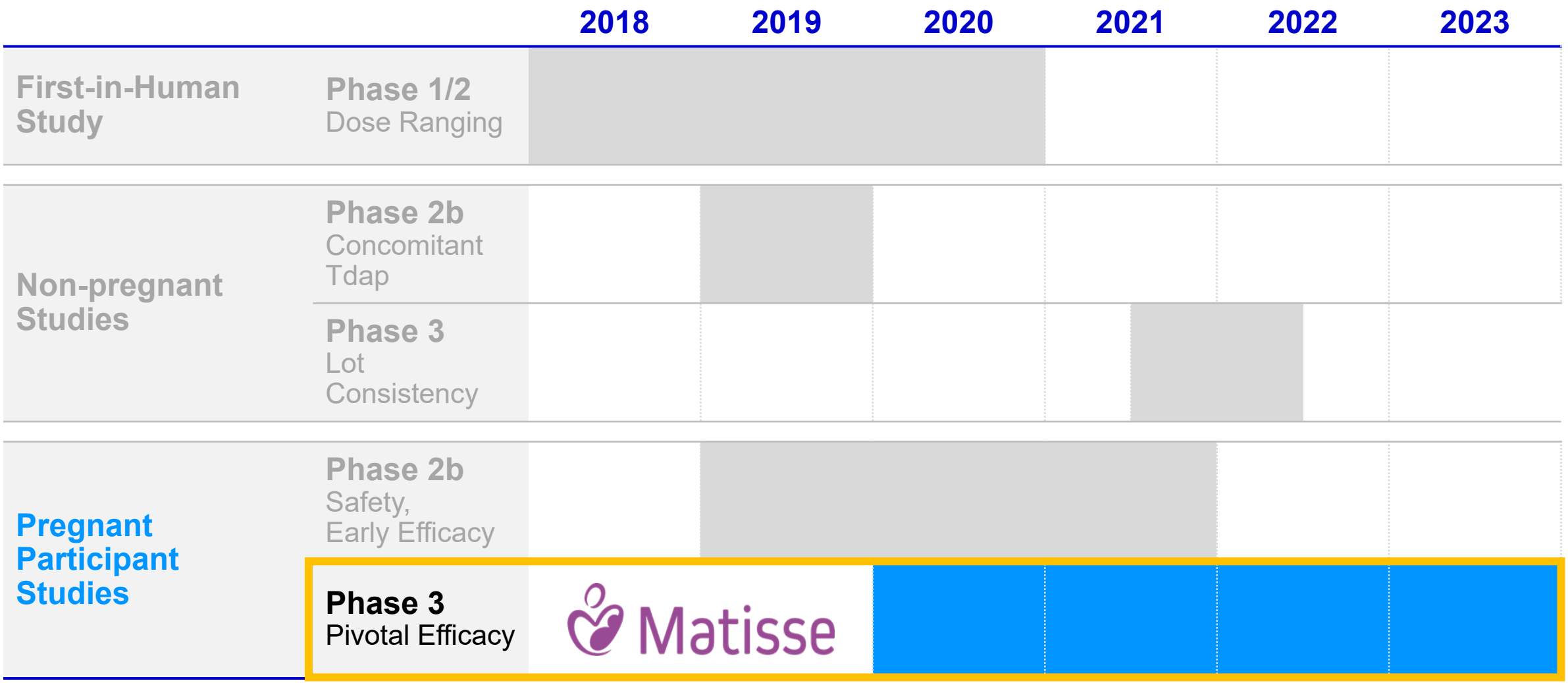
Palivizumab reference line = 50% A/B neutralizing titer of a 100ug/mL palivizumab dose, demonstrated to be efficacious in preventing infant RSV-associated ICU admission
(Forbes ML, Kumar VR, Yogev R, et al. *Hum Vaccin Immunother* 2014;10:2789-94.)

Infant Neutralizing Titers Persist, Remaining High Through 6 Months of Age



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, Yogev R, et al. *Hum Vaccin Immunother* 2014;10:2789-94.)

RSVpreF Maternal Immunization Clinical Development Program



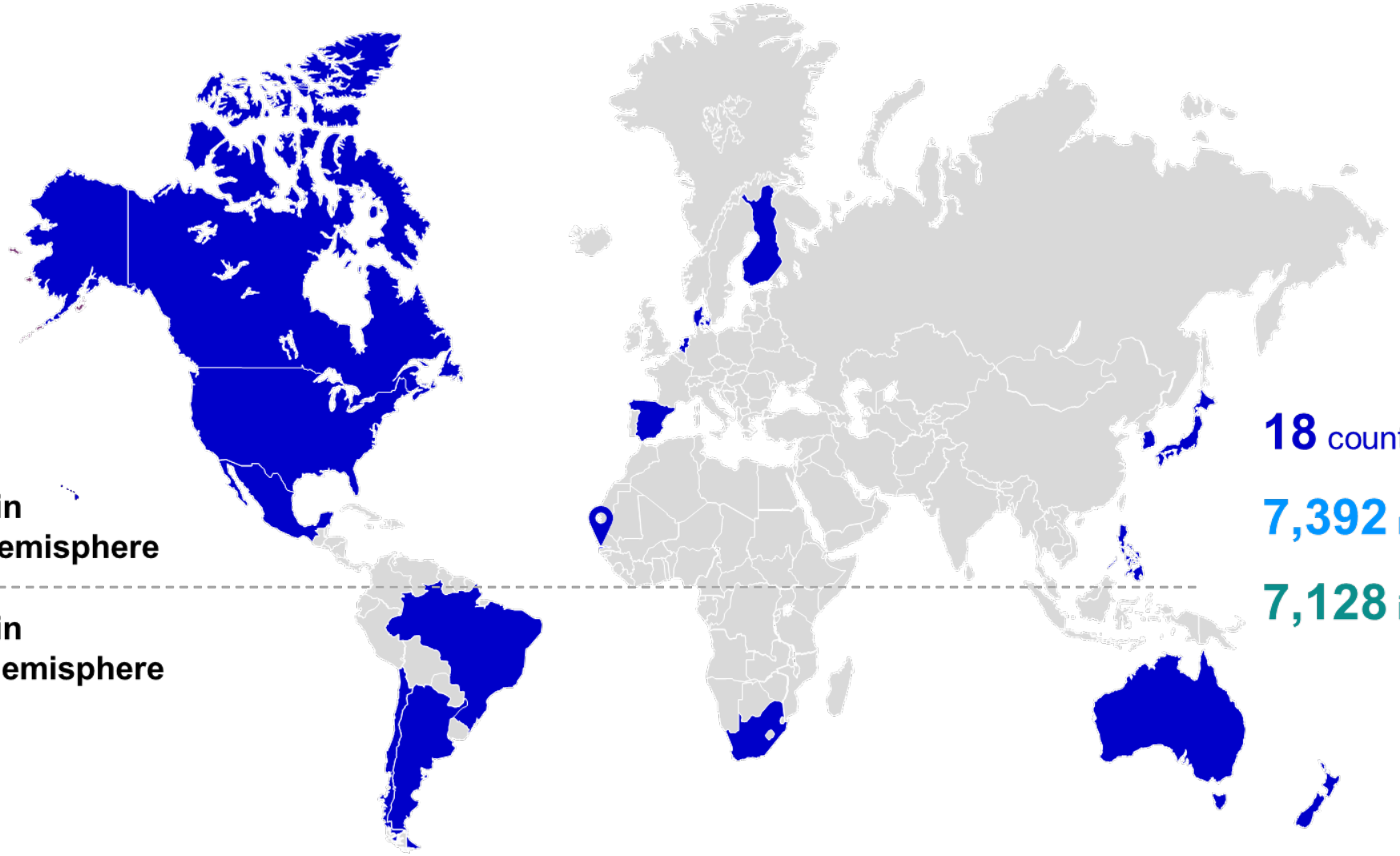
MATernal **I**mmunization **S**tudy for **S**afety and **E**fficacy

Matisse

- **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



2 seasons in Northern Hemisphere

2 seasons in Southern Hemisphere

18 countries

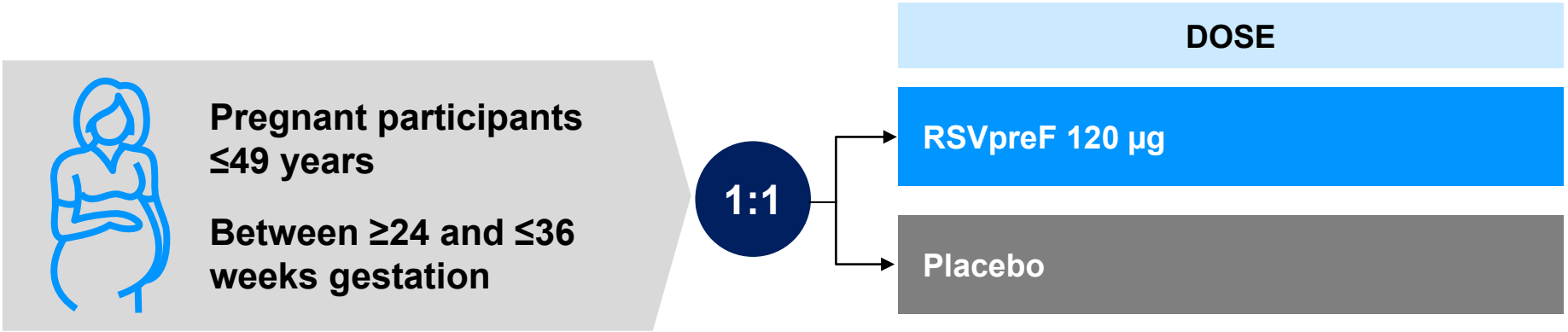
7,392 maternal participants

7,128 infants enrolled

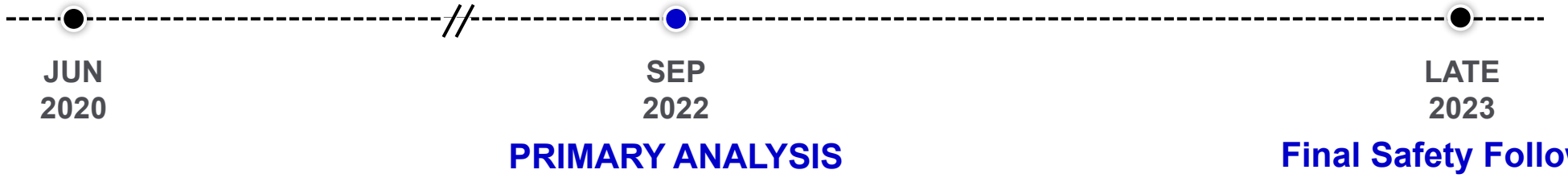
Gambia

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 (%)
Age at Vaccination* (years)			
Mean (SD)	29.1 (5.64)	29.0 (5.74)	29.0 (5.69)
Range	16 – 45	14 – 47	14 – 47
Gestational Age (GA) at Vaccination**			
≥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 (%)
Sex			
Male	1816 (50.9)	1793 (50.4)	3609 (50.6)
Female	1752 (49.1)	1765 (49.6)	3517 (49.4)
Race			
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)
Ethnicity			
Hispanic/Latino	1033 (29.0)	1039 (29.2)	2072 (29.1)

