

Appendix 1. Additional Methods

Study conduct

The study protocol, investigator list, and table of representativeness for this population have been published previously.⁴

Concomitant vaccinations and treatments for pregnant participants

The following concomitant vaccinations and treatments were prohibited:

- Investigational vaccines, drugs, or medical devices
- Receipt of blood/plasma products or immunoglobulin from 60 days before investigational product administration, or planned receipt through delivery, apart from Rho(D) immune globulin, which could be given at any time
- Immunosuppressive therapy
- Non-study vaccines were not to be given concomitantly with the investigational product or within 7 days after investigational product administration, except if medically necessary (eg, during an outbreak or pandemic situation)
- Licensed vaccines containing pertussis were not to be coadministered with the investigational product or given within 14 days after investigational product administration, except if medically necessary (eg, during an outbreak or pandemic situation)

The following concomitant vaccines and treatments were permitted:

- Licensed vaccines (including influenza vaccine, tetanus toxoid, tetanus diphtheria vaccines, licensed COVID-19 vaccines, and COVID-19 vaccines authorized for temporary or emergency use) could be given during the study starting 7 days after investigational product administration, apart from licensed vaccines containing pertussis, which could be given starting 14 days after investigational product administration
- Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids and short-term systemic corticosteroid (equivalent of <20 mg/day of prednisone) use for ≤14 days before administration of investigational product
- The use of antipyretics and other pain medication to treat symptoms associated with investigational product administration

Ethical study conduct

The study was conducted according to the protocol and consensus ethical principles derived from international guidelines, which include the Declaration of Helsinki Council and CIOMS International Ethical Guidelines, applicable ICH GCP Guidelines, applicable ISO 14155 guidelines, medical device guidelines, and other applicable laws and regulations, including privacy laws.

Pregnant participants and their parent(s)/legal guardian (if a minor) provided signed informed consent for themselves and for their newborns at the time of study entry. No reconsent was required for infant participants at the time of birth unless required based on country-specific and local applicable laws and regulations. Informed consent was obtained from the father of the fetus/infant if mandated by local requirements. A study-specific assent form was provided to pregnant participants who were minors as required by local regulations. Minor participants who reached the age of majority during the study, as recognized under local law, were reconsented as adults to remain in the study.

Madhi SA, Kampmann B, Simões EAF, Zachariah P, Pahud BA, Radley D, et al. Preterm birth frequency and associated outcomes from the Maternal Immunization Study for Safety and Efficacy (MATISSE) maternal trial of the bivalent respiratory syncytial virus prefusion F protein vaccine. *Obstet Gynecol* 2025;145.

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Determination of gestational age

Gestational age was based upon 1 of the following composite criteria using timing and availability of data on the last menstrual period and an ultrasound examination performed in the first or second trimester. The earliest ultrasound data available during the current pregnancy was to be used. In countries where the routine practice was for the gestational age determination to be based upon the first trimester ultrasound examination alone, without the last menstrual period, this routine practice was accepted.

First-trimester data available (data obtained at $\leq 13\ 6/7$ weeks)

The date of the first day of the reported last menstrual period could be used to establish the gestational age if corroborated by a first-trimester ultrasound examination. If there was a discrepancy of >5 days between the last menstrual period-determined gestational age and an ultrasound result at $\leq 8\ 6/7$ weeks or if the date of the first day of the last menstrual period was uncertain/unknown, then the gestational age was determined using the first-trimester ultrasound result. If there was a discrepancy of >7 days between the last menstrual period-determined gestational age and an ultrasound result at $9\ 0/7$ to $13\ 6/7$ weeks or if the date of the first day of the last menstrual period was uncertain/unknown, then the gestational age was determined using the first-trimester ultrasound result.

Second-trimester data available (data obtained at $14\ 0/7$ to $27\ 6/7$ weeks)

The date of the first day of the reported last menstrual period could be used to establish the gestational age if corroborated by a second-trimester ultrasound result. If there was a discrepancy of >7 days between the last menstrual period-determined gestational age and the ultrasound result at $14\ 0/7$ to $15\ 6/7$ weeks or if the date of the first day of the last menstrual period was uncertain or unknown, then the gestational age was determined using the second-trimester ultrasound result. If there was a discrepancy of >10 days between the last menstrual period-determined gestational age and the ultrasound result at $16\ 0/7$ to $21\ 6/7$ weeks or if the date of the first day of the last menstrual period was uncertain or unknown, then the gestational age was determined using the second-trimester ultrasound result. If there was a discrepancy of >14 days between the last menstrual period-determined gestational age and the ultrasound result at $22\ 0/7$ to $27\ 6/7$ weeks or if the date of the first day of the last menstrual period was uncertain or unknown, then the gestational age was determined using the second-trimester ultrasound result.

