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Original Research

Preterm Birth Frequency and Associated Outcomes From the MATISSE (Maternal Immunization Study for Safety and Efficacy) Maternal Trial of the Bivalent Respiratory Syncytial Virus Prefusion F Protein Vaccine

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OBJECTIVE: To describe preterm birth frequency and newborn and infant outcomes overall and among preterm children in the MATISSE (Maternal Immunization Study for Safety and Efficacy) trial of maternal vaccination with bivalent respiratory syncytial virus (RSV) prefusion F protein–based vaccine

See related editorial on page 144.

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Pfizer designed and conducted the trial; was responsible for data collection, analysis, interpretation; and manufactured the RSVpreF and placebo. Medical writing support was provided by Tricia Newell, PhD, and Sheena Hunt, PhD, at ICON (Blue Bell, Pennsylvania) and was funded by Pfizer Inc.

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(RSVpreF) to protect infants against severe RSV-associated illness.

METHODS: MATISSE was a global, phase 3, randomized, double-blind trial. Pregnant individuals received single injections of RSVpreF or placebo. Adverse events of special interest, including preterm birth (gestational age less than 37 weeks) and low birth weight (2,500 g or less), were collected through 6 months after delivery (pregnant participants) and from birth through age 12 or 24 months (pediatric participants).

RESULTS: Overall, 7,386 pregnant participants received RSVpreF (n=3,698) or placebo (n=3,688); 7,305 newborns and infants were included in the analysis. Most children in both groups were born full term (more than 93%) with normal birth weight (95% or higher). Newborn and infant outcomes, including rates of low birth weight and neonatal hospitalization, were favorable and comparable between groups. Preterm birth rates were 5.7% in the RSVpreF arm and 4.7% in the placebo arm (relative risk [RR] 1.20, 95% CI, 0.98–1.46); most were late preterm. Newborn and infant outcomes, including rates of low birth weight and neonatal hospitalization, were comparable between groups. Twenty-two newborn or infant deaths occurred during the study (RSVpreF n=8, placebo n=14). When stratified by income region, preterm birth rates in RSVpreF and placebo recipients were both 5.0% in high-income countries. Rates in non–high-income countries were 7.0% and 4.0% in the RSVpreF and placebo groups, respectively, and 8.3% and 4.0% in South Africa (RR 2.06, 95% CI, 1.21–3.51).

CONCLUSION: In this study of maternal RSVpreF vaccination, no clinically significant increase in adverse events of special interest, including preterm birth, low birth weight, or neonatal hospitalization, was observed among pregnant people in the overall analysis. In subgroup analysis of non–high-income countries, an elevated risk of preterm birth was observed. More research is needed to better ascertain preterm delivery risk factors, particularly aimed at minimizing disparities among geographic regions.

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Respiratory syncytial virus (RSV)–associated disease causes substantial burden in infants worldwide.[1] Poor health care access contributes to increased morbidity in infants born outside high-income countries, who also experience high fatality rates.[1] Maternal vaccination decreases disease burden in early infancy caused by influenza, tetanus, pertussis, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[2,3] and could contribute to decreasing infant RSV-associated disease burden.

In the global MATISSE (Maternal Immunization Study for Safety and Efficacy) phase 3 trial of bivalent RSV prefusion F protein–based maternal vaccine (RSVpreF) administered at 24–36 weeks of gestation, RSVpreF efficacy in preventing severe medically attended RSV-associated lower respiratory tract illness in infants was 81.8% (99.5% CI, 40.6–96.3%) and 69.4% (44.3–84.1%) within 90 and 180 days after birth, respectively, meeting success criterion for this primary endpoint.[4]

Maternal RSVpreF vaccination is now licensed in several regions with varying recommendations for gestational age at administration (24–36 weeks, 28–36 weeks, or 32–36 weeks).[5,6] A consideration for these recommendations was concern about preterm births occurring among pediatric participants during the study for which available trial data were insufficient to verify or exclude causal links with RSVpreF vaccination.[5]

To further study preterm births and associated outcomes that occurred in the trial, this descriptive analysis from MATISSE reports preterm birth frequency and newborn and infant outcomes using entire trial data after study completion in October 2023.

METHODS

The MATISSE design and conduct were described previously.[4] Briefly, MATISSE was a phase 3, double-blind, randomized, placebo-controlled efficacy trial conducted in more than 7,000 participants in 18 countries over four RSV seasons (two per hemisphere) during the coronavirus disease 2019 (COVID-19) pandemic. The primary efficacy outcome was prevention of RSV-associated illness in newborns and infants. Primary safety endpoints were reactogenicity and adverse events occurring in pregnant participants and adverse events and newly diagnosed chronic medical conditions occurring in newborns and infants.

Pregnant participants 49 years and younger at 24–36 weeks of gestation at enrollment with uncomplicated, singleton pregnancies and no increased pregnancy complication risks as determined by investigators and their newborns and infants were included. To ensure diversity across the study population and the generalizability of results, there was no restriction in the enrollment of pregnant participants across racial or ethnic groups. Pregnant participants had to meet qualifying criteria, including receiving country-specific standard prenatal care. Pregnant participants with underlying stable conditions before enrollment were eligible for inclusion (eg, treated

thyroid disease and controlled prepregnancy disorders of glucose intolerances or occurring during pregnancy if uncontrolled at the time of consent). Gestational age determination at study entry used composite criteria based on availability of last menstrual period date and first- or second-trimester ultrasound examination (Appendix 1, available online at http://links.lww.com/AOG/D944). If not already performed as a part of routine prenatal care, pregnant participants had an ultrasound examination before randomization for confirmation of gestational age and fetal anomaly assessment.