MATISSE

(**MAT**ernal **I**mmunization **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

DMC

Adverse Events of Special Interest (AESI)

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

*SARS-CoV-2 when not associated with respiratory qualifying symptoms per protocol
AESI=Adverse Event of Special Interest; NDCMC=newly diagnosed chronic medical condition; SAE=serious adverse event

Maternal Safety Assessments

Day -90	Day 1	Day 28	Delivery	6-Months Post Delivery
Pre-Screening (ultrasounds)[a]	Vaccination	1-Month	Labor & Delivery[b]	Maternal Follow-Up

Daily solicited reactogenicity: 7 days

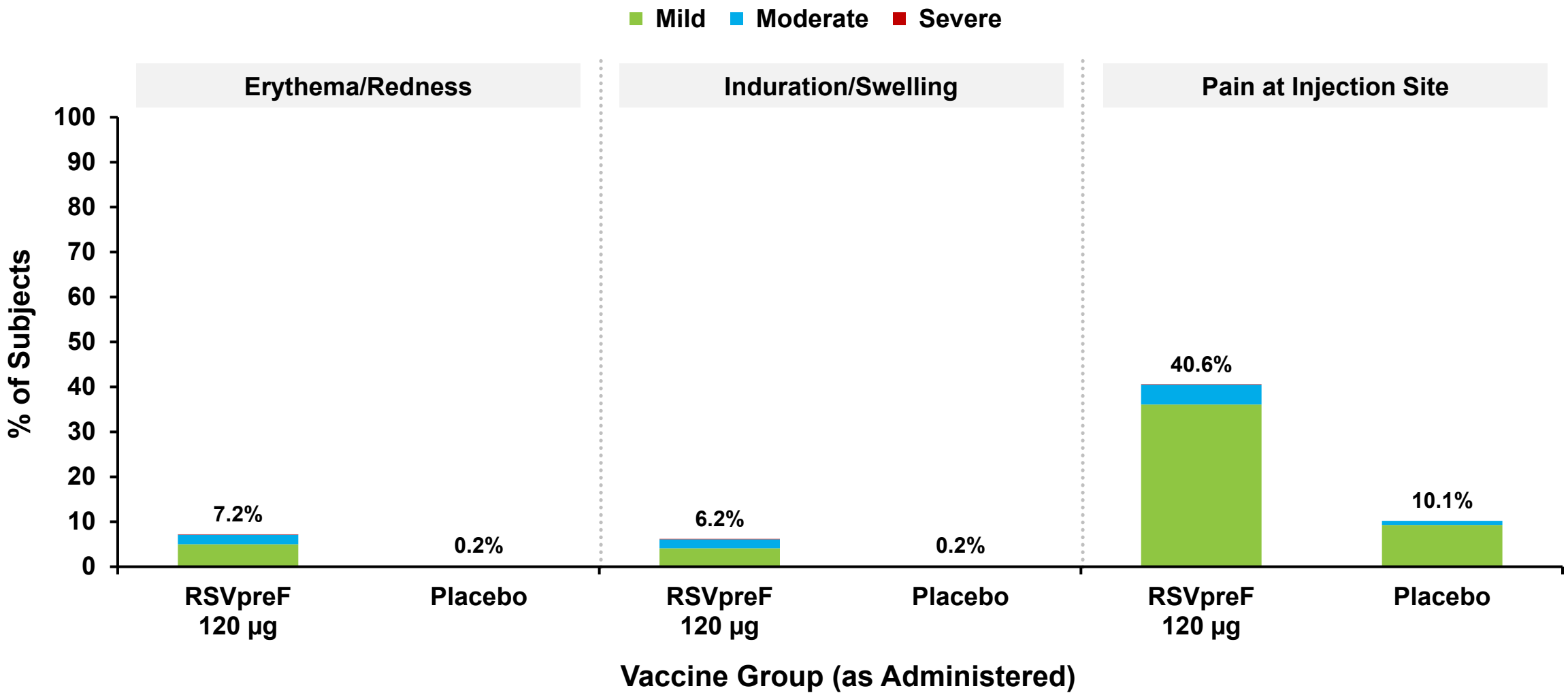
Unsolicited AEs: 1 Month

AESI, SAEs: Trial Duration

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

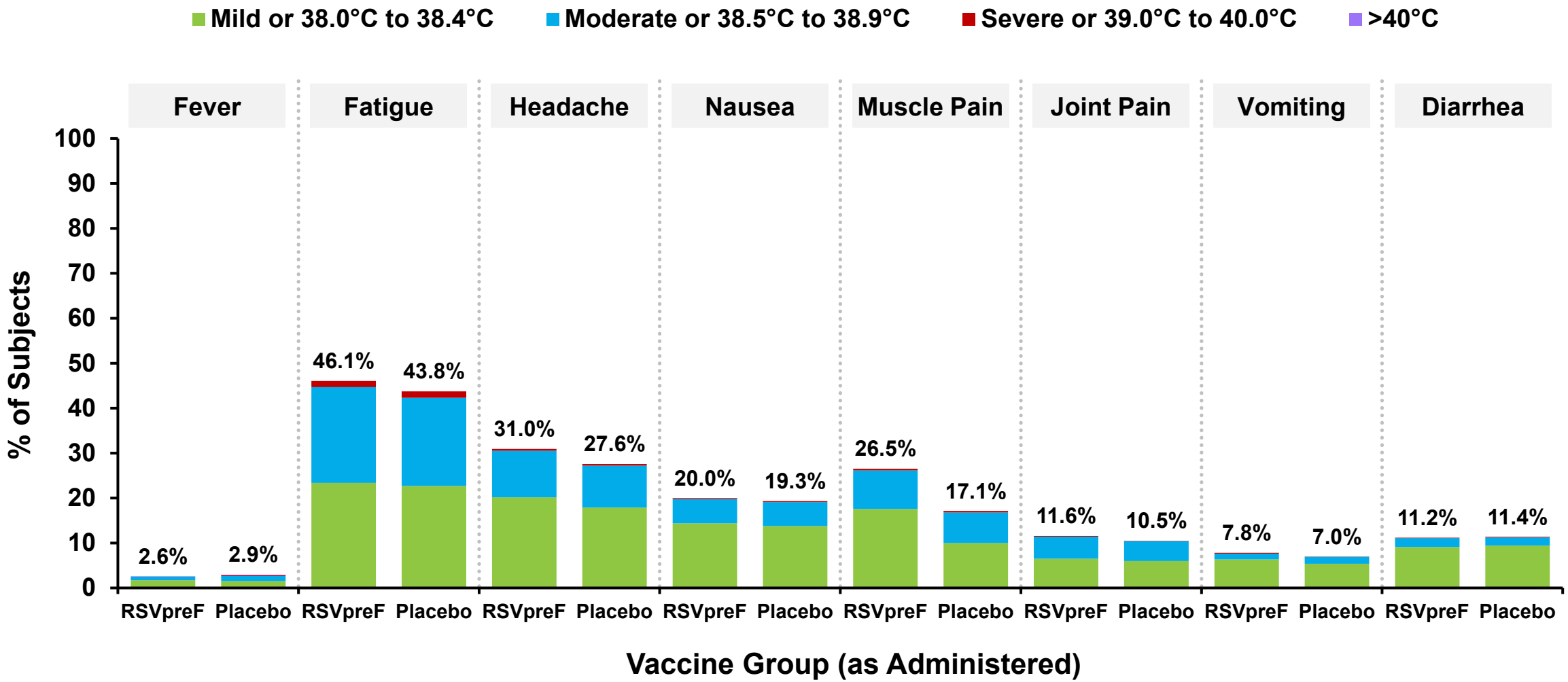
Maternal Participants



Local Reactions, by Maximum Severity, within 7 Days After Vaccination

Solicited Systemic Events were Mild to Moderate and Resolved Quickly

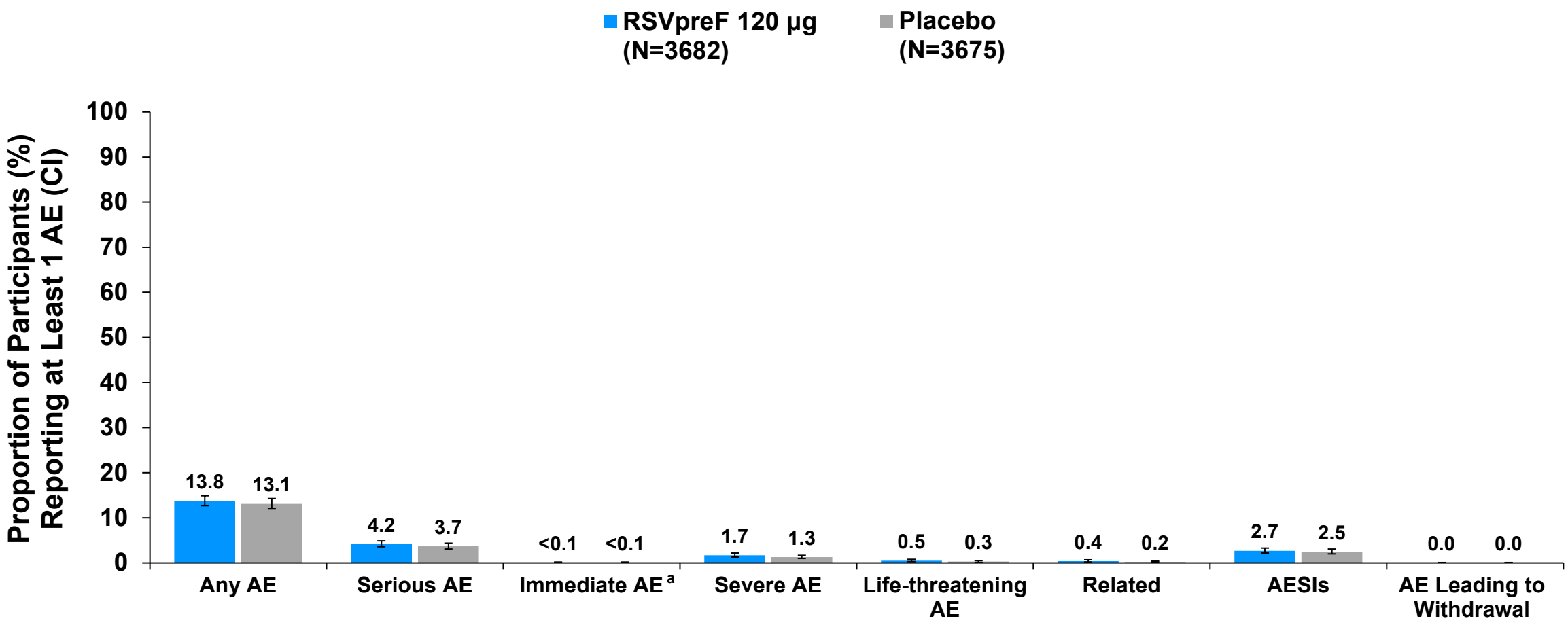
Maternal Participants



Systemic Events, by Maximum Severity, Within 7 Days After Vaccination

Adverse Events Comparable Between RSVpreF and Placebo

Maternal Participants within 1 Month After Vaccination

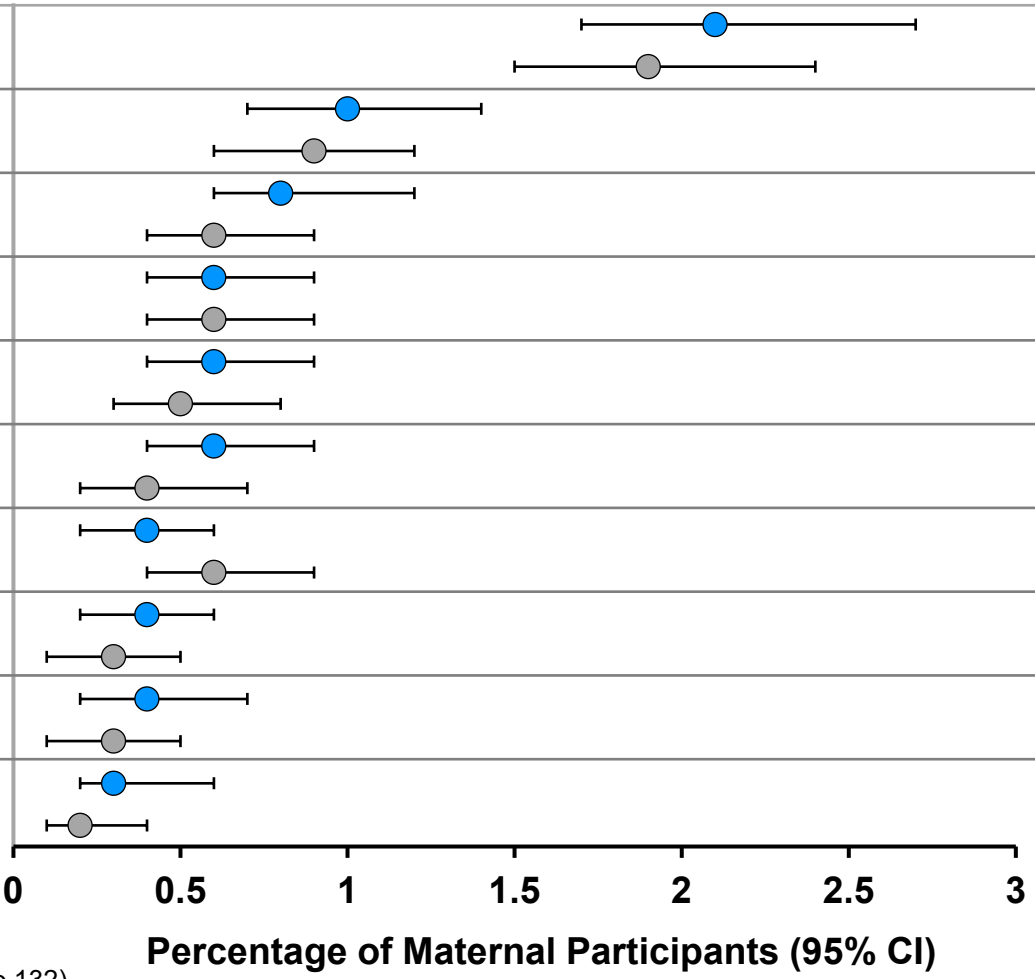


The severity of the event is in the determination of the investigator.
a. An immediate AE is defined as any AE that occurred within the first 30 minutes of vaccination.
AE=Adverse Event; AESI=Adverse Events of Special Interest