Timing of safety assessments

AEs were collected 1 month after vaccination and 1 month after birth for pregnant and newborn participants, respectively. AESIs and SAEs were collected from signing of maternal consent (pregnant participants) and birth (infants) until study completion (6 months after delivery for pregnant participants; 1–2 years after birth for infants).

Analysis of SARS-CoV-2 baseline data

Laboratory analysis was also conducted for maternal SARS-CoV-2 infections using nucleocapsid (N)–binding antibody levels for a subset of pregnant participants. This analysis subset included all pregnant participants who delivered preterm infants from countries with the highest enrollment (ie, United States, South Africa, and Argentina) along with a 1:1 matched set of pregnant participants who delivered term infants, matching by country, gestational age at vaccination, year and month of enrollment, and vaccination group. Data on N antibody levels are presented as positive at baseline, seroconversion between study entry and delivery.

Baseline SARS-CoV-2 positivity and seroconversion

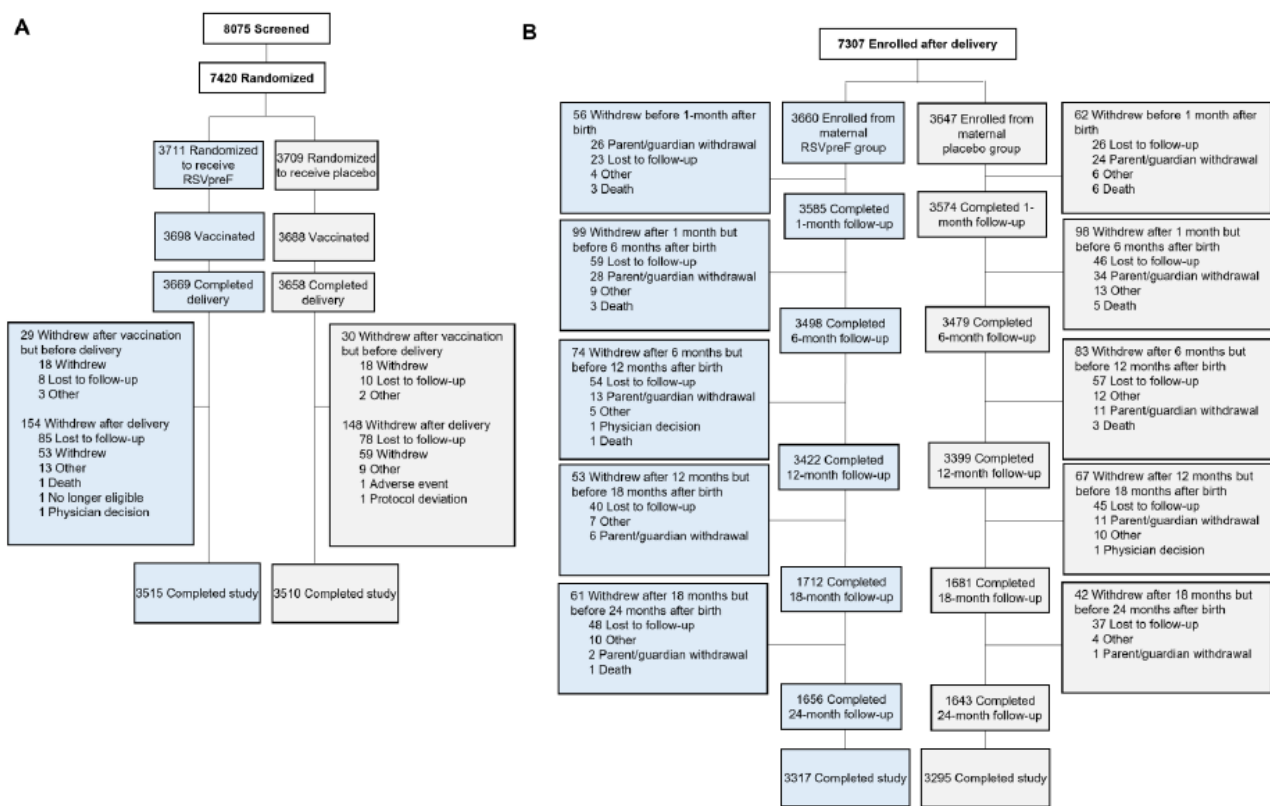
Overall rates of maternal participant seropositivity for SARS-CoV-2 at study entry measured using the COVID-19 N-binding assay were 41.0% for RSVpreF recipients and 35.1% for placebo recipients. Evidence of SARS-CoV-2 infection was 61.7% and 57.8% of mothers in South Africa and Argentina, respectively, compared with 25.1% in the United States. Rates of seroconversion for baseline SARS-CoV-2–negative pregnant participants between study entry and time of delivery in those who delivered term infants were 5.6% for RSVpreF and 4.1% for placebo; corresponding rates for those who delivered preterm were 5.3% and 4.5%, respectively.