Pregnant participants were randomized (1:1) to receive a single intramuscular injection of RSVpreF or placebo. Licensed/authorized maternal vaccines could be given 14 days before or 7 days (14 days for pertussis-containing vaccines) after study vaccine administration (Appendix 1, http://links.lww.com/AOG/D944). The ethics committee at each site approved the protocol. Informed consent and ethical study conduct are further summarized in Appendix 1 (http://links.lww.com/AOG/D944).

The primary maternal safety endpoints were adverse events of special interest for pregnant participants and included preterm delivery (less than 37 weeks of gestation) and positive SARS-CoV-2 test results (active COVID-19 surveillance was not undertaken). Adverse events of special interest for newborns and infants included preterm birth (less than 37 weeks of gestation), low birth weight (2,500 g or less), developmental delay, and positive SARS-CoV-2 test results. Appendix 1, http://links.lww.com/AOG/D944, gives adverse event and adverse event of special interest collection timings, as well as SARS-CoV-2 baseline testing and analysis of pregnant participants. An independent external Data Monitoring Committee assessed unblinded safety data at defined intervals or other timepoints per its discretion or sponsor request.

Preterm birth (ie, before 37 weeks of gestation) and overall newborn and infant and preterm infant outcomes (ie, low birth weight, serious adverse event–related hospitalization, adverse events within 1 month of birth, low Apgar score, death within 24 months of birth) described in this post hoc analysis are presented using categorical variables and Clopper–Pearson 95% CIs. Relative risk (RR) of preterm birth was determined with associated 95% CIs using normal approximations to the log RR for the overall maternal population, by gestational age at vaccination, by country, and by other subgroups. No multiplicity adjustments were made. Preterm delivery rates were assessed by demographic characteristics and maternal medical history, including number of previous pregnancies, smoking or alcohol use, anemia, genitourinary infections, diabetes, hypertension, and vaccination status. Outcomes were stratified by World Bank income subcategories of high-income country compared with non–high-income country (including low-income, lower-middle–income, upper-middle–income country) (Appendix 2, available online at http://links.lww.com/AOG/D944).

RESULTS

From June 17, 2020, to October 27, 2022, 7,386 pregnant individuals participated in the trial and received RSVpreF (n=3,698) or placebo (n=3,688) (Appendix 3, available online at http://links.lww.com/AOG/D944). Among pregnant participants, median gestational age at vaccination was 31.3 weeks (range 24.0–36.9 weeks) with 25.1% (n=1,850) vaccinated at 24 to less than 28 weeks of gestation (Appendices 4 and 5, available online at http://links.lww.com/AOG/D944). First-trimester dating ultrasonograms were performed in 68.8% of participants and more frequently in those from high-income countries (77.2%) compared with those from non–high-income countries (50.3%). Final data from 7,305 children born to pregnant participants are included here (Appendix 3, http://links.lww.com/AOG/D944).

Participants represented a diverse population and geographic distribution across high-income countries and non–high-income countries (Appendices 4 and 5, http://links.lww.com/AOG/D944). Median gestational age at delivery was 39.1 weeks, and 99.7% of deliveries were live births (Appendix 6, available online at http://links.lww.com/AOG/D944). Most children were born at term (RSVpreF 93.6%, placebo 94.3%) (Appendix 7, available online at http://links.lww.com/AOG/D944). Median days between vaccination and delivery were similar between groups (RSVpreF 54 days, placebo 55 days) (Appendix 6, http://links.lww.com/AOG/D944). Overall, 84.8% (RSVpreF 84.5%, placebo 85.0%) of deliveries occurred more than 30 days after vaccination, with comparable distribution of time of vaccination to delivery between groups (Table 1).

No safety concerns were expressed by the independent Data Monitoring Committee, which reviewed safety events throughout study conduct. Rates of preterm birth and low birth weight, low Apgar scores, and serious adverse event–related hospitalization in the neonatal period were comparable between newborns whose mothers received RSVpreF and newborns whose mothers received placebo (Fig. 1A). Preterm birth rates were 5.7% in newborns whose mothers received RSVpreF and 4.7% in those whose mothers received placebo (RR 1.20, 95% CI,

Table 1. Characteristics of Pregnant Participants With Preterm and Term Deliveries