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

Maternal Participants: Terms Consistent with Conditions Associated with Pregnancy[a]

10 Most Common Preferred Terms	Percentage with Event	
	RSVpreF 120 µg N=3682	Placebo N=3675
Premature delivery	**2.1**	**1.9**
Pre-eclampsia	**1.0**	**0.9**
Gestational hypertension	**0.8**	**0.6**
SARS-CoV-2 test positive	**0.6**	**0.6**
Urinary tract infection	**0.6**	**0.5**
Gestational diabetes	**0.6**	**0.4**
Anemia	**0.4**	**0.6**
Premature labor	**0.4**	**0.3**
Threatened labor	**0.4**	**0.3**
Premature rupture of membranes	**0.3**	**0.2**



a. Mean time from vaccination to delivery, 57.5 days (Range 1 to 132)

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)	

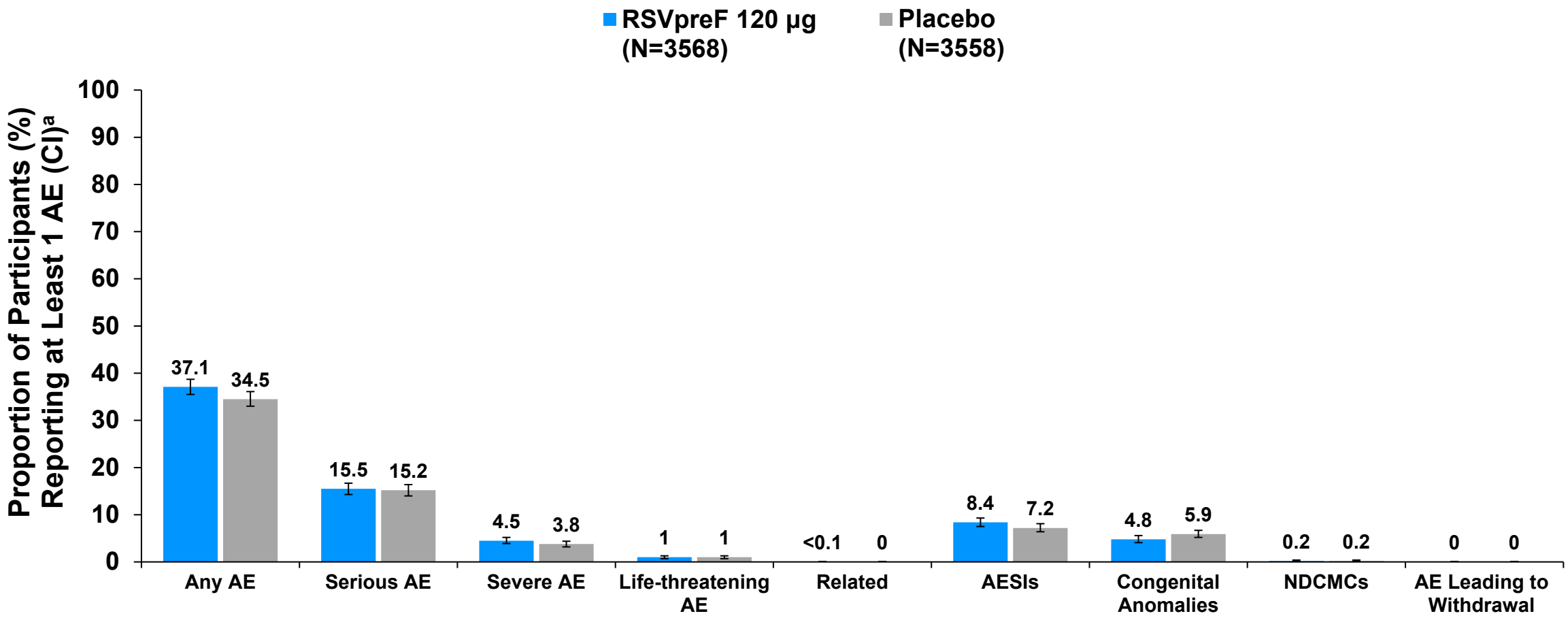
Unsolicited AEs: 1 Month

AESI, SAEs, and NDCMCs: Trial Duration

AESI=AE of Special Interest including preterm birth, low birth weight, developmental delay, and SARS-CoV-2 test positive; NDCMC=Newly Diagnosed Chronic Medical Condition
SAE=Serious Adverse Event

Adverse Events Comparable Between RSVpreF and Placebo

Infant Participants Within 1 Month After Birth

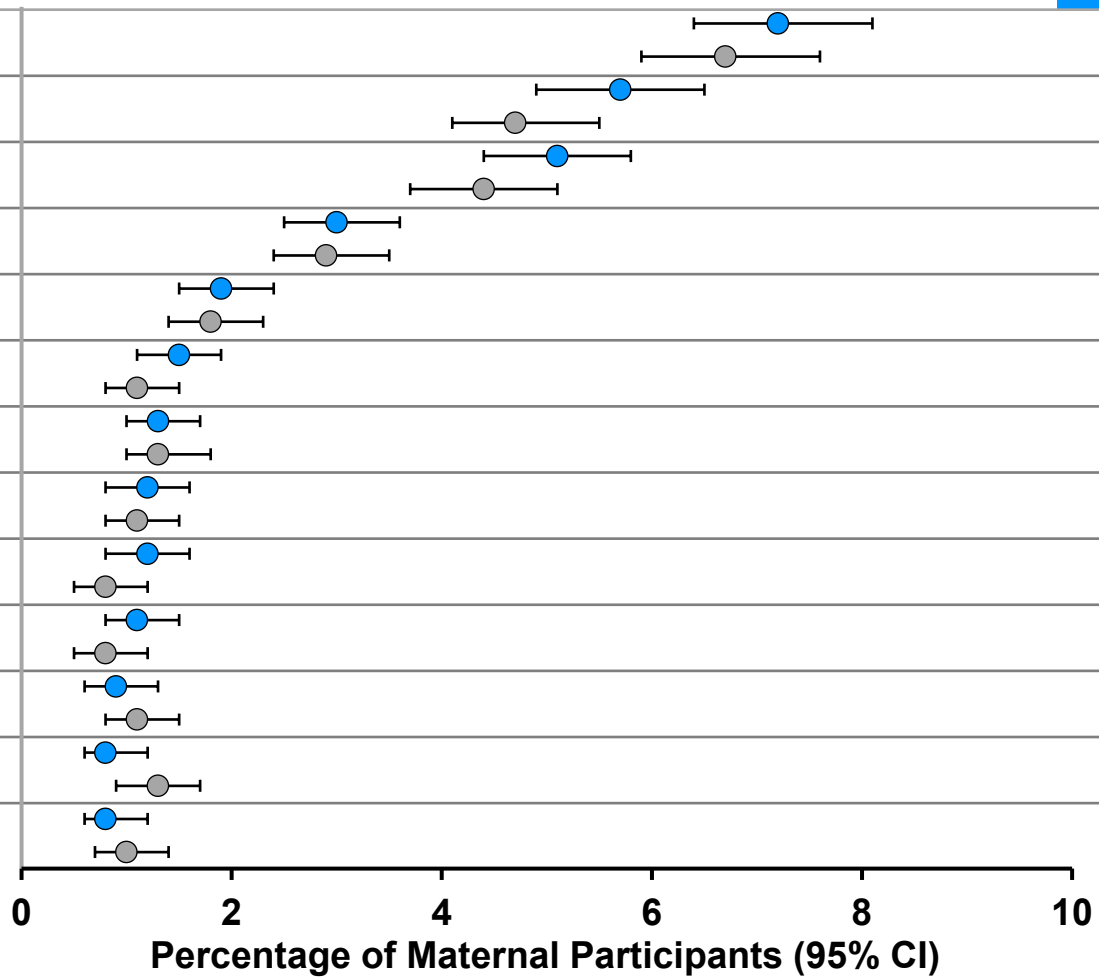


The severity of the event is in the determination of the investigator. a. Exact 2-sided confidence interval (CI) calculated using the Clopper and Pearson method.
AE=Adverse Event; AESI=Adverse Events of Special Interest; NDCMCs=Newly Diagnosed Chronic Medical Conditions