Appendix 2. Subcategorization of Countries by Income Level and Number of Infants Born to Vaccinated Pregnant Participants by Country*

Economy	Country	Number of infants born to vaccinated pregnant participants	
		RSVpreF	Placebo
Low-income	Gambia	97	96
Lower-middle income	Philippines	38	39
Upper-middle income	Argentina	467	458
	Brazil	35	37
	Mexico	37	37
	South Africa	469	471
High-income	Australia	11	13
	Canada	27	28
	Chile	86	85
	Denmark	30	31
	Finland	75	73
	Japan	231	231
	South Korea	7	5
	Netherlands	97	95
	New Zealand	50	48
	Spain	118	124
	Taiwan	130	130
	United States	1654	1645

* Countries that randomized participants were further subcategorized according to the World Bank country and lending groups as of May 19, 2021. Data from The World Bank. World Country and Lending Groups. Accessed October 23, 2024. <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>

Appendix 3. Disposition of (A) pregnant and (B) newborn and infant participants.



Note: 7305 infants are included in the safety population due to no longer meeting eligibility criteria.

Appendix 4. Demographic Characteristics of Pregnant Participants

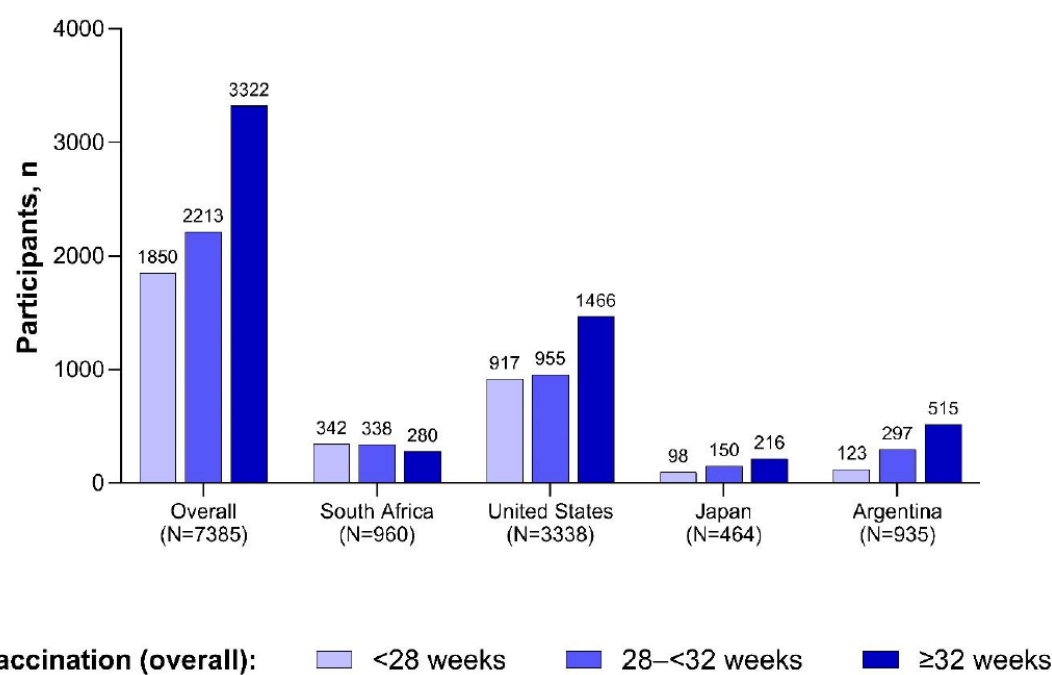
Characteristic	RSVpreF (N=3698*)	Placebo (N=3687*)
Age at vaccination, years		
Mean (SD)	29.0 (5.6)	29.0 (5.8)
Median (range)	29.0 (16–45)	29.0 (14–47)
Gestational age at vaccination, weeks		
Mean (SD)	30.9 (3.54)	30.8 (3.55)
Median (range)	31.3 (24.0–36.6)	31.3 (24.0–36.9)
24–<28 weeks, n (%)	942 (25.5)	908 (24.6)
28–<32 weeks, n (%)	1084 (29.3)	1129 (30.6)
32–36 weeks, n (%)	1669 (45.1)	1644 (44.6)
>36 weeks	3 (<0.1)	6 (0.2)
Race, n (%)		
White	2397 (64.8)	2375 (64.4)
Black	720 (19.5)	725 (19.7)
Asian	456 (12.3)	464 (12.6)
American Indian or Alaska Native	38 (1.0)	37 (1.0)
Native Hawaiian or other Pacific Islander	9 (0.2)	12 (0.3)
Multiracial	30 (0.8)	21 (0.6)
Not reported	41 (1.1)	45 (1.2)
Unknown	7 (0.2)	8 (0.2)
Ethnicity, n (%)		
Hispanic/Latino	1063 (28.7)	1086 (29.5)
Non-Hispanic/non-Latino	2605 (70.4)	2568 (69.7)
Not reported or unknown	30 (0.8)	33 (0.9)