Characteristic	Preterm Delivery			Term Delivery		
	RSVpreF (n=206)*	Placebo (n=172)	Total (n=378)	RSVpreF (n=3,450)	Placebo (n=3,471)	Total (n=6,921)
Geographic distribution						
Africa	41 (19.9)	21 (12.2)	62 (16.4)	523 (15.2)	545 (15.7)	1,068 (15.4)
Europe	10 (4.9)	7 (4.1)	17 (4.5)	310 (9.0)	316 (9.1)	626 (9.0)
North America	95 (46.1)	88 (51.2)	183 (48.4)	1,585 (45.9)	1,583 (45.6)	3,168 (45.8)
Latin America	44 (21.4)	29 (16.9)	73 (19.3)	581 (16.8)	588 (16.9)	1,169 (16.9)
Asia Pacific	16 (7.8)	27 (15.7)	43 (11.4)	451 (13.1)	439 (12.6)	890 (12.9)
GA at vaccination (wk)						
24–less than28	62 (30.1)	59 (34.3)	121 (32.0)	859 (24.9)	834 (24.0)	1,693 (24.5)
28–less than 32	73 (35.4)	53 (30.8)	126 (33.3)	995 (28.8)	1,058 (30.5)	2,053 (29.7)
32–36	71 (34.5)	60 (34.9)	131 (34.7)	1,593 (46.2)	1,573 (45.3)	3,166 (45.7)
More than 36	0	0	0	3 (less than 0.1)	6 (0.2)	9 (0.1)
Time from vaccination to delivery (d)						
7 or less	8 (3.9)	9 (5.2)	17 (4.5)	0	2 (less than 0.1)	2 (less than 0.1)
8–30	72 (35.0)	62 (36.0)	134 (35.4)	487 (14.1)	473 (13.6)	960 (13.9)
More than 30	126 (61.2)	101 (58.7)	227 (60.1)	2,963 (85.9)	2,996 (86.3)	5,959 (86.1)
GA at delivery (wk)						
24–less than 28	1 (0.5)	1 (0.6)	2 (0.5)	0	0	0
28–less than 34	21 (10.2)	11 (6.4)	32 (8.5)	0	0	0
34–less than 37	184 (89.3)	160 (93.0)	344 (91.0)	0	0	0
37–less than 42	0	0	0	3,423 (99.2)	3,437 (99.0)	6,860 (99.1)
42 or more	0	0	0	27 (0.8)	34 (1.0)	61 (0.9)
No. of prior pregnancies						
0	88 (42.7)	60 (34.9)	148 (39.2)	1,121 (32.5)	1,156 (33.3)	2,277 (32.9)
1–3	104 (50.5)	92 (53.5)	196 (51.9)	2,074 (60.1)	2,069 (59.6)	4,143 (59.9)
4 or more	14 (6.8)	20 (11.6)	34 (9.0)	255 (7.4)	246 (7.1)	501 (7.2)
History of preterm birth	10 (4.9)	2 (1.2)	12 (3.2)	48 (1.4)	58 (1.7)	106 (1.5)
Maternal nonstudy vaccination in 2nd and 3rd trimesters						
None	92 (44.7)	62 (36.0)	154 (40.7)	1,280 (37.1)	1,300 (37.5)	2,580 (37.3)
1 or more	114 (55.3)	110 (64.0)	224 (59.3)	2,170 (62.9)	2,171 (62.5)	4,341 (62.7)
1 or more in HIC	72 (35.0)	78 (45.3)	150 (39.7)	1,529 (44.3)	1,518 (43.7)	3,047 (44.0)
1 or more in non-HIC	42 (20.4)	32 (18.6)	74 (19.6)	641 (18.6)	653 (18.8)	1,294 (18.7)
Newborn birth weight (g)						
Extremely low (1,000 or lower)	1 (0.5)	2 (1.2)	3 (0.8)	0	0	0
Very low (1,001–1,500)	3 (1.5)	5 (2.9)	8 (2.1)	0	1 (less than 0.1)	1 (less than 0.1)
Low (1,501–2,500)	83 (40.3)	63 (36.6)	146 (38.6)	98 (2.8)	87 (2.5)	185 (2.7)
Normal (more than 2,500)	118 (57.3)	102 (59.3)	220 (58.2)	3,344 (96.9)	3,371 (97.1)	6,715 (97.0)

RSVpreF, respiratory syncytial virus prefusion F protein–based vaccine; GA, gestational age; HIC, high-income country.
Data are n (%) and are for the maternal safety population.
* Includes a set of twins.

0.98–1.46). Most preterm newborns were delivered late preterm (34 to less than 37 weeks of gestation; RSVpreF 89.3%, placebo 93.0%) (Table 1 and Fig. 2). Very or extremely preterm births (less than 32 weeks of gestation) were uncommon (seven [less than 0.2%] each in both groups, RR 1.00, 95% CI, 0.35–2.84). Percentages of newborns with small-for-gestational-age birth weight[7] were comparable between both groups (RSVpreF 6.9% [253/3,659], placebo 6.4% [232/3,646]). Overall, 58.2% of newborns born preterm had normal birth weight (more than 2,500 g); extremely low (1,000 g or less) and very low (1,001–1,500 g) birth weight rates were comparable between the RSVpreF and placebo groups (0.5% vs 1.2% and 1.5% vs 2.9%, respectively) (Table 1).

