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Original Research

Efficacy, Safety, and Immunogenicity of the MATISSE (Maternal Immunization Study for Safety and Efficacy) Maternal Respiratory Syncytial Virus Prefusion F Protein Vaccine Trial

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OBJECTIVE: To evaluate descriptive efficacy data, exploratory immunogenicity data, and safety follow-up through study completion from the global, phase 3 MATISSE (Maternal Immunization Study for Safety and Efficacy) maternal vaccination trial of bivalent respiratory syncytial virus (RSV) prefusion F protein vaccine (RSVpreF).

METHODS: MATISSE was a phase 3, randomized, double-blinded, placebo-controlled trial. Healthy pregnant participants aged 49 years or younger at 24–36 weeks of gestation were randomized (1:1) to receive a single RSVpreF 120 micrograms or placebo dose. Primary efficacy endpoints included newborn and infant severe RSV-associated medically attended lower respiratory tract illness within 180 days after birth. The RSV-A and RSV-B serum neutralizing antibody titers were determined in a subset of pregnant participants and their newborns.

RESULTS: In this final analysis, 7,420 pregnant participants were randomized, and 7,307 children were born (RSVpreF n=3,660, placebo n=3,647). *Vaccine efficacy*, defined as protection against newborn and infant severe RSV-associated medically attended lower respiratory tract illness, was 82.4% (95% CI, 57.5–93.9) and 70.0% (95% CI, 50.6–82.5) within 90 and 180 days of birth, respectively. The RSVpreF induced robust immune responses in pregnant participants and resulted in highly efficient transfer of maternal antibodies to their newborns across subgroups (by gestational age at delivery and at vaccination, number of days from vaccination to delivery, country, maternal age). Final RSVpreF safety results in pregnant and newborn and infant participants were consistent with the primary analysis with no new safety concerns identified.

CONCLUSION: This final analysis of MATISSE trial data confirms the primary analysis conclusions: Maternal vaccination with RSVpreF has a favorable safety profile in both pregnant and newborn and infant participants and demonstrates efficacy against RSV-associated lower respiratory tract illness in infants through age 6 months. The RSVpreF induces robust immune responses in pregnant individuals, with corresponding high RSV-neutralizing titers in their newborns.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, NCT04424316.

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Respiratory syncytial virus (RSV)–associated illnesses in infants and children present a substantial global clinical burden.[1] Infants are at morbidity and mortality risk from RSV-associated disease during their first months of life.[1] Severe RSV illness is most commonly reported in infants aged younger than 6 months, and case fatality ratios are highest in infants aged younger than 3 months.[1,2] Children and infants from outside high-income countries have substantially worse outcomes from RSV illness than those in high-income countries.[1,3] Other than supportive care, no treatment options exist.[4,5] Although the monoclonal antibody nirsevimab is effective at preventing RSV-associated disease in newborns and young infants, costs may be prohibitively high.[6] If effective, widespread maternal vaccination with a bivalent RSV prefusion F protein (RSVpreF) vaccine could help reduce both infant RSV–lower respiratory tract illness global burden and RSV-associated health inequities.

The global MATISSE (Maternal Immunization Study for Safety and Efficacy) phase 3 maternal vaccination trial assessed the safety and efficacy of RSVpreF in preventing RSV-associated lower respiratory tract illness in newborns and infants.[7] In the primary analysis that included 85% of scheduled follow-

See related editorial on page 144.

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up data from 7,392 pregnant participants randomized and 7,128 newborns and infants enrolled from June 17, 2020, through October 2, 2022, RSVpreF demonstrated 81.8% and 69.4% efficacy in preventing severe RSV-associated medically attended lower respiratory tract illness within 90 and 180 days after birth, respectively, meeting its primary endpoint and supporting authorization globally.[7–9] In addition, RSVpreF showed favorable safety profiles in pregnant individuals and their newborns and infants in this primary analysis.[7] To augment and complement these primary results, the objective of this analysis is to present final descriptive efficacy data for primary, secondary, and exploratory endpoints, up to 2 years' safety follow-up of children through study completion, and exploratory immunogenicity data from MATISSE.