SD, standard deviation.

Data are for the maternal safety population.

* Number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.

Appendix 5. Gestational age at vaccination overall and by country (in countries that enrolled >400 pregnant participants).



Numbers above the bars are numbers of maternal participants who received RSVpreF or placebo in each GA range. Data are for the maternal safety population. GA, gestational age.

Appendix 6. Pregnancy Outcomes Among Pregnant Participants

Pregnancy outcome	RSVpreF (N=3669*)	Placebo (N=3657*)
Days between vaccination and delivery		
N	3669	3657
Mean (SD)	57.6 (26.0)	57.9 (26.1)
Median (range)	54 (2–121)	55 (1–132)
Gestational age at delivery, weeks		
N	3656	3643
Mean (SD)	39.1 (1.4)	39.1 (1.4)
Median (range)	39.1 (27.4–43.9)	39.1 (27.9–44.3)
Outcome at delivery, n (%)		
Live delivery	3659 (99.7)	3648 (99.8)
Stillbirth	10 (0.3)	9 (0.2)
Mode of delivery, n (%)		
Vaginal	2577 (70.2)	2569 (70.2)
Cesarean	1092 (29.8)	1087 (29.7)
Elective	613 (16.7)	631 (17.3)
Semi-elective	230 (6.3)	208 (5.7)
Emergency	249 (6.8)	248 (6.8)

Data are for the maternal safety population.

* Number of pregnant participants who completed the delivery; this value is the denominator for the percentage calculations.

Appendix 7. Demographic Characteristics and Live Birth Outcomes of Newborn Participants

Characteristic and live birth outcome	RSVpreF (N=3659*)	Placebo (N=3646*)
Sex, n (%)		
Male	1865 (51.0)	1831 (50.2)
Female	1794 (49.0)	1815 (49.8)
Country subcategory,† n (%)		
High income	2516 (68.8)	2508 (68.8)
Upper-middle income	1008 (27.5)	1003 (27.5)
Lower-middle income	38 (1.0)	39 (1.1)
Low income	97 (2.7)	96 (2.6)
Gestational age at birth, n (%)		
24–<28 weeks	1 (<0.1)	1 (<0.1)
28–<34 weeks	21 (0.6)	11 (0.3)
34–<37 weeks	185 (5.1)	160 (4.4)
37–<42 weeks	3423 (93.6)	3437 (94.3)
≥42 weeks	27 (0.7)	34 (0.9)
APGAR score, 5 minutes, n (%)		
n‡	3618	3602
<4	8 (0.2)	5 (0.1)
4–<7	29 (0.8)	27 (0.7)
7–10	3581 (99.0)	3570 (99.1)
Median (range)	9.0 (1–10)	9.0 (2–10)
Outcome, n (%)		
Normal	3225 (88.1)	3193 (87.6)
Congenital malformation/anomaly	205 (5.6)	245 (6.7)
Other neonatal problems	226 (6.2)	202 (5.5)
Extremely low birth weight (≤1000 g)	1 (<0.1)	2 (<0.1)
Very low birth weight (>1000–1500 g)	3 (<0.1)	6 (0.2)
Low birth weight (>1500–2500 g)	182 (5.0)	150 (4.1)
Developmental delay	25 (0.7)	17 (0.5)

SD, standard deviation.