Twenty-two newborn and infant deaths occurred in the study (RSVpreF n=8, placebo n=14) (Fig. 1B). One RSV-associated infant death occurred in the placebo group. Of three preterm deaths, one occurred in the RSVpreF group. This child was born at 27 weeks

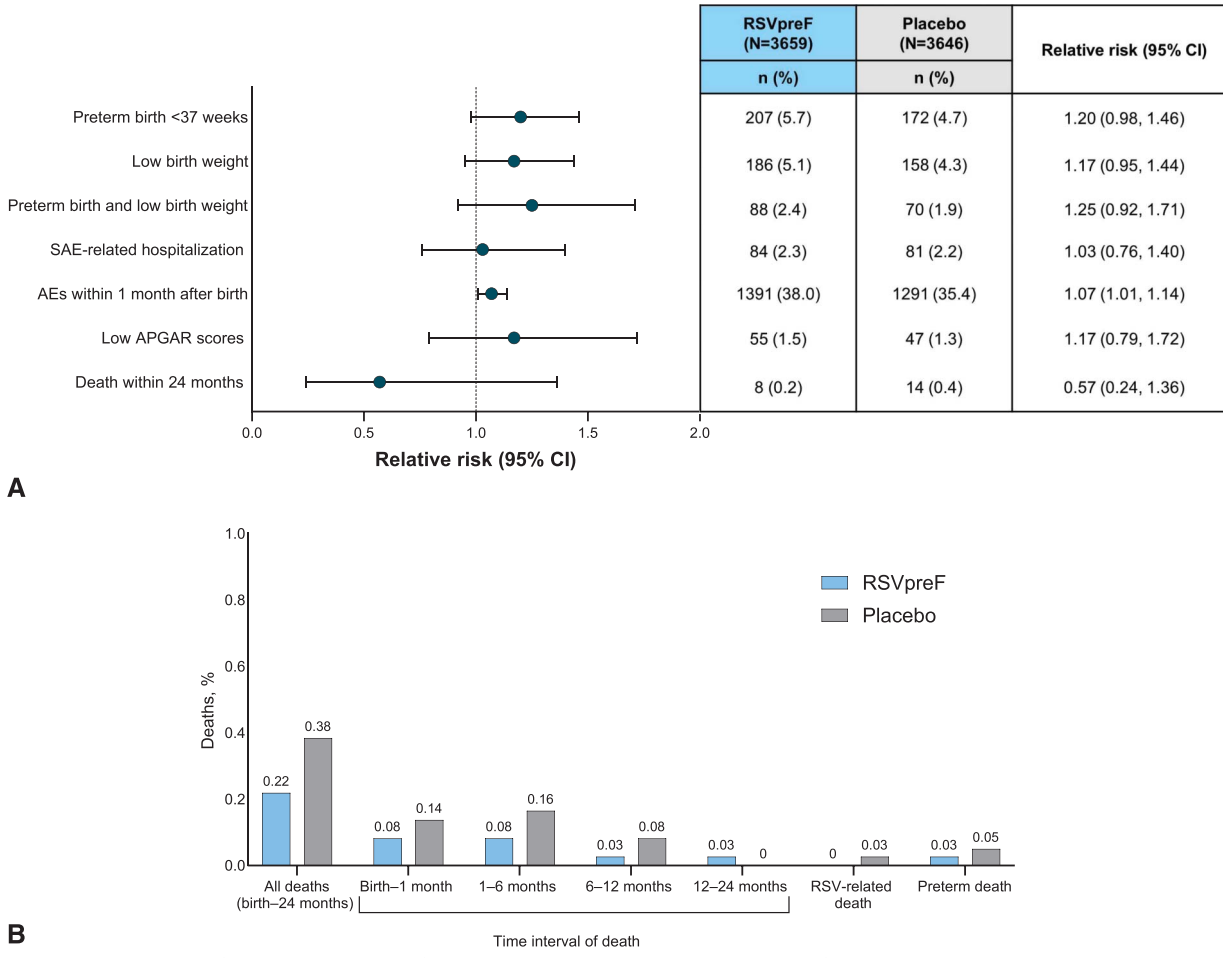

Fig. 1. Relative risk for newborn and infant outcomes (**A**) and newborn and infant deaths during the study (**B**). Shown are data from the newborn and infant safety population. Serious adverse event (SAE)–related hospitalizations were within the neonatal period (ie, 4 weeks). Low Apgar scores were a first score lower than 4 or last score lower than 7. AE, adverse event; RSVpreF, respiratory syncytial virus prefusion F protein–based vaccine.

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of gestation to a participant who developed spontaneous labor within 2 weeks after RSVpreF vaccination; the newborn died of prematurity-related complications within 1 week of birth. Underlying preterm birth risk factors were not identified other than maternal young age (18 years); the investigator did not consider the death vaccine related.

Overall, 60.1% of preterm deliveries (RSVpreF 61.2%, placebo 58.7%) occurred more than 30 days after vaccination (Table 1). When stratified by timing of vaccination, preterm birth rates were similar between the RSVpreF and placebo groups for vaccination given at 24 to less than 28 weeks of gestation (RSVpreF 6.8%, placebo 6.6%, RR 1.03, 95% CI, 0.73–1.46) and 32 or more weeks of gestation (RSVpreF 4.3%, placebo 3.7%, RR 1.16, 95% CI, 0.83–1.63) (Fig. 3). Preterm birth rates for vaccination given at 28 to less than 32 weeks of gestation were 6.8% in the RSVpreF group and 4.8% in the placebo group (RR 1.43, 95% CI, 1.02–2.02).