METHODS

The design of the phase 3, multicenter, double-blinded, placebo-controlled MATISSE trial was reported previously (NCT04424316).[7] Briefly, RSVpreF was administered to healthy pregnant participants aged 49 years or younger at 24–36 weeks of gestation of a singleton pregnancy with no known increased pregnancy complication risk. Eligible participants were randomized (1:1) to receive a single dose of RSVpreF (120 micrograms: 60 micrograms RSV-A, 60 micrograms RSV-B prefusion F antigen) or placebo (lyophile matched). The protocol, protocol amendments, informed consent document, and all other relevant documents were reviewed and approved by the sponsor and the IRB/ethics committee at each site before study initiation. Further eligibility criteria and ethical trial conduct details are provided in Appendix 1, available online at http://links.lww.com/AOG/D942.

Primary efficacy endpoints were severe RSV-associated medically attended lower respiratory tract illness and RSV-associated medically attended lower respiratory tract illness in newborns and infants within 180 days after birth. Secondary endpoints included RSVpreF efficacy in reducing RSV-associated hospitalization incidence and all-cause medically attended lower respiratory tract illness within 360 days after birth. Exploratory endpoints included efficacy against RSV-associated medically attended respiratory tract illness, RSV-A and RSV-B subtypes, severe RSV-associated medically attended lower respiratory tract illness and RSV-associated hospitalizations within 730 days of birth, and effects on health care utilization. Case definitions and the Endpoint Adjudication Committee role are provided in Appendix 2, available online at http://links.lww.com/AOG/D942. Respiratory illness surveillance and whole-viral-genome sequencing methodology to assess mutations in the RSV F protein are detailed in Appendix 1, http://links.lww.com/AOG/D942.

RSV-A and RSV-B serum neutralizing titers were assessed before vaccination and at delivery (pregnant individuals) and birth (newborns) in a subset of pregnant participants and their newborns. The RSV-A, RSV-B, and RSV-A/RSV-B combined serum neutralizing antibody titers were determined as described previously.[10] Placental transfer ratios in parent–newborn pairs (ratio of newborn's serum neutralizing titer at birth to pregnant individual's serum neutralizing titer at delivery) were assessed. Serum sample collection and serum neutralizing assays are further detailed in Appendix 1, http://links.lww.com/AOG/D942.

An independent external data monitoring committee conducted ongoing unblinded safety monitoring. Primary safety objectives were to describe RSVpreF safety and tolerability in pregnant participants and RSVpreF safety in their newborns and infants. For each pregnant participant (including their fetus), adverse event collection was from signing of informed consent through 1 month after vaccination; serious adverse event collection continued until 6 months after delivery. For pediatric participants, adverse events were collected from birth through age 1 month and serious adverse events and newly diagnosed chronic medical conditions were collected from birth until age 12 or 24 months. Special-interest adverse events for pregnant individuals and children were predefined for systematic collection throughout the entire study duration (Appendix 1, http://links.lww.com/AOG/D942).

Appendix 3, available online at http://links.lww.com/AOG/D942, describes study populations. Sample size determination, primary analysis hypothesis testing, and vaccine efficacy determination were reported previously.[7] Vaccine efficacy was calculated as $(1–RR)\times100$, where RR is the relative risk of the efficacy endpoint based on the incidence in the RSVpreF group compared with the placebo group. Here, a vaccine efficacy of zero means that there was no effect between vaccine and placebo. Thus, a lower vaccine efficacy might lead to a negative lower bound of the 95% CI. Blinding was maintained until final analysis, and all vaccine efficacy analyses are descriptive and presented with unadjusted 95% CIs.