* Number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.

† The subcategorization of countries by income level and the number of newborns in each country are provided in **Appendix 2**.

‡ Denominator value for the percentage calculations of APGAR scores.

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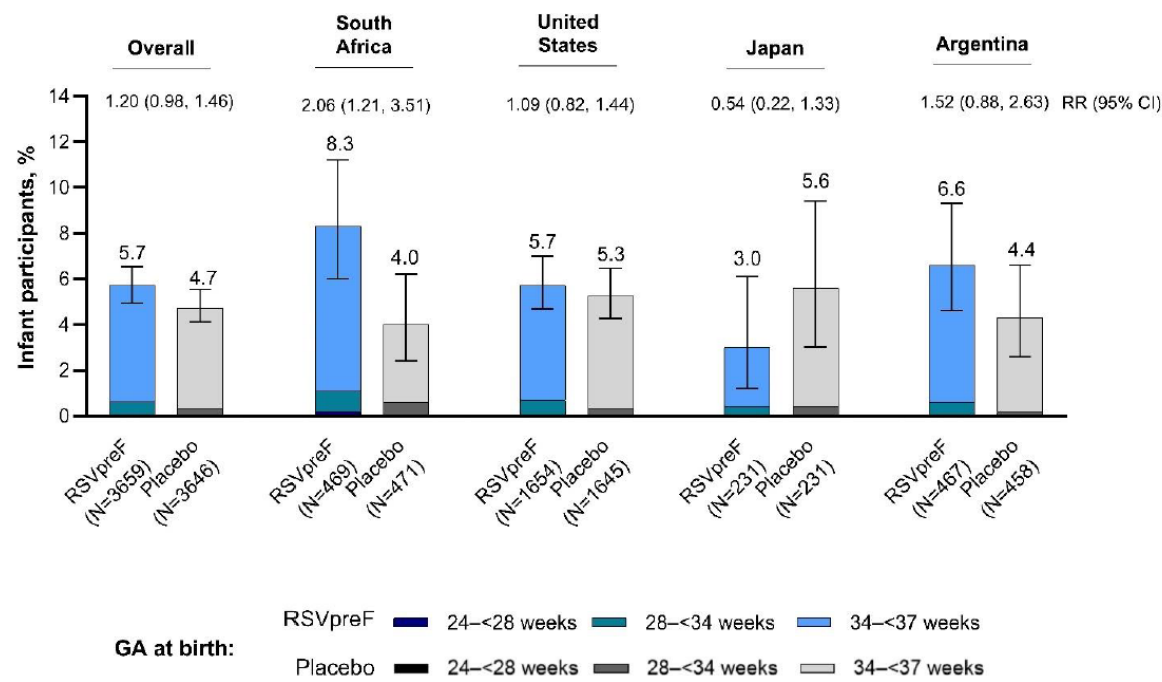
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Appendix 8. Preterm births by country



Data are for the infant safety population. Numbers above the bars are the preterm rate (<37 weeks GA) overall and by country that enrolled >400 infants. GA, gestational age; RR, relative risk.

Appendix 9. Race, Ethnicity, and Relevant Maternal Medical History of Pregnant Participants With Preterm Delivery