When stratified by income region, preterm birth rates in the RSVpreF and placebo groups were both 5.0% in high-income countries (RR 1.00, 95% CI, 0.79–1.28) (Fig. 4A). Preterm birth rates in non–high-income countries were 7.0% in RSVpreF recipients and 4.0% in placebo recipients (RR 1.73, 95% CI, 1.22–2.47). This difference was attributable mostly to upper-middle–income countries (RSVpreF 7.5%, placebo 4.2%, RR 1.80, 95% CI, 1.25–2.60), which included the two higher enrolling non–high-income countries (South Africa and Argentina). No difference was seen in the low-income country/lower-middle–

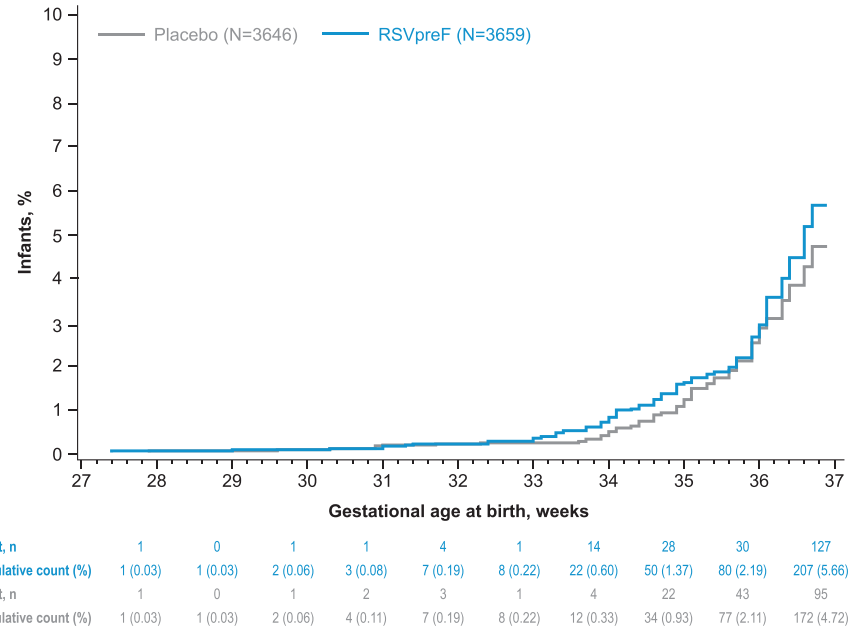

Fig. 2. Cumulative distribution, case counts, and cumulative case counts of gestational age at birth among newborns and infants born at less than 37 weeks of gestation. RSVpreF, respiratory syncytial virus prefusion F protein–based vaccine.

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income country groups (3.0% in both groups), which overall enrolled fewer participants. Variability in RR across countries was observed, with only South Africa having a lower-bound 95% CI not crossing 1 (RR 2.06, 95% CI, 1.21–3.51) (Fig. 4B). Overall and across countries, preterm births occurred predominantly at 34 to less than 37 weeks of gestation (Appendix 8, available online at http://links.lww.com/AOG/D944).

Among preterm children, 42.7% in the RSVpreF group and 34.9% in the placebo group were born to primigravid individuals; previous preterm delivery rates were 4.9% in the RSVpreF group and 1.2% in the placebo group (Table 1). When pregnant participants with a history of preterm birth were excluded, the imbalance in the rates of preterm birth in the study remained but was no longer statistically significant (RSVpreF 5.4%, placebo 4.7%, RR 1.15, 95% CI, 0.94–1.40). No notable differences were seen for pregnant participants who delivered preterm by reported demographic characteristics, other medical history, or lifestyle habits possibly associated with spontaneous

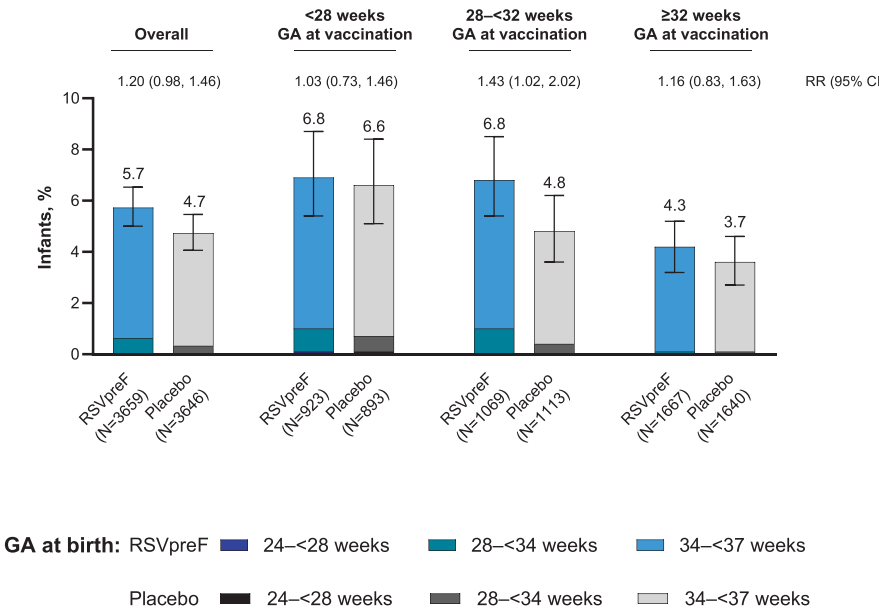

Fig. 3. Preterm births by gestational age (GA) at vaccination. Shown are data from the infant safety population. *Numbers above the error bars* are the preterm birth rate (less than 37 weeks of gestation) overall and by GA at vaccination. Also shown is the relative risk (95% CI). In the overall and less than 28 weeks of gestation at vaccination groups, the rate of GA at birth of 24–less than 28 weeks was less than 0.1% (n=1) in both the respiratory syncytial virus prefusion F protein–based vaccine (RSVpreF) and placebo groups.