Immunogenicity analyses were conducted by subgroup in specific participant subsets (ie, less than 37 weeks of gestation at delivery, delivered before 14 and before 30 days after vaccination, from selected countries, maternal age less than 18 years) in evaluable immunogenicity populations of pregnant and newborn participants. For pregnant individuals and newborns

with births at less than 37 weeks of gestation and maternal age younger than 18 years, comparison groups comprising participants with births at or after 37 weeks and maternal age 18 years or older, respectively, were created and based on additional serology testing required for regulatory purposes in some regions. For analyses by country, 84 parent–newborn pairs were randomly selected per country (except for the Philippines, which included all participants), with equal participant numbers selected across vaccination groups and across gestational age at vaccination (24–less than 28 weeks, 28–less than 32 weeks, 32–36 weeks). The RSV-A, RSV-B, and RSV-A/RSV-B combined neutralizing antibody titers were logarithmically transformed for analysis. Geometric mean titers (GMTs), geometric mean ratios, geometric mean fold rises, and placental transfer ratio calculations and their associated CIs are given in Appendix 1, http://links.lww.com/AOG/D942. Spearman rank correlation coefficients between maternal and newborn titers were reported. Safety endpoints are presented as point estimates with associated exact two-sided Clopper–Pearson 95% CIs.

RESULTS

In this final analysis including data from June 17, 2020, to October 27, 2023, 7,420 pregnant participants were randomized; 7,307 children born to pregnant individuals were randomized to receive RSVpreF (n=3,660) or placebo (n=3,647), with 3,803 planned to complete 24 months of follow-up (Appendix 4, available online at http://links.lww.com/AOG/D942). Overall, 98.0% (7,159/7,307), 95.5% (6,977/7,307), and 86.7% (6,821/7,307) of children completed the 1-, 6-, and 12-month follow-up; 86.7% (3,299/3,803) completed the 24-month follow-up; and 90.5% (6,612/7,307) completed the study. Median duration of follow-up for children was 398 days (range 1–939 days) and 392 days (1–1,004 days) among those whose parent received RSVpreF and placebo, respectively.

Demographic characteristics of pregnant participants and newborn and infant birth outcomes were generally similar across study groups (Appendix 5, available online at http://links.lww.com/AOG/D942). Overall, 65% of pregnant participants were White, 20% were Black, and 29% were Hispanic or Latina. Median age at vaccination was 29 years (range 14–47 years), and median gestational age was 31.3 weeks (range 24.0–36.9 weeks). Half of newborns were female, and 93.6% were born at term (37–less than 42 weeks of gestation).

At final analysis, vaccine efficacy was consistent with the primary analysis and all timepoints after birth. For the first primary endpoint of severe RSV-associated medically attended lower respiratory tract illness among newborns and infants within 90 days of birth, vaccine efficacy was 81.8% (99.5% CI, 40.6–96.3) in the primary analysis and 82.4% (95% CI, 57.5–93.9) in the final analysis (Fig. 1A) (Appendix 6, available online at http://links.lww.com/AOG/D942). Corresponding vaccine efficacy within 180 days of birth in the final analysis was 70.0% (95% CI, 50.6–82.5). For the second primary endpoint of RSV-associated medically attended lower respiratory tract illness, vaccine efficacy was 57.1% (99.5% CI, 14.7–79.8) and 57.6% (95% CI, 31.3–74.6) within 90 days after birth in the primary and final analyses, respectively (Fig. 1B) (Appendix 6, http://links.lww.com/AOG/D942). Vaccinations were administered throughout the trial with case accruals occurring every month through 6 months after birth, as indicated by overall and incremental cases each month (Fig. 1C and D). Although the cumulative efficacy against RSV-associated lower respiratory tract illness, severe RSV-associated lower respiratory tract illness, and RSV-associated hospitalization was maintained through 6 months, accrued case counts beyond 6 months were similar in both groups (Appendix 7, available online at http://links.lww.com/AOG/D942).