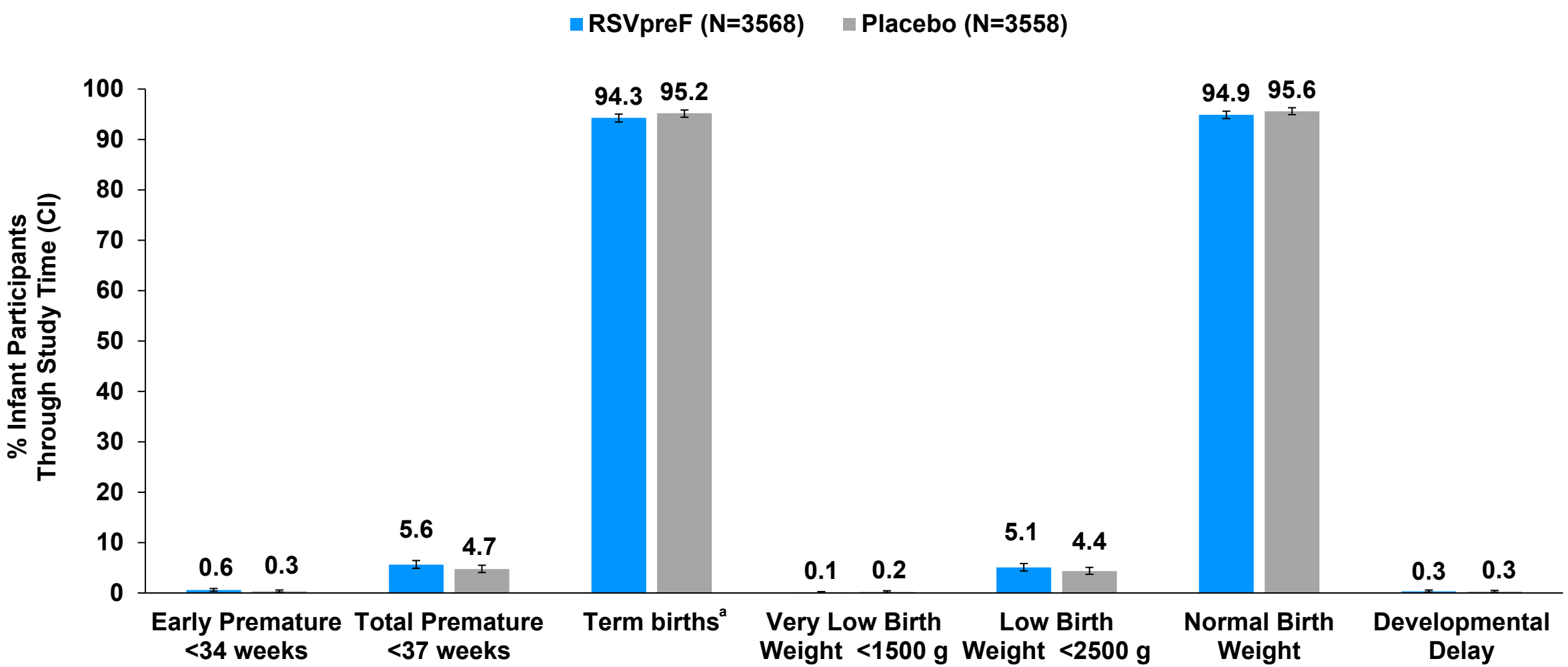
AEs ≥1.0% Comparable Between RSVpreF & Placebo Within 1 Month After Birth

Infant Participants: Terms Consistent with Neonatal Conditions

Terms Reported in ≥ 1%	Percentage with Event	
	RSVpreF 120 µg N=3568	Placebo N=3558
Jaundice neonatal	7.2	6.7
Premature baby	5.7	4.7
Low birth weight baby	5.1	4.4
Hyperbilirubinemia neonatal	3.0	2.9
Respiratory distress	1.9	1.8
Ankyloglossia congenital	1.5	1.1
Transient tachypnoea of the newborn	1.3	1.3
Hypoglycemia	1.2	1.1
Congenital naevus	1.2	0.8
Hypoglycemia neonatal	1.1	0.8
Small for dates baby	0.9	1.1
Atrial septal defect	0.8	1.3
Dermatitis diaper	0.8	1.0

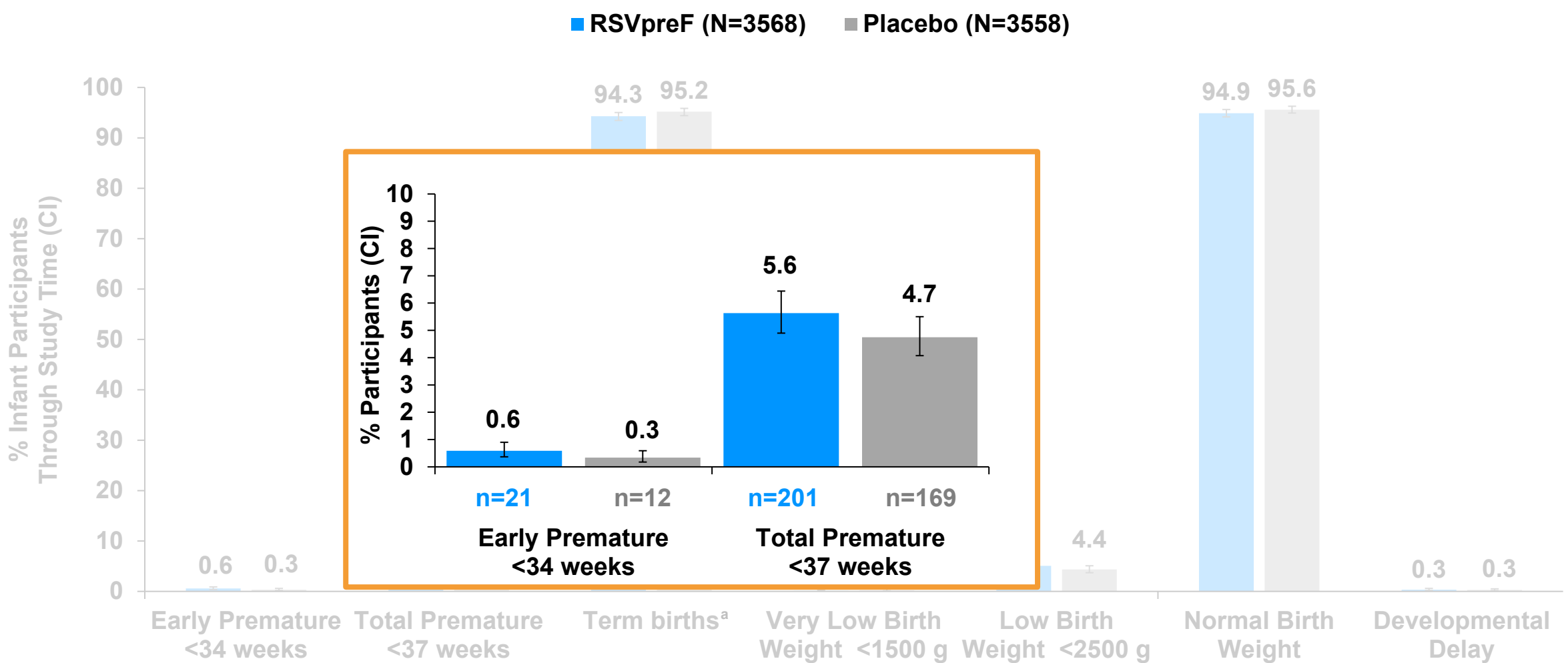


Birth Outcomes and Developmental Delay Comparable Between RSVpreF and Placebo



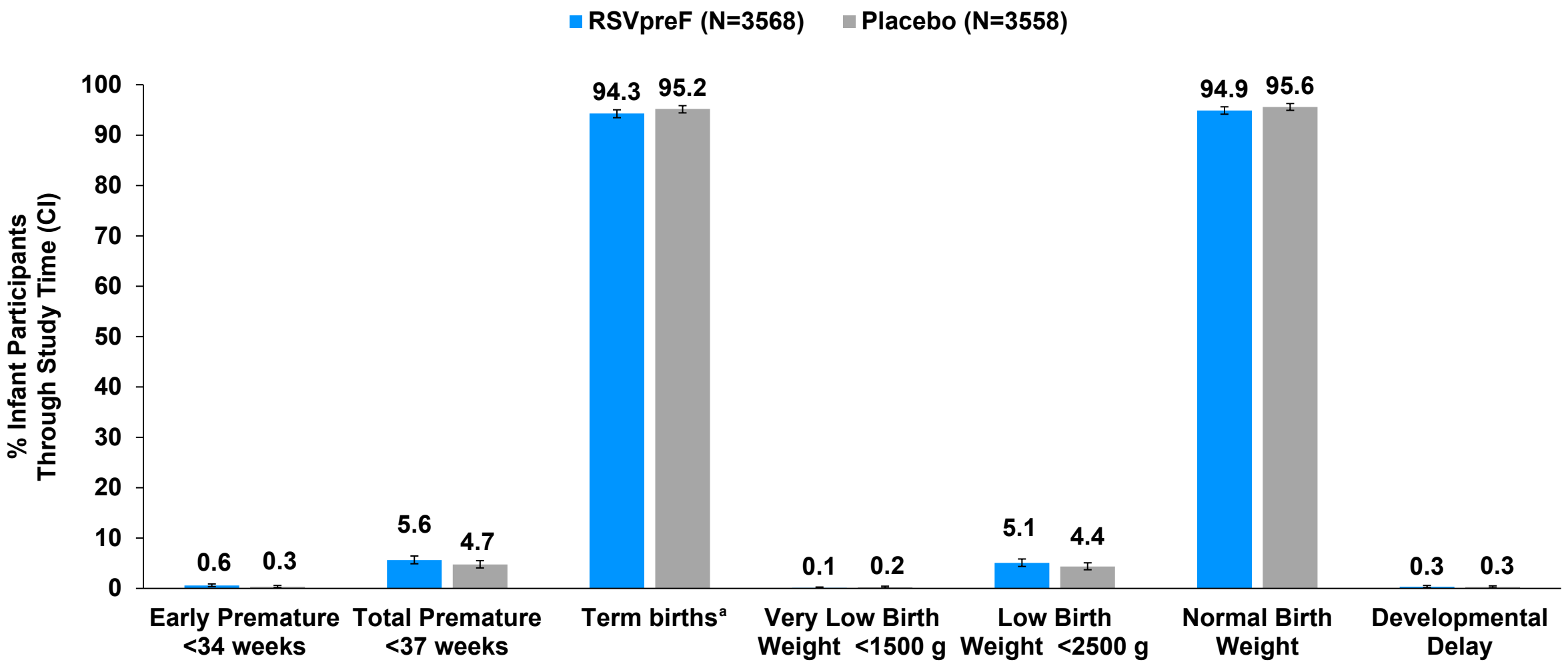
a. Term births: infants born ≥37 weeks

Birth Outcomes:
Prematurity and Extreme Prematurity Rates



a. Term births: infants born ≥37 weeks

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 **I**mmunization **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