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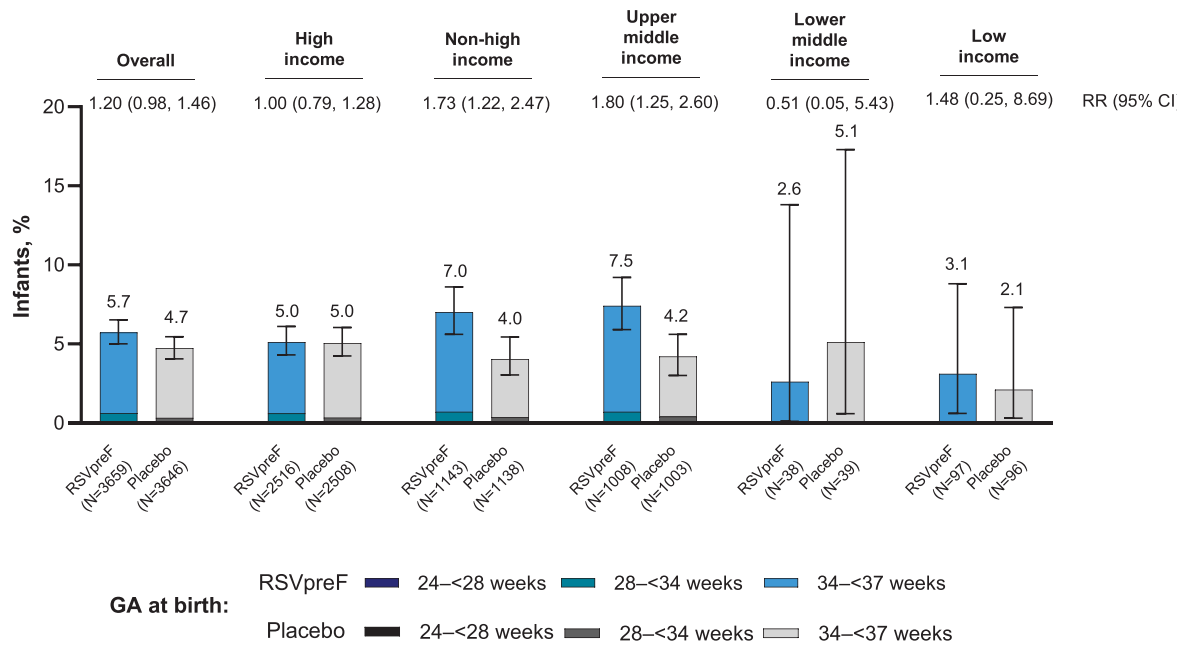

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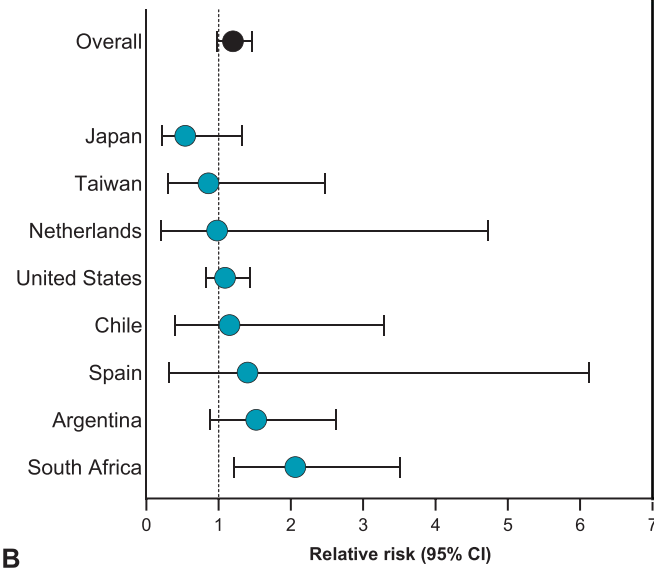

	Preterm infants				Relative risk (95% CI)
	RSVpreF		Placebo		
	%	n/N	%	n/N	
Overall	5.7	207/3659	4.7	172/3646	1.20 (0.98, 1.46)
Japan	3.0	7/231	5.6	13/231	0.54 (0.22, 1.33)
Taiwan	4.6	6/130	5.4	7/130	0.86 (0.30, 2.48)
Netherlands	3.1	3/97	3.2	3/95	0.98 (0.20, 4.73)
United States	5.7	95/1654	5.3	87/1645	1.09 (0.82, 1.44)
Chile	8.1	7/86	7.1	6/85	1.15 (0.40, 3.29)
Spain	3.4	4/118	2.4	3/124	1.40 (0.32, 6.13)
Argentina	6.6	31/467	4.4	20/458	1.52 (0.88, 2.63)
South Africa	8.3	39/469	4.0	19/471	2.06 (1.21, 3.51)