Sensitivity analyses of overall RSV-associated medically attended lower respiratory tract illness efficacy through 180 days were not affected by palivizumab receipt, which occurred in 13 infants (2 RSVpreF, 11 placebo), none of whom had RSV-associated medically attended lower respiratory tract illness. Ten children (4 RSVpreF, 6 placebo) were born prematurely (before 37 weeks of gestation) and had RSV-associated medically attended lower respiratory tract illness within 180 days. Overall, 65.7% of children were breastfed for 6 months or more and 14.0% were breastfed exclusively. No efficacy differences by breastfeeding duration were observed (Appendix 8, available online at http://links.lww.com/AOG/D942).

Consistent with the primary analysis, final vaccine efficacy for RSV-associated hospitalization was 69.7% (95% CI, 37.1–86.7) and 55.3% (95% CI, 23.8–74.6) within 90 and 180 days after birth, respectively (Appendix 9, available online at http://links.lww.com/AOG/D942). In exploratory analyses, vaccine efficacy (95% CI) against Endpoint Adjudication Committee–confirmed RSV-associated medically attended respiratory tract illness was 41.7% (95% CI, 21.8–56.9) and 37.9% (95% CI, 25.2–48.5) within 90 and 180 days after birth. Vaccine efficacy against RSV-associated medically attended lower respiratory tract illness with oxygen saturation less than 90% or supplemental oxygen of any type was 76.5% (95% CI,