MA-LRTI=Medically Attended Lower Respiratory Tract Illness

Infant Efficacy Surveillance

Birth Day 1	28 Days After	6-Mo	12-Mo	18-Mo	24-Mo

Birth & Endpoint Surveillance

12-Mo Follow-up (45% infants)

24-mo Follow-up (55% infants)

Weekly contact with caregiver

Swabs for all MA-LRTIs

Monthly contact with caregiver

Medical Records for All MA-LRTIs and Swabs for Hospitalization and Severe Disease

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
RSV LRTI Medically attended visit and ≥1:	• Tachypnea (RR **≥60** (<2 M [60 days]) or **≥50** (≥2 to <12 M) • SpO2 measured **<95%** • Chest wall indrawing
Severe RSV LRTI Medically attended visit and ≥1:	• Tachypnea (RR **≥70** (<2 M [60 days]) or **≥60** (≥2 to <12 M) • SpO2 measured **<93%** • High-flow nasal cannula or mechanical ventilation • ICU admission for >4 hours • Unresponsive/unconscious

Positive validated RT-PCR

Medically attended (MA) visit: Infant participant taken to or seen by a healthcare provider (e.g., outpatient or inpatient visit, emergency room, urgent care, or home visit)
LRTI=Lower Respiratory Tract Illness; SpO2=peripheral capillary oxygen saturation

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

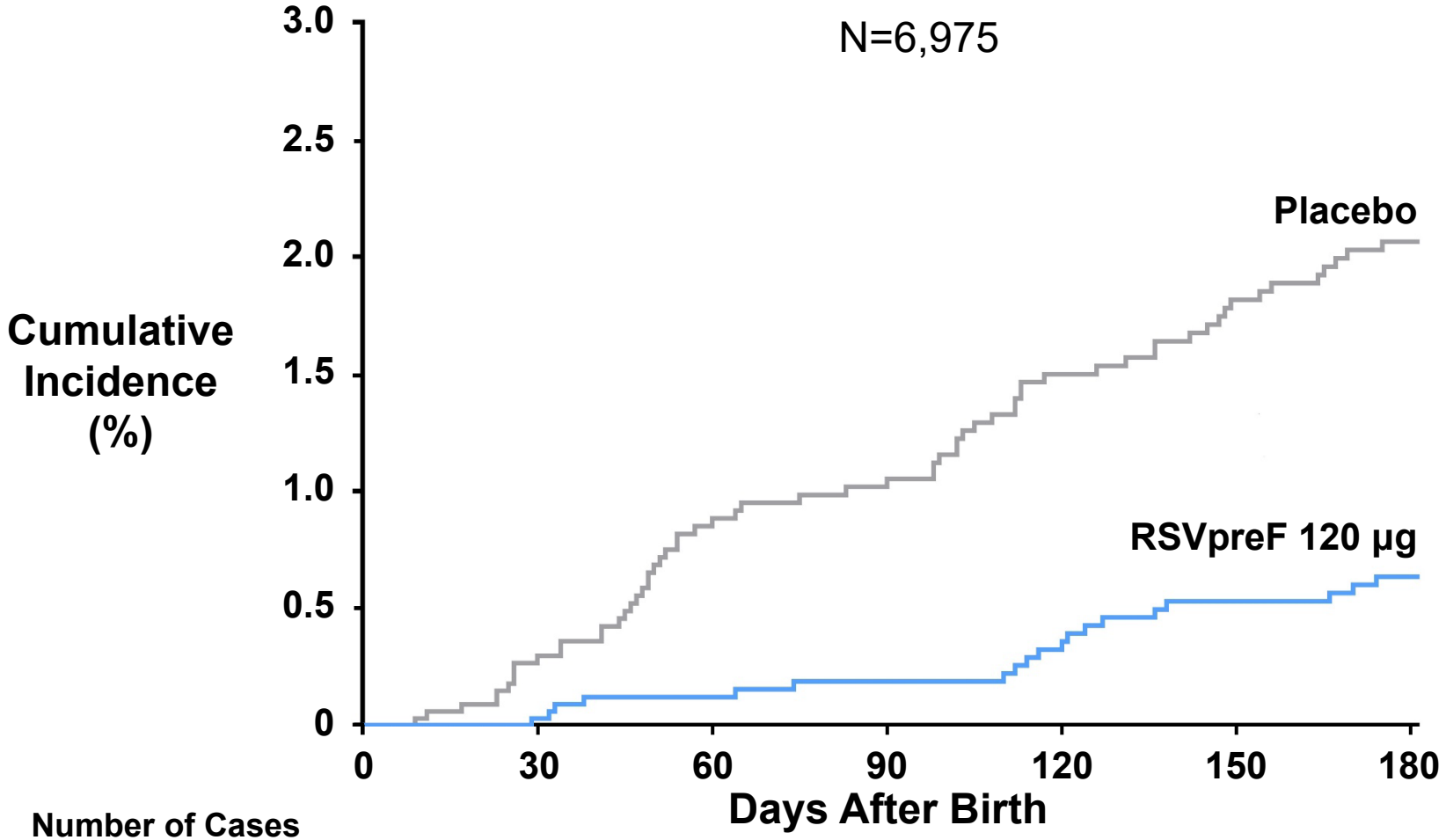
Primary Endpoint: RSV-Positive Severe MA-LRTI

Time Interval	Maternal Vaccine Group (as Randomized) RSVpreF 120 µg N = 3495 n	Placebo N = 3480 n	Vaccine Efficacy (97.58-99.5% CI*)
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

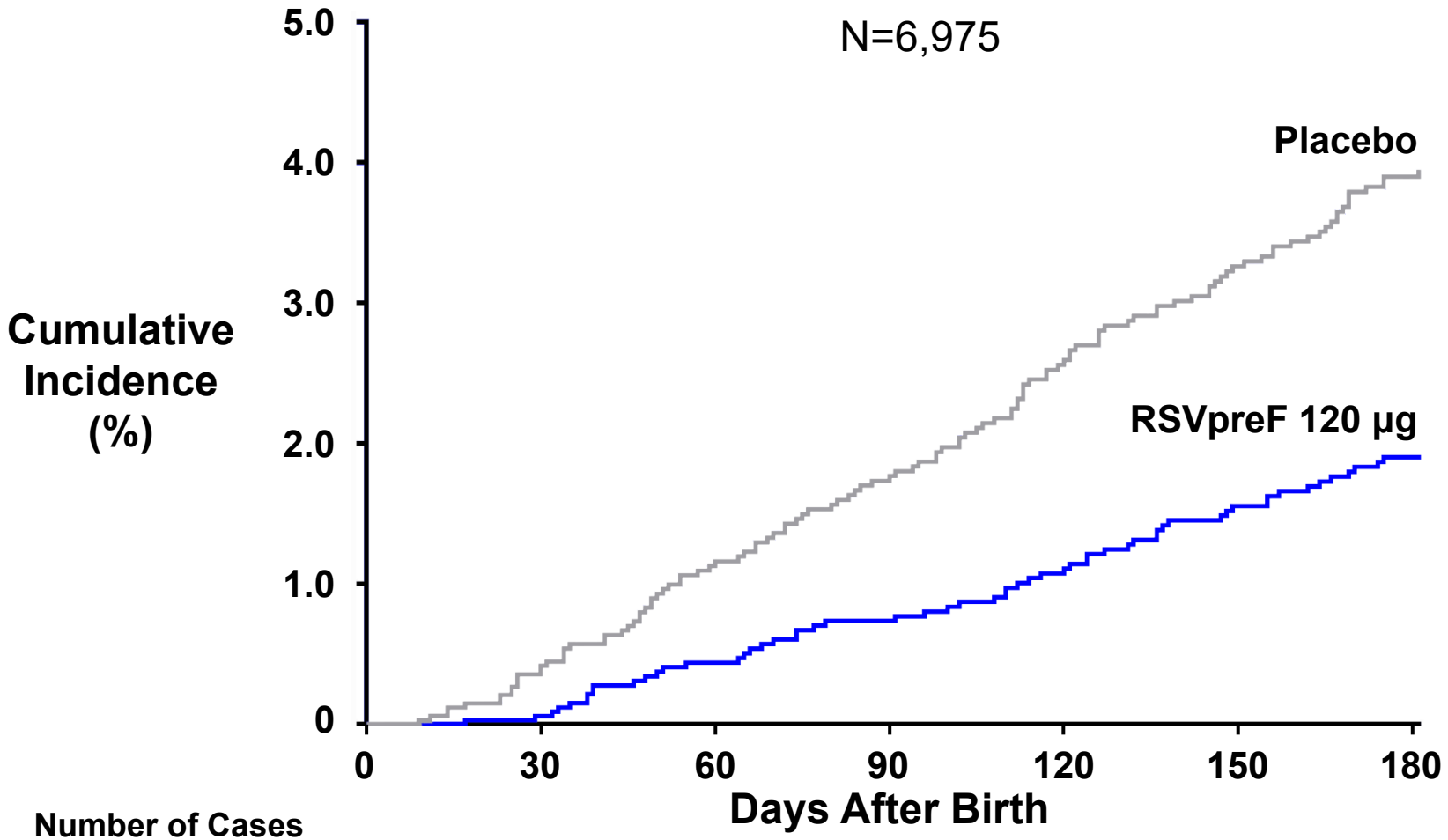
MA-LRTI=Medically Attended Lower Respiratory Tract Illness

Primary Endpoint: RSV-Positive MA-LRTI

Time Interval	Maternal Vaccine Group (as Randomized) 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

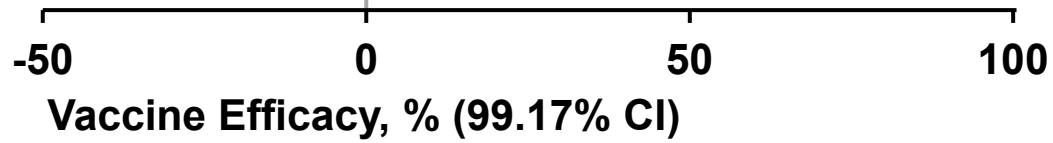


Number of Cases						
RSVpreF	2	14	24	35	47	57
Placebo	15	37	56	81	99	117

MA-LRTI=Medically Attended Lower Respiratory Tract Illness

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

Time Interval	Case Split (RSVpreF/Placebo)	VE %
90 days after birth	24/56	57.1
120 days after birth	35/81	56.8
150 days after birth	47/99	52.5
180 days after birth	57/117	51.3
210 days after birth	70/127	44.9
240 days after birth	76/133	42.9
270 days after birth	82/137	40.1
360 days after birth	92/156	41.0