B

Fig. 4. Preterm births by income region (**A**) and relative risk for preterm birth overall and by country (**B**). Shown are data from the newborn and infant safety population. **A.** *Numbers above the bars* are the preterm birth rate (less than 37 weeks of gestational age [GA]) overall and by World Bank income region. Also shown is the relative risk (95% CI). In the overall group, the rate of GA at birth of 24–less than 28 weeks was less than 0.1% (n=1) in both the respiratory syncytial virus prefusion F protein–based vaccine (RSVpreF) and placebo groups. In the high-income group, the preterm birth rate at a GA at birth of 24–less than 28 weeks was less than 0.1% (n=1) in the placebo group. In the non–high-income group, the preterm birth rate at a GA at birth of 24–less than 28 weeks was less than 0.1% (n=1) in the RSVpreF group. In the upper-middle–income group, the preterm birth rate at a GA at birth of 24–less than 28 weeks was less than 0.1% (n=1) in the RSVpreF group. **B.** Countries with more than five preterm births overall. Countries included in each income region are summarized in Appendix 2, available online at http://links.lww.com/AOG/D944. n, number of newborns and infants born preterm; N, total number of infants.

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preterm delivery, including smoking or alcohol use, anemia, genitourinary infections, diabetes, or hypertension (Appendix 9, available online at http://links.lww.com/AOG/D944). Group B streptococcus colonization rates were similar between study groups (RSVpreF 13.3%, placebo 12.3%).

More than one-third of pregnant participants with preterm deliveries reported additional adverse events other than preterm delivery (RSVpreF 42.2%, placebo 33.1%), which were most commonly preeclampsia (RSVpreF 11.7%, placebo 5.8%), any premature rupture of membranes (RSVpreF 6.8%, placebo 8.1%), and gestational hypertension (RSVpreF 3.9%, placebo 2.9%). Potential indications for preterm delivery[8,9] among maternal participants, including maternal–fetal indications and pregnancy complications (*Medical Dictionary of Regulatory Activities* terms of cholestasis of pregnancy, diabetes mellitus, gestational diabetes, anemia, amniotic cavity infection, fetal growth restriction, placental insufficiency, premature placental separation, threatened uterine rupture), were overall similar between study groups (Appendix 10, available online at http://links.lww.com/AOG/D944). Rates of maternal hypertensive conditions of pregnancy (gestational hypertension; preeclampsia and eclampsia; and hemolysis, elevated liver enzymes, and low platelet count [HELLP] syndrome) were 20.4% and 14.5% in mothers who delivered preterm and received RSVpreF and placebo, respectively (RR 1.40, 95% CI, 0.89–2.20).

Overall, 62.5% of pregnant participants received nonstudy antenatal vaccines (Table 1). Similar percentages of those from non–high-income countries (68.7%) received nonstudy antenatal vaccinations compared with those from high-income countries (63.4%) (Appendix 11, available online at http://links.lww.com/AOG/D944). Among pregnant participants who received nonstudy antenatal vaccines, preterm delivery rates were similar between groups (RSVpreF 5.0%, placebo 4.8%, RR 1.04, 95% CI, 0.80–1.34) (Appendix 12, available online at http://links.lww.com/AOG/D944). In pregnant participants who did not receive nonstudy antenatal vaccines, preterm delivery rates were 6.7% in those who received RSVpreF and 4.6% among placebo recipients (RR 1.47, 95% CI, 1.08–2.01). When stratified by receipt of additional nonstudy antenatal vaccinations in high-income countries compared with non–high-income countries, preterm delivery rates in the RSVpreF group were highest among pregnant participants in non–high-income countries not receiving additional nonstudy antenatal vaccinations (RSVpreF 8.1%, placebo 3.1%, RR 2.61, 95% CI, 1.43–4.76).

During the study, passive reporting showed that 2.9% of pregnant participants developed COVID-19 or tested positive for SARS-CoV-2. The SARS-CoV-2–positive serostatus of pregnant participants before vaccination was 61.7% in South Africa, 57.8% in Argentina, and 25.6% in the United States (Appendix 1, http://links.lww.com/AOG/D944). In the RSVpreF group, 4.4% of pregnant participants who had preterm deliveries reported testing positive for SARS-CoV-2 during pregnancy compared with 2.3% in the placebo group (RR 1.88, 95% CI, 0.59–5.99). Among SARS-CoV-2–seronegative pregnant participants at enrollment who delivered prematurely, percentages who seroconverted by delivery were 5.3% in the RSVpreF compared with 4.5% in the placebo group.

Temporal variation in preterm birth distribution between RSVpreF and placebo groups by month of birth compared with monthly COVID-19 cases was assessed in South Africa, where preterm birth rate differences between the RSVpreF and placebo groups were most prominent (Appendix 13, available online at http://links.lww.com/AOG/D944). South African study vaccinations started in November 2020, but observed differences in preterm birth rates between RSVpreF and placebo were first notable in July 2021 at the Delta wave peak and were pronounced in the last quarter of 2021, coinciding with the Omicron wave.