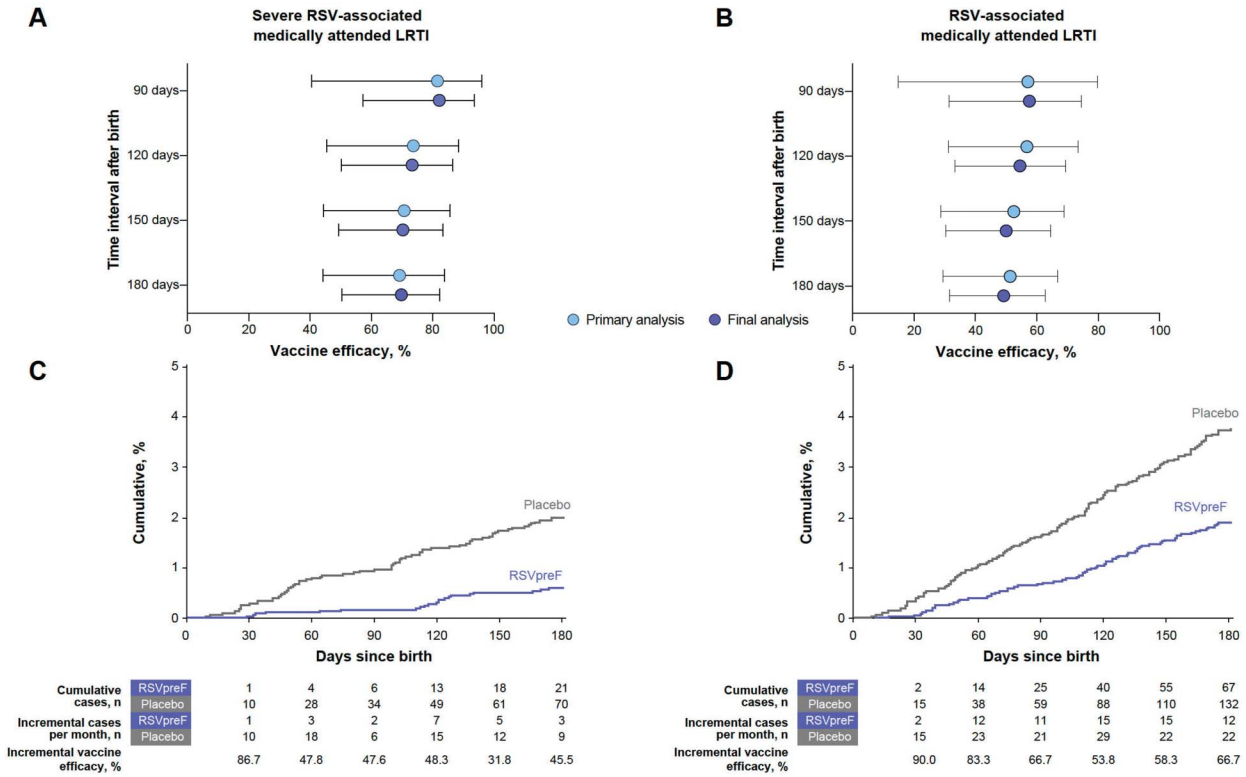

Fig. 1. Vaccine efficacy in newborns and infants. Vaccine efficacy for severe respiratory syncytial virus (RSV)–associated medically attended lower respiratory tract illness (LRTI) (**A**) and for RSV-associated medically attended LRTI occurring within 180 days after birth in newborns and infants in the primary and final analyses (**B**). **C** and **D**. Cumulative case curves for severe RSV-associated medically attended LRTI and RSV-associated medically attended LRTI, respectively, for the final analysis. Data are for the evaluable efficacy population. RSV-associated LRTI cases of any severity were confirmed by the Endpoint Adjudication Committee. The criterion for vaccine efficacy with respect to the primary analysis was a lower boundary of the CI of more than 20%. *Error bars* for the primary analysis are 99.5% CIs for 90 days after birth and 97.58% CIs for later timepoints as described previously.[7] *Error bars* for the final analysis are 95% CIs. For the primary analysis, 3,495 newborns and infants were in the RSV prefusion F protein vaccine (RSVpreF) group and 3,480 were in the placebo group; corresponding numbers for the final analysis were 3,585 and 3,563. The associated data are provided in Appendix 6 (available online at http://links.lww.com/AOG/D942).

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27.9–94.2) and 48.0% (95% CI, −5.6 to 75.6) within 90 and 180 days after birth (Appendix 10, available online at http://links.lww.com/AOG/D942). No differences were seen in health care utilization parameters in newborns and infants with RSV-associated medically attended lower respiratory tract illness within 180 days of birth (Appendix 11, available online at http://links.lww.com/AOG/D942). Vaccine efficacy was 4.1% (95% CI, −9.5 to 16.0) against all-cause medically attended lower respiratory tract illness within 90 days, 31.0% (95% CI, 2.4–51.5) against all-cause medically attended lower respiratory tract illness requiring hospitalization at 180 days, and 23.3% (95% CI, 3.2–39.3) against all-cause severe medically attended lower respiratory tract illness at 180 days after birth.

Eight and 17 severe RSV-A–associated medically attended lower respiratory tract illness cases occurred in newborns and infants within 180 days of birth in the RSVpreF and placebo groups, respectively (vaccine efficacy 52.9%, 95% CI, −15.1 to 82.4), and 24 and 32 cases of RSV-A–associated medically attended lower respiratory tract illness (vaccine efficacy 25.0%, 95% CI, –31.4 to 57.7) (Appendix 12, available online at http://links.lww.com/AOG/D942). Corresponding values for RSV-B were 12 and 49 cases of severe medically attended lower respiratory tract illness (vaccine efficacy 75.5%, 95% CI, 53.3–88.1) and 43 and 96 cases of medically attended lower respiratory tract illness (vaccine efficacy 55.2%, 95% CI, 35.2–69.5). Sequencing analyses of the RSV F protein among RSV cases showed that more than 80% of RSV-B

cases in both the RSVpreF and placebo groups had mutations localized primarily to antigenic site Ø; no RSV-A site zero mutations were observed (Appendix 13A, available online at http://links.lww.com/AOG/D942). The most common sequence difference combinations in RSV-B site Ø were I206M/Q209R/S211N and I206M/Q209R (Appendix 13B, http://links.lww.com/AOG/D942). Sequence variability was generally similar between the RSVpreF and placebo groups, including in the four highest enrolling countries (United States, South Africa, Argentina, Japan); overall efficacy against severe RSV-associated medically attended lower respiratory tract illness in high-income countries and non–high-income countries was similar (Appendix 14, available online at http://links.lww.com/AOG/D942). Efficacy by maternal gestational age at vaccination is also shown in Appendix 14.