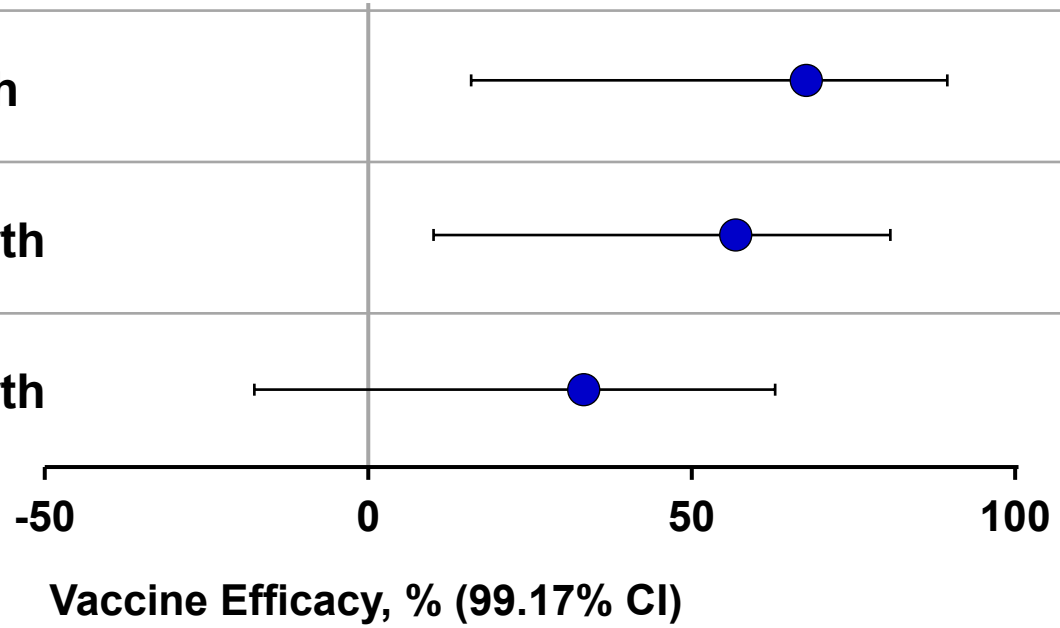


Met Statistical Criteria for Success (CI LB>0%)

The confidence interval was adjusted using Bonferroni procedure and accounting for the primary endpoints results.
MA-LRTI=Medically Attended Lower Respiratory Tract Illness

Secondary Endpoint: Hospitalizations Due to RSV Demonstrate Efficacy Through 6 Months

Time Interval	Case Split (RSVpreF/Placebo)	VE %
90 days after birth	10/31	67.7
180 days after birth	19/44	56.8
360 days after birth	38/57	33.3

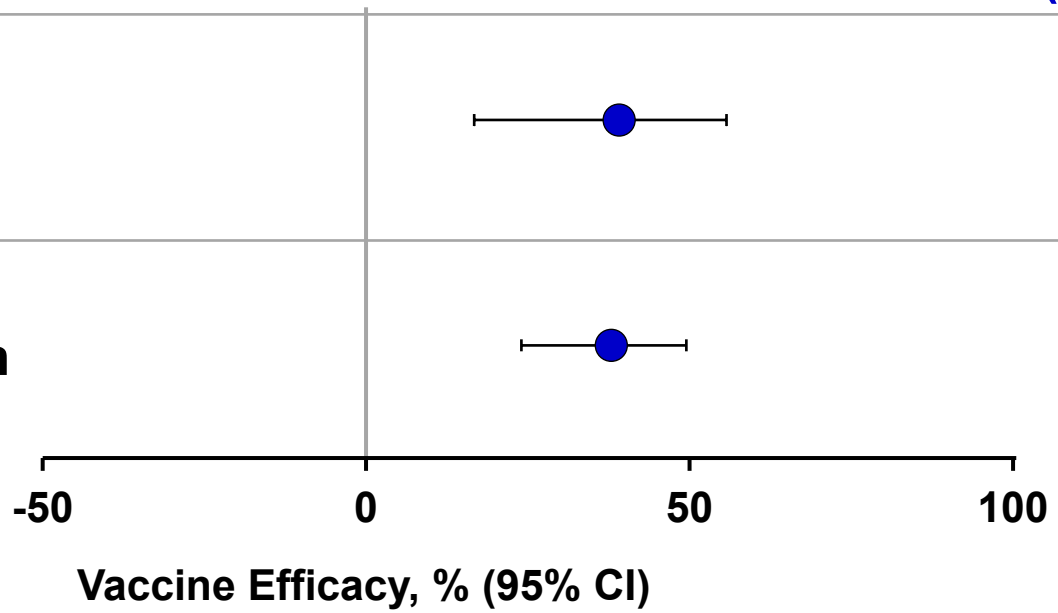


Met Statistical Criteria for Success Through 180 Days (CI LB>0%)

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

Exploratory Endpoint: Efficacious Against RSV MA-RTI

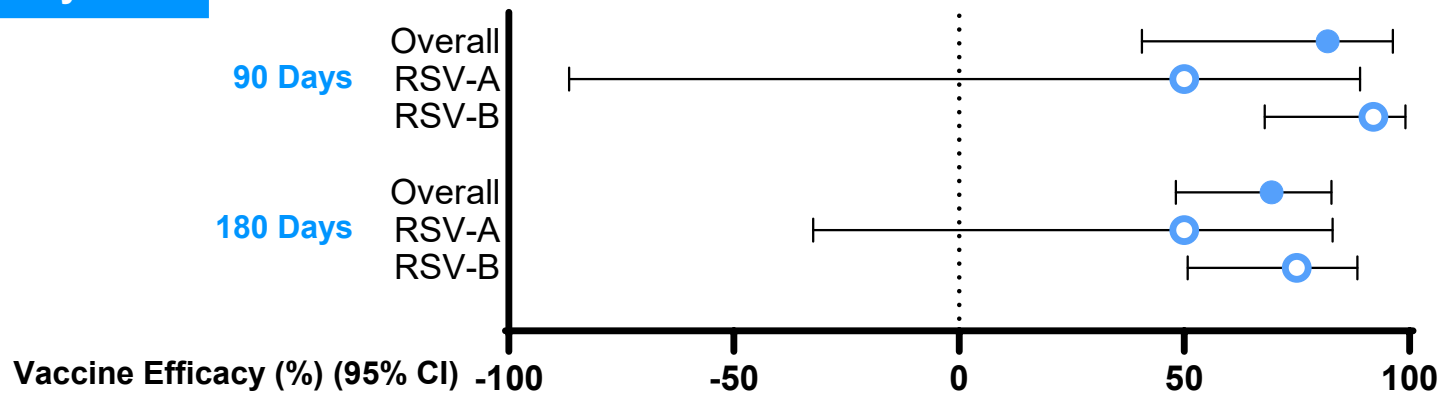
Time Interval	Case Split (RSVpreF/Placebo)	VE %
90 days after birth	67/110	39.1
180 days after birth	157/253	37.9



MA-RTI=Medically Attended Respiratory Tract Illness

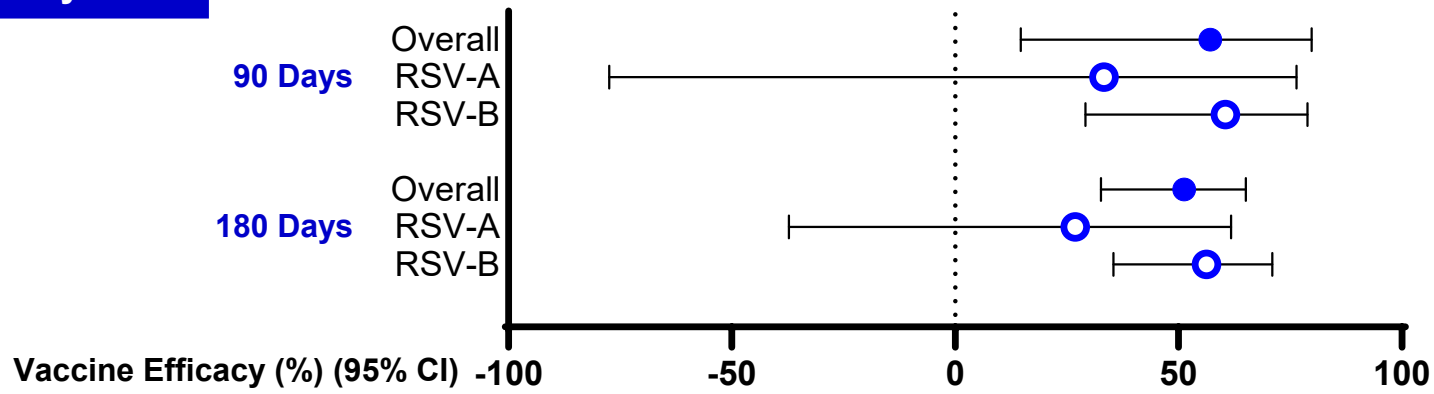
Consistent Efficacy Was Observed Across RSV Subgroups A and B

RSV Severe MA-LRTI
90, 180 Days



	Case Split (RSVpreF/Placebo)	VE
90 Days Overall	6:33	81.8%
90 Days RSV-A	4:8	50.0%
90 Days RSV-B	2:25	92.0%
180 Days Overall	19:62	69.4%
180 Days RSV-A	7:14	50.0%
180 Days RSV-B	11:44	75.0%

RSV MA-LRTI
90, 180 Days



	Case Split (RSVpreF/Placebo)	VE
90 Days Overall	24:56	57.1%
90 Days RSV-A	8:12	33.3%
90 Days RSV-B	17:43	60.5%
180 Days Overall	57:117	51.3%
180 Days RSV-A	19:26	26.9%
180 Days RSV-B	38:87	56.3%

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

*Confidence intervals are 99.5% CI at 90 days and 97.58% CI at later intervals for severe MA-LRTI and a 99.17% CI for MA-LRTI as a secondary endpoint.
MA-LRTI=Medically Attended Lower Respiratory Tract Illness

Pharmacovigilance Plan

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[a]

- 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

FDA = Food and Drug Administration
a. Final list of endpoints to be developed in consultation with the FDA

Conclusions and Benefit Risk Assessment

Bill Gruber, MD

Conclusions

- 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

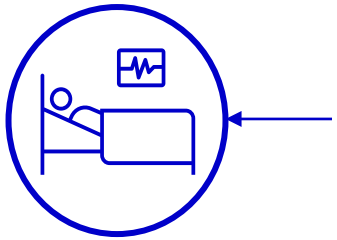
RSVpreF has the Potential to Annually Prevent

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

*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[a]:



16,000
RSV hospitalizations

in infants <6 months old

322,000
medically attended RSV illnesses

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.