DISCUSSION

In post hoc descriptive analyses of preterm birth and newborn and infant outcomes from the global phase 3 maternal MATISSE vaccination trial, no differences were observed in preterm birth and associated adverse effects, including neonatal mortality risk, low birth weight, and neonatal hospitalization rates, in the overall analysis. Differences in preterm birth rates were observed in non–high-income countries (RR 1.73, 95% CI, 1.22–2.47), with South Africa (RR 2.06, 95% CI, 1.21–3.51) the primary contributor. Definitive causes between vaccination and preterm birth were not identified, but evaluation is limited by low event numbers.

Most children in MATISSE were born more than 30 days after vaccination, and timing of birth from vaccination was similar between study groups. Despite one-quarter of mothers being vaccinated earlier in pregnancy (24 to less than 28 weeks of gestation), there was no difference in preterm births before 32 weeks; most preterm children were born after 34 weeks of gestation.

The overall preterm birth rate in MATISSE was lower than background rates in countries with sufficient participant–event numbers enabling interpretation (Argentina, Japan, South Africa, United States);

for example, in South Africa, the RSVpreF group preterm birth rate was 8.3% compared with the national estimate of 13%.[10] Eligibility criteria for study entry limiting participants with preterm birth risk factors and enhanced screening associated with conduct of a large clinical trial likely contributed to this finding.

The clinical significance of observed preterm birth imbalances between study groups noted in non–high-income countries (primarily South Africa and Argentina) is unknown; these were not observed in high-income countries despite the 2.5-times higher number of participants. First-trimester gestational age–determination ultrasonograms were performed more frequently in high-income countries, which could provide more reliable gestational age estimates than those done in non–high-income countries, of which half were second-trimester ultrasonograms; however, dating errors would be expected to affect the RSVpreF and placebo groups equally.

In South Africa, a preterm birth rate imbalance was first observed in mid-2021, coinciding with the period after the Delta peak. Seroconversion rates were observed to be higher in the RSVpreF group and higher in non–high-income countries. No conclusions can be drawn about associations between maternal COVID-19 and observed RSVpreF preterm deliveries given the rapidly changing COVID-19 pandemic landscape during MATISSE.

Underlying causes of preterm delivery are often multifactorial,[11] and no obvious relationships between preterm births and maternal medical history or reported adverse events were identified. Increased preterm delivery risk has not been detected as a possible adverse event with other maternal vaccines (eg, COVID-19; influenza; and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis [Tdap]).[12–15] In a previously completed maternal immunization trial with a monovalent subunit vaccine candidate based on F not stabilized in the prefusion conformation, preterm birth rates were similar between the vaccine and placebo groups.[16] However, a maternal phase 3 trial of a monovalent RSV prefusion F subunit vaccine candidate, RSVpreF3, was terminated early because of imbalances in neonatal deaths (attributed to prematurity) between the vaccine and placebo groups, with the RR of preterm birth determined to be statistically significant 43 days after delivery (RR 1.74, 95% CI, 1.08–1.74, P=.001).[17] Seven preterm deaths occurred in infants in the vaccine group compared with none in the placebo group (with a 2:1 randomization ratio). This finding differed from our phase 3 MATISSE trial of bivalent RSVpreF, which showed fewer overall newborn and infant deaths in the RSVpreF compared with placebo group and that most preterm births were late preterm. In the monovalent RSVpreF3 trial, peak preterm birth imbalance in non–high-income countries coincided with SARS-CoV-2 Delta dominance, similar to findings described here, but no causal factors were identified. Differences in vaccine candidate formulations and participating country footprint (eg, inclusion of South Asian countries in RSVpreF3 trial) limit direct comparison of RSVpreF3 trial results with those from MATISSE.[17,18]

Limitations of this study include that this was a post hoc descriptive analysis that was not powered for statistical comparisons between groups. In addition, although the expectation is that participant characteristics should be balanced in the setting of a randomized trial, all potential confounding risk factors for preterm delivery may not have been captured, and COVID-19 rates were likely underestimated because of passive reporting and the inability to assess reinfections.

After a long history of a lack of options to prevent RSV-associated illness in newborns and young infants,[19] active protection of this vulnerable population from birth is now possible. The maternal RSVpreF vaccine ABRYSVO is licensed in multiple countries with varied recommendations for administration timing.[5,6] Licensure was based predominantly on the MATISSE primary analysis. Estimates in the United States suggest that vaccination of 115 and 242 pregnant individuals would prevent an RSV-related infant emergency department visit and hospitalization, respectively.[20] Robust pharmacovigilance is ongoing after RSVpreF implementation to assess for real-world safety in several outcomes, including premature births. More research is needed to better ascertain preterm delivery pathogeneses, particularly aimed at minimizing disparities among geographic regions.

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Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *Yes.*

What data in particular will be shared? *On request, and subject to review, Pfizer will provide the data that support the findings of this study.*

What other documents will be available? *Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual deidentified participant data.*

When will data be available (start and end dates)? *Not applicable.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *See* https://pfizer.com/science/clinical-trials/trial-data-and-results *for more information.*

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