RSVpreF elicited robust immune responses in pregnant participants and robust neutralizing titers in their newborns compared with placebo (Fig. 2). Maternal combined RSV-A/RSV-B–neutralizing geometric mean fold rises were 7.7–16.5 in RSVpreF recipients across subgroups (gestational age at delivery, days from vaccination to delivery, country, maternal age at vaccination). In the RSVpreF group, RSV-A and RSV-B GMTs were similar at birth (pregnant people) and delivery (newborns) when analyzed by subgroup (Appendix 15, available online at http://links.lww.com/AOG/D942). Among newborns in the RSVpreF group, GMTs were lower in those born less than 14 days compared with those born 14–29 days or 30 or more days after maternal vaccination; combined RSV-A/RSV-B–neutralizing geometric mean ratios of the RSVpreF to the placebo group were lower in those born less than 14 days (4.1) compared with those born 14–29 days (10.2) or 30 or more days (12.2) after maternal vaccination (Fig. 3). Among pregnant participants in the RSVpreF group, RSV-neutralizing GMTs were 20,111 (95% CI, 17,234.8–23,466.4) in participants who delivered preterm (less than 37 weeks of gestation) and 16,915 (95% CI, 16,029.6–17,850.3) in participants delivering at term; geometric mean fold rises in these two groups were 11.2–12.5. Among newborns in the RSVpreF group, combined RSV-A/-B–neutralizing GMTs were 17,201 (95% CI, 14,842.8–19,935.0) in those born preterm and 22,048 (95% CI, 20,921.6–23,236.1) in those born at term. In the RSVpreF group, maternal and newborn combined RSV-A/RSV-B–neutralizing GMTs and geometric mean fold rises (maternal) were generally similar across the five countries analyzed and by maternal age.

In the majority of newborn subgroups, combined RSV-A/RSV-B–neutralizing titer parent-to-newborn placental transfer ratios in the RSVpreF group were more than 1 or approached 1, except for those born less than 14 days (0.32) or 14–29 days (0.67) after maternal vaccination (Fig. 4). Overall, a strong correlation (0.89–0.90) was observed between parent–newborn paired neutralizing titers for RSV-A and RSV-B for the RSVpreF and placebo groups (Appendix 16, available online at http://links.lww.com/AOG/D942).

Reactogenicity events occurring in pregnant participants and safety to data cutoff (September 2, 2022) were reported previously.[7] Reported here are final reactogenicity (Appendix 17, available online at http://links.lww.com/AOG/D942) and safety analysis results, which are consistent with primary analyses. Percentages of pregnant participants with any adverse events reported within 1 month after vaccination were similar in the RSVpreF (14.0%, 95% CI, 12.9–15.1) and placebo (13.2%, 95% CI, 12.2–14.4) groups; most were mild to moderate (Appendix 18, available online at http://links.lww.com/AOG/D942). No adverse events led to study withdrawal among pregnant RSVpreF recipients (one adverse event led to withdrawal [premature delivery] in a placebo recipient).

Adverse events considered related to study intervention by the investigator were infrequent (RSVpreF 0.4%, placebo 0.1%); all but two occurred before delivery (Appendix 19, available online at http://links.lww.com/AOG/D942). Three serious adverse events considered vaccine related were reported in RSVpreF recipients (severe extremity pain, premature labor, eclampsia), and one was reported in the placebo group (moderate premature placenta separation); all resolved.