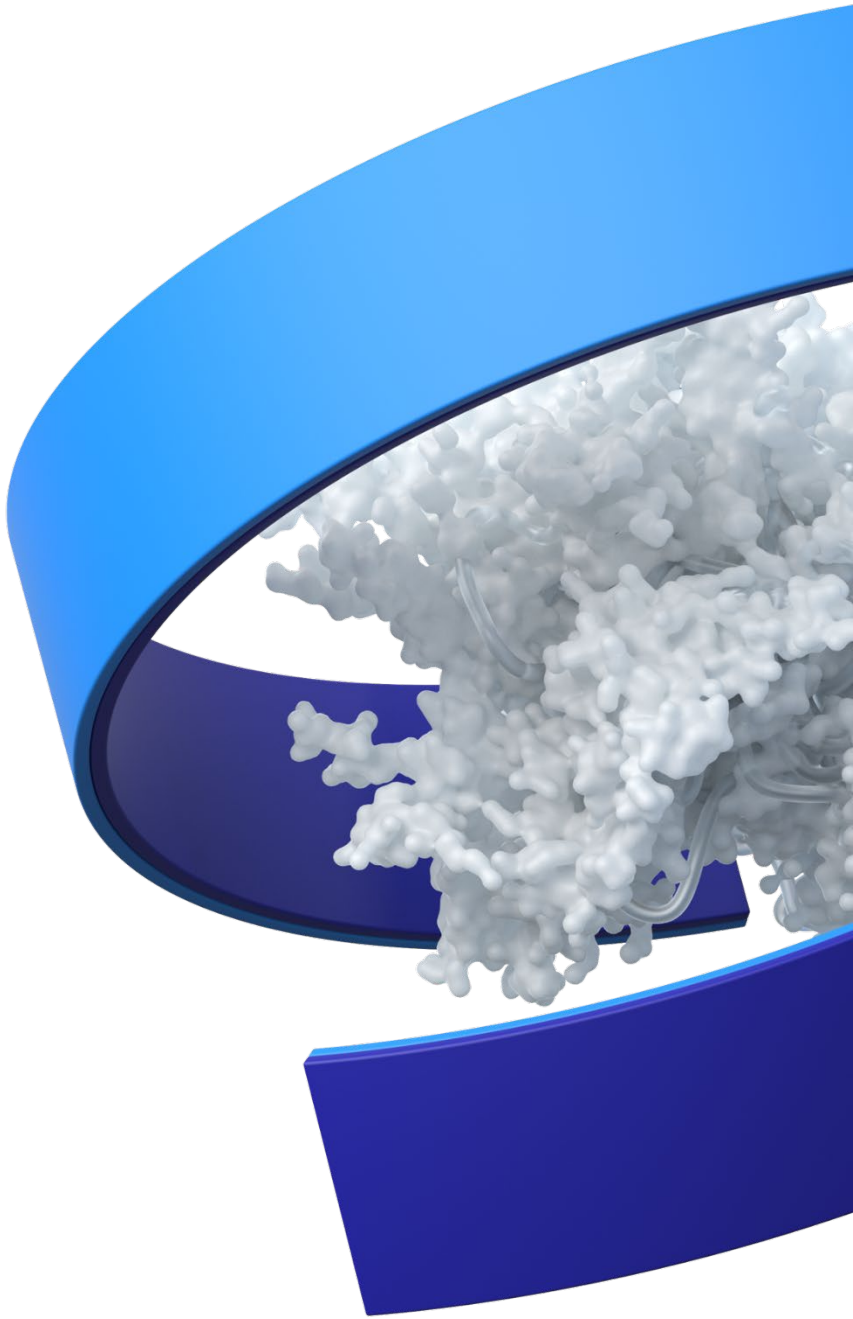
Bivalent RSV Prefusion F Vaccine

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



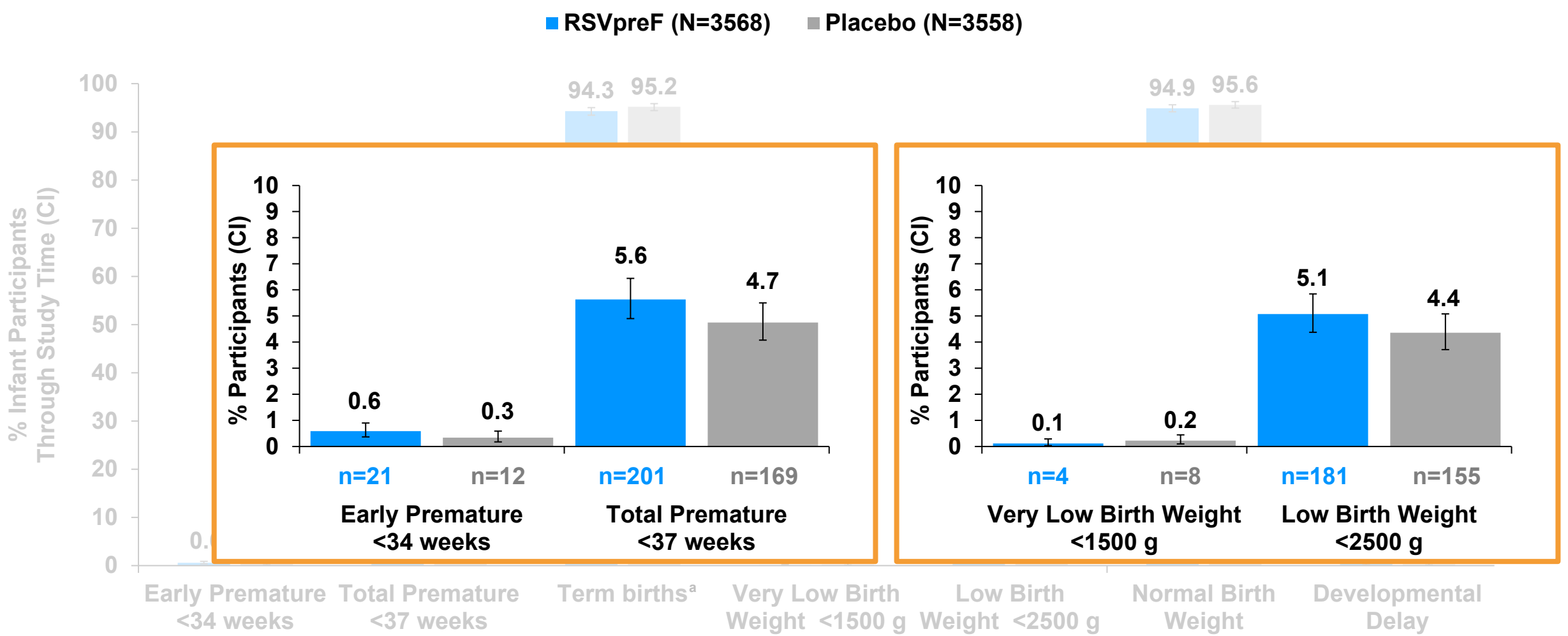
Pfizer

Sponsor Backup Slides Presented to VRBPAC

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 ≥37 weeks

BU-524

Vaccine Efficacy by Interval Months

	Time Interval (months)	RSVpreF 120 µg # Cases	Placebo # Cases	Total # Cases	Vaccine Efficacy %
MA-LRTI	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

MA-LRTI=Medically Attended Lower Respiratory Tract Illness

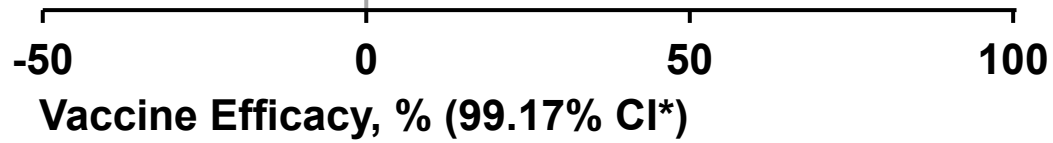
Vaccine Efficacy by Interval Months

	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

MA-LRTI=Medically Attended Lower Respiratory Tract Illness

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

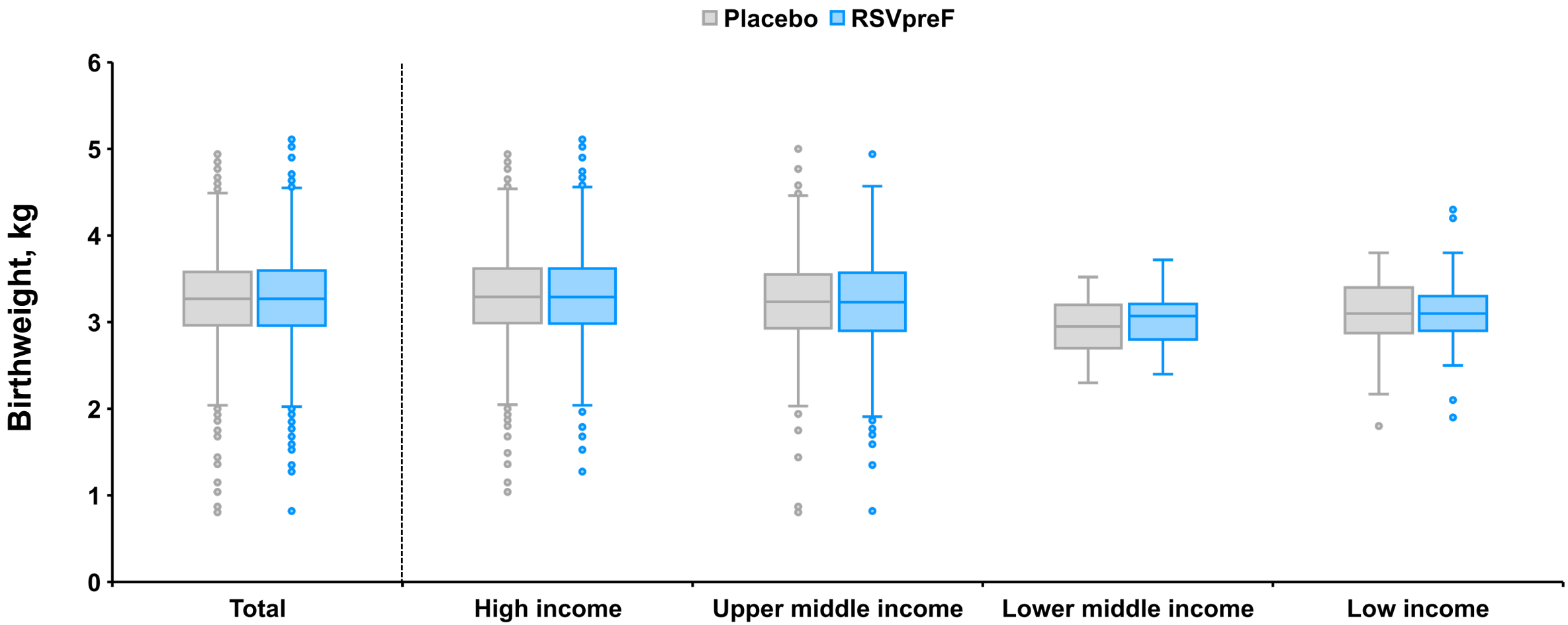
Time Interval	Case Split (RSVpreF/Placebo)	VE %
90 days after birth	24/56	57.1
120 days after birth	35/81	56.8
150 days after birth	47/99	52.5
180 days after birth	57/117	51.3
210 days after birth	70/127	44.9
240 days after birth	76/133	42.9
270 days after birth	82/137	40.1
360 days after birth	92/156	41.0



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

*The confidence interval was adjusted using Bonferroni procedure and accounting for the primary endpoints results. 99.5% CI shown for 90 days, 97.58% at 120-180, and 99.17% from 210-360 after birth time interval. MA-LRTI=Medically Attended Lower Respiratory Tract Illness