	RSVpreF (N=206) n (%)	Placebo (N=172) n (%)	Total (N=378) n (%)
Race			
White	136 (66.0)	108 (62.8)	244 (64.6)
Black	45 (21.8)	32 (18.6)	77 (20.4)
Asian	15 (7.3)	24 (14.0)	39 (10.3)
None of the above	8 (3.9)	5 (2.9)	13 (3.4)
Not reported/not known	2 (1.0)	3 (1.7)	5 (1.3)
Ethnicity			
Hispanic/Latino	72 (35.0)	59 (34.3)	131 (34.7)
Any medical history	104 (50.5)	93 (54.1)	197 (52.1)
Anemia	7 (3.4)	8 (4.7)	15 (4.0)
Congenital uterine anomaly	0	2 (1.2)	2 (0.5)
Asymptomatic bacteriuria	0	1 (0.6)	1 (0.3)
Bacterial vaginosis	0	1 (0.6)	1 (0.3)
Bacterial vulvovaginitis	0	1 (0.6)	1 (0.3)
COVID-19 or SARS-CoV-2 test positive	4 (2.0)	4 (2.3)	8 (2.1)
Chlamydial infection	0	1 (0.6)	1 (0.3)
Cystitis	1 (0.5)	1 (0.6)	2 (0.5)
Genital herpes	3 (1.5)	1 (0.6)	4 (1.1)
Herpes simplex	0	1 (0.6)	1 (0.3)
HELLP syndrome	1 (0.5)	0	1 (0.3)
Pelvic inflammatory disease	0	1 (0.6)	1 (0.3)
Sexually transmitted disease	1 (0.5)	0	1 (0.3)
Syphilis	1 (0.5)	0	1 (0.3)
Urinary tract infection	2 (1.0)	4 (2.3)	6 (1.6)
Vulvovaginal candidiasis	1 (0.5)	0	1 (0.3)
Vulvovaginal mycotic infection	0	1 (0.6)	1 (0.3)
Type 2 diabetes mellitus	0	4 (2.3)	4 (1.1)
Hypertension	5 (2.4)	6 (3.5)	11 (2.9)

HELLP, hemolysis, elevated liver enzymes, and low platelets.

Data are for the maternal safety population.

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Appendix 10. Adverse Events that are Potential Indications for Preterm Delivery Among Pregnant Participants With Preterm Delivery

	RSVpreF (N=206) n (%)	Placebo (N=172) n (%)	Total (N=378) n (%)
Amniotic cavity infection	1 (0.5)	2 (1.2)	3 (0.8)
Anemia	3 (1.5)	1 (0.6)	4 (1.1)
Cholestasis of pregnancy	1 (0.5)	1 (0.6)	2 (0.5)
Diabetes mellitus	1 (0.5)	0	1 (0.3)
Eclampsia	2 (1.0)	1 (0.6)	3 (0.8)
Fetal growth restriction	7 (3.4)	4 (2.3)	11 (2.9)
Gestational diabetes	4 (1.9)	3 (1.7)	7 (1.9)
Gestational hypertension	9 (4.4)	5 (2.9)	14 (3.7)
HELLP syndrome	1 (0.5)	2 (1.2)	3 (0.8)
Hemorrhage in pregnancy	2 (1.0)	1 (0.6)	3 (0.8)
Placental insufficiency	1 (0.5)	0	1 (0.3)
Pre-eclampsia	30 (14.6)	17 (9.9)	47 (12.4)
Premature separation of placenta	8 (3.9)	7 (4.1)	15 (4.0)
Threatened uterine rupture	0	2 (1.2)	2 (0.5)

HELLP, hemolysis, elevated liver enzymes, and low platelets.

Data are for the maternal safety population.

Appendix 11. Receipt of Antenatal Non–Study Vaccines Among Pregnant Participants

	RSVpreF	Placebo	Total
Overall			
Pregnant participants vaccinated, N	3698	3687	7385
Receipt of non-study vaccine, n (%)	2397 (64.8)	2406 (65.3)	4803 (65.0)
High-income country			
Pregnant participants vaccinated, N	2535	2532	5067
Receipt of non-study vaccine, n (%)	1606 (63.4)	1605 (63.4)	3211 (63.4)
Non–high-income country			
Pregnant participants vaccinated, N	1163	1155	2318
Receipt of non-study vaccine, n (%)	791 (68.0)	801 (69.4)	1592 (68.7)
Upper-middle-income country			
Pregnant participants vaccinated, N	1025	1018	2043
Receipt of non-study vaccine, n (%)	685 (66.8)	700 (68.8)	1385 (67.8)
Lower-middle-income country			
Pregnant participants vaccinated, N	40	39	79
Receipt of non-study vaccine, n (%)	27 (67.5)	23 (59.0)	50 (63.3)
Low-income country			
Pregnant participants vaccinated, N	98	98	196
Receipt of non-study vaccine, n (%)	79 (80.6)	78 (79.6)	157 (80.1)

Data are for the maternal safety population.