Nineteen stillbirths were reported in pregnant participants (RSVpreF n=10, placebo n=9) (Appendix 20, available online at http://links.lww.com/AOG/D942). No maternal deaths or stillbirths were assessed as related to study vaccination. No additional maternal deaths or spontaneous abortions in subsequent pregnancies were reported after primary analysis.

Percentages of newborn participants with any adverse events reported within 1 month after birth were similar in the RSVpreF (38.0%, 95% CI, 36.4–39.6) and placebo (35.4%, 95% CI, 33.9–37.0) groups; most were mild to moderate (Appendix 18, http://links.lww.com/AOG/D942). No adverse events led to study withdrawal among children in the RSVpreF group.

Special-interest adverse events in children occurred at similar frequencies among those whose parent received RSVpreF and those who received placebo, including low birth weight (RSVpreF 5.1%,

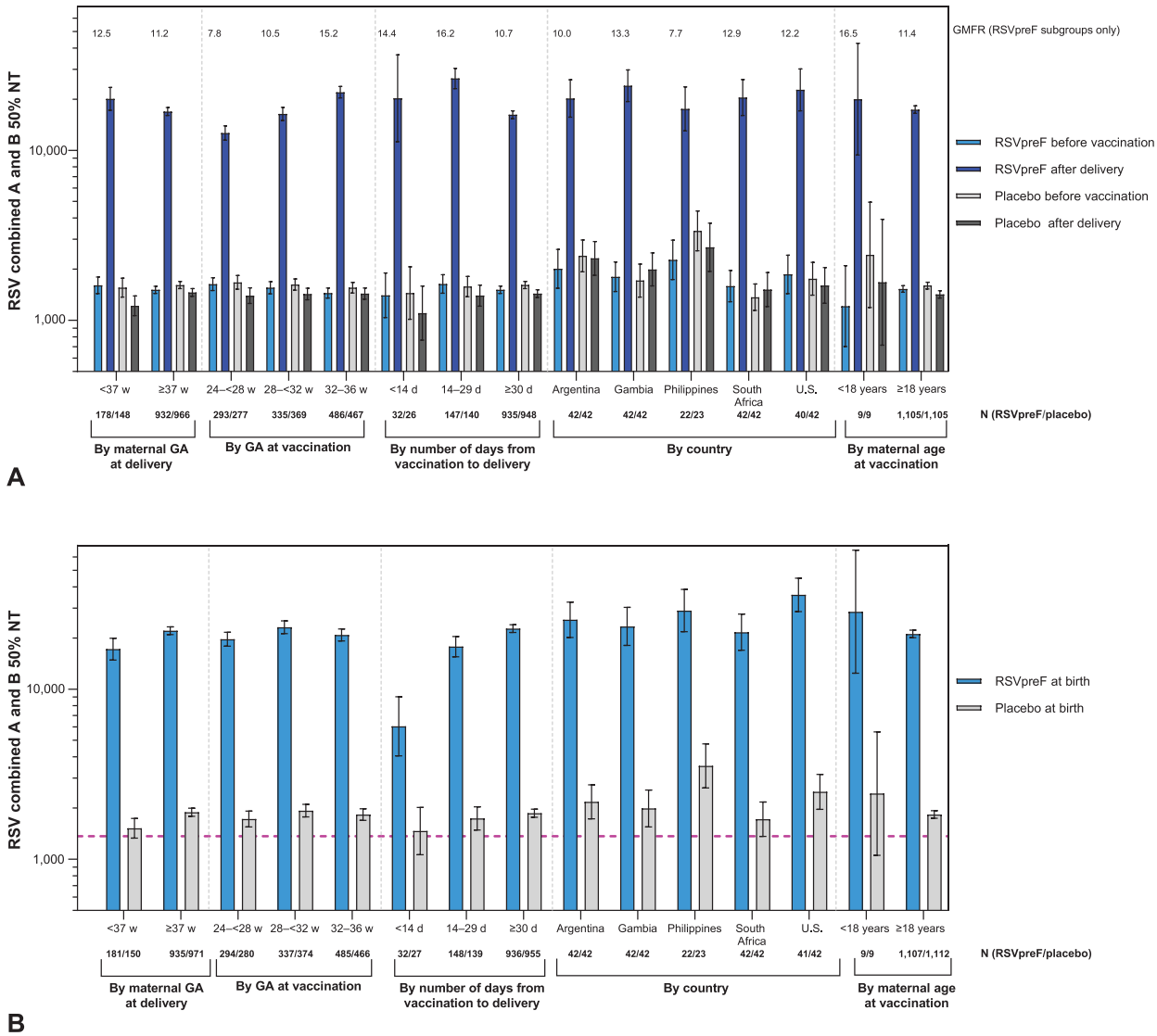

Fig. 2. Parental (**A**) and newborn (**B**) combined respiratory syncytial virus (RSV)-A/RSV-B geometric mean titers by subgroup. Geometric mean titers after delivery (**A**) or birth (**B**) and corresponding two-sided Student *t* distribution CIs and geometric mean fold rises from before vaccination to delivery (**A**. RSV prefusion F protein vaccine [RSVpreF] only) were calculated by exponentiating the mean logarithm of the titers or fold rises, respectively. Assay results below the lower limit of quantitation were set to 0.5 times the lower limit of quantitation. In both panels, *error