Mean Birthweight by Region Overall, and by Income Category

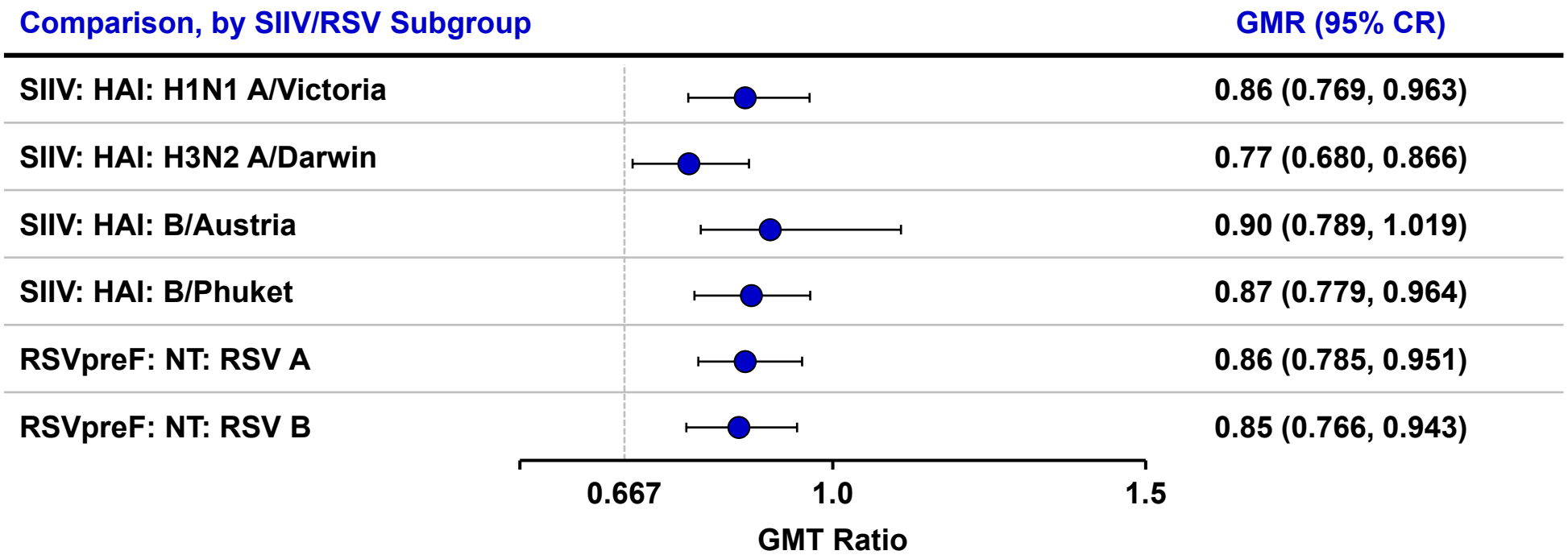


	Total	High income	Upper middle income	Lower middle income	Low income
Mean:	3.3 / 3.3 kg	3.3 / 3.3 kg	3.2 / 3.2 kg	2.9 / 3.0 kg	3.1 / 3.1 kg

BU-423

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)
Preterm <37 weeks				
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)
Low Birth Weight ≤2500g				
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)

HIC=High Income Countries; LIC=Low Income Countries LMIC=Lower-Middle Income Countries; UMIC=Upper Middle-Income Countries

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[a] n (%)[b]	Placebo N=3558[a] n (%)[b]	Total N=7126[a] n (%)[b]
Preterm Deliveries	201	169	370
≤7 days[c]	11 (5.5)	13 (7.7)	24 (6.5)
>7 days to ≤30 days[c]	69 (34.3)	58 (34.3)	127 (34.3)
>30 days[c]	121 (60.2)	98 (58.0)	219 (59.2)
At Term Deliveries	3364	3386	6750
≤7 days[c]	1 (<0.1)	2 (<0.1)	3 (<0.1)
>7 days to ≤30 days[c]	516 (15.3)	498 (14.7)	1014 (15.0)
>30 days[c]	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.

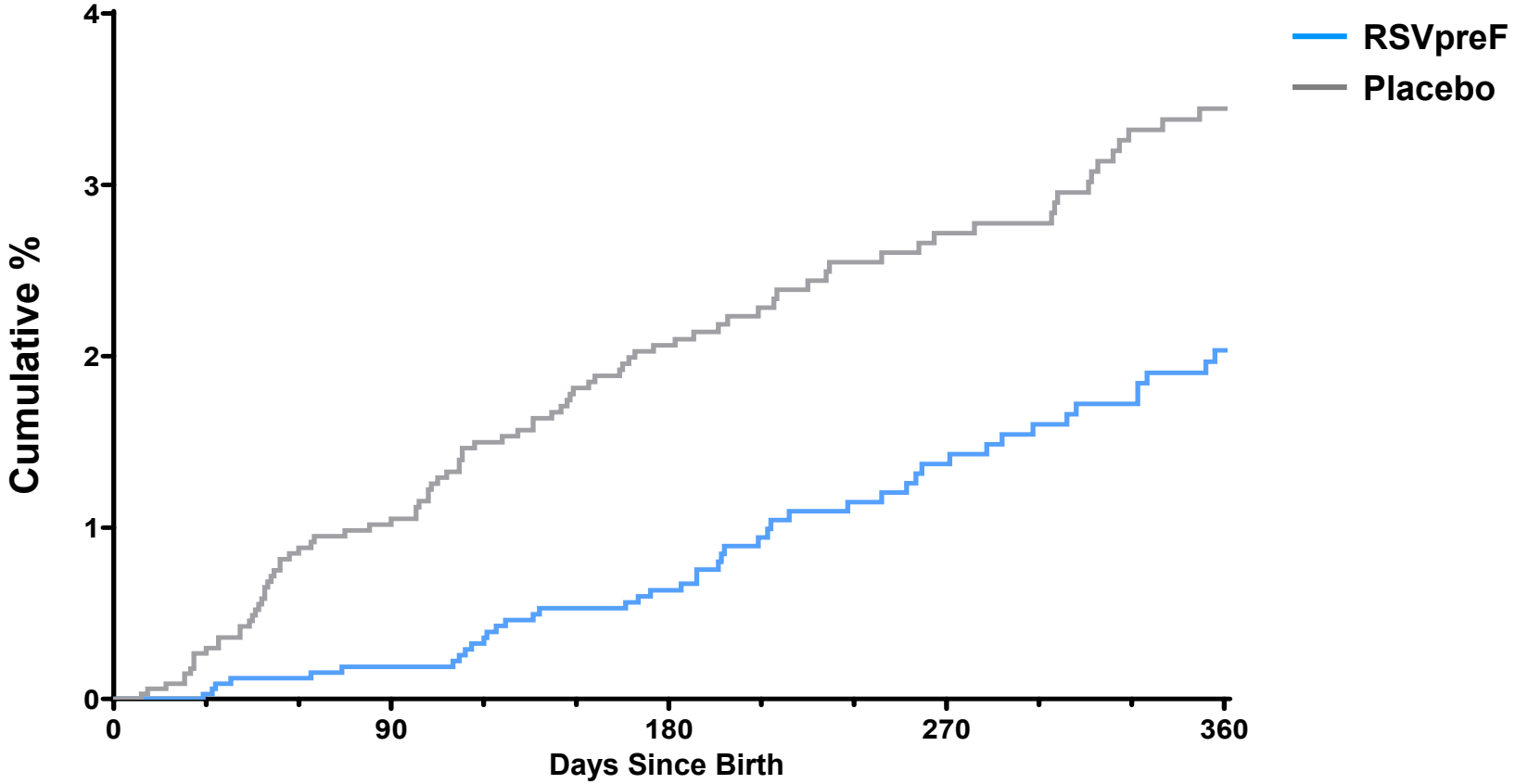
Demographic and Baseline Characteristics US Safety Population

All Maternal Participants

	RSVpreF N=1671 n (%)	Placebo N=1666 n (%)	Total N=3337 n (%)	US Census[1] %
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%

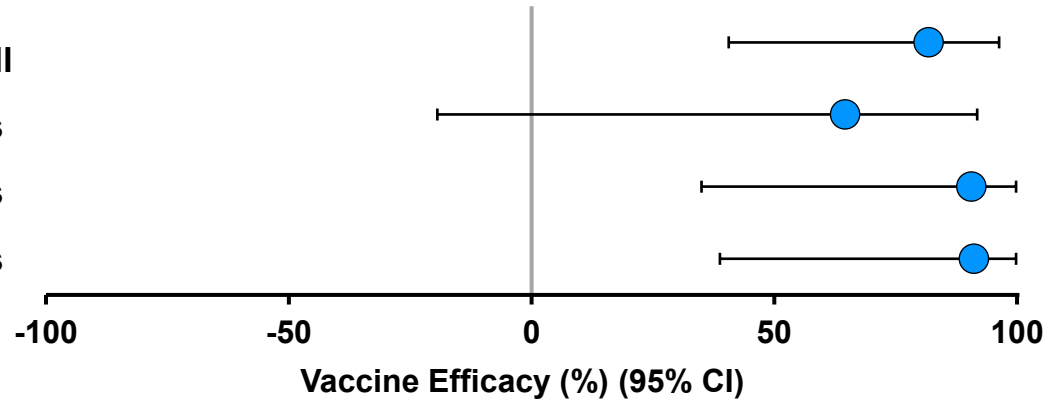
Infant Outcomes by Race and Ethnicity (US)

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)

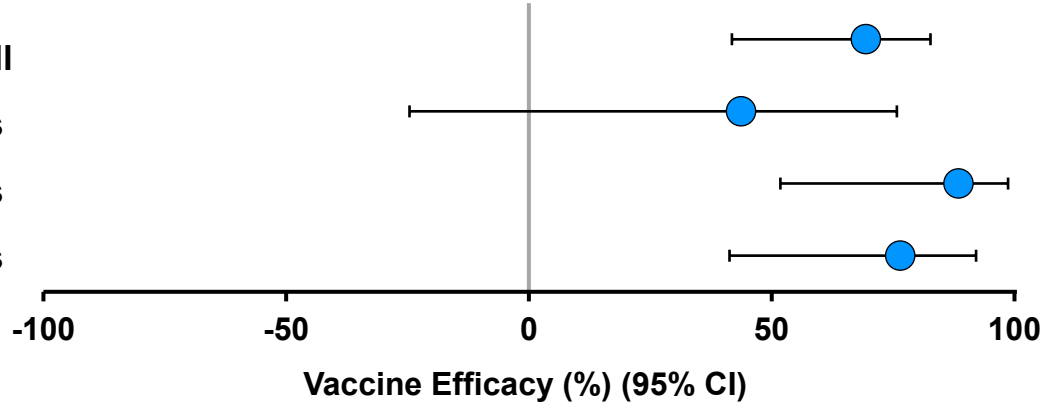
Exploratory Analysis - Efficacy by Timing of Dosing During Pregnancy: RSV Severe MA-LRTI

RSV Severe MA-LRTI 90 Days



	RSVpreF/Placebo N=3495/3480	VE
Overall	6:33	81.8%
24 to <28 weeks	4:11	64.6%
28 to <32 weeks	1:11	90.6%
32 to <36 weeks	1:11	91.1%

RSV Severe MA-LRTI 180 Days



	RSVpreF/Placebo N=3495/3480	VE
Overall	19:62	69.4%
24 to <28 weeks	11:19	43.7%
28 to <32 weeks	2:18	88.5%
32 to <36 weeks	6:25	76.5%