Countries included in each income region are summarized in **Appendix 2**.

Appendix 12. Preterm Delivery Rates Stratified by Receipt of Antenatal Non–Study Vaccines Among Pregnant

Participants

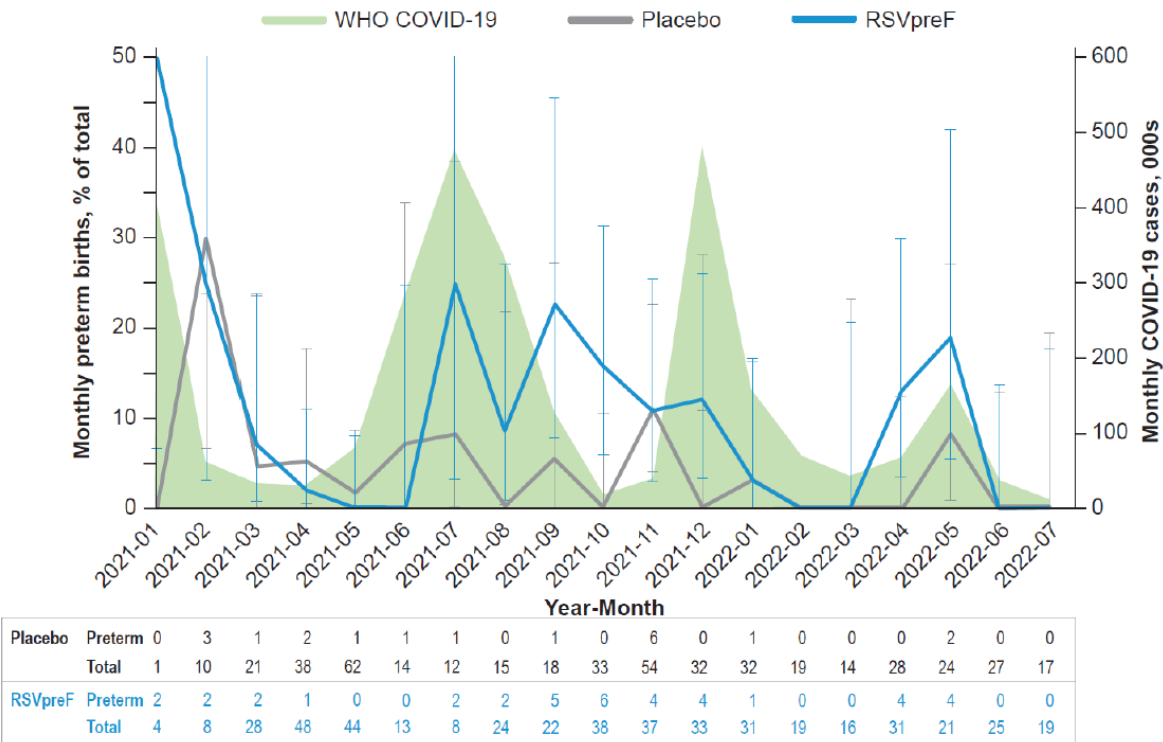
	RSVpreF		Placebo		RR	95% CI
	n/N	%	n/N	%		
Overall						
≥1 non-study vaccination	114/2284	5.0	110/2281	4.8	1.04	(0.80–1.34)
No non-study vaccination	92/1372	6.7	62/1362	4.6	1.47	(1.08–2.01)
HIC						
≥1 non-study vaccination	72/1601	4.5	78/1596	4.9	0.92	(0.67–1.26)
No non-study vaccination	55/914	6.0	48/910	5.3	1.14	(0.78–1.66)
Non-HIC						
≥1 non-study vaccination	42/683	6.1	32/685	4.7	1.32	(0.84–2.06)
No non-study vaccination	37/458	8.1	14/452	3.1	2.61	(1.43–4.76)

GA, gestational age; HIC, high-income country; RR, relative risk.

Data are for the maternal safety population with live births.

Countries included in each income region are summarized in **Appendix 2**.

Appendix 13. Preterm births in the respiratory syncytial virus prefusion F (RSVpreF) and placebo groups by calendar month and monthly coronavirus disease 2019 (COVID-19) cases in South Africa.



Error bars indicate 95% CIs and COVID-19 case numbers were derived from the WHO database of regional surveillance reports (<https://covid19.who.int/region/afro/country/za>). WHO, World Health Organization.