bars* represent 95% CIs. *Horizontal dashed purple line* in **B** refers to the 50% RSV-neutralizing titers of a serum palivizumab concentration of 100 mg/mL providing 97.5% or higher protection from pediatric intensive care unit admission for newborns and infants at high risk for severe RSV disease attributed to RSV-A/RSV-B. GA, gestational age (weeks); NT, neutralizing titer.

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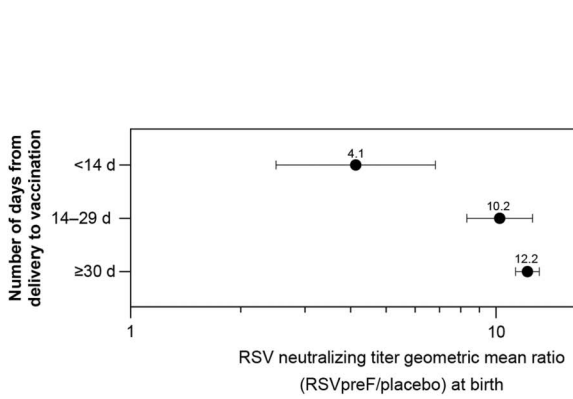
placebo 4.3%), premature birth (5.7%, 4.7%), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test positive (3.3%, 3.0%), and developmental delay (0.1%, less than 0.1%) (Fig. 5A). Newly diagnosed chronic medical conditions were reported at similar frequencies in pediatric participants in the RSVpreF (3.9%) and placebo (4.5%) groups (Fig. 5B); none led to withdrawal. Diagnoses of asthma-like respiratory symptoms reported during medically attended lower respiratory tract illness visits or as adverse events occurred at similar frequencies for the RSVpreF (6.8%) and placebo (6.3%) groups (Appendix 21, available online at http://links.lww.com/AOG/D942).

The most common serious adverse events in newborn and infant participants reported up to age 24 months were neonatal jaundice, neonatal



	RSVpreF		Placebo	
	N	GMT (95% CI)	N	GMT (95% CI)
<14 d	32	6,047 (4,050.2, 9,028.2)	27	1,465 (1,062.4, 2,019.1)
14–29 d	148	17,788 (15,509.9, 20,399.6)	139	1,738 (1,487.4, 2,031.3)
≥30 d	936	22,724 (21,573.7, 23,935.6)	955	1,864 (1,764.9, 1,968.7)

Fig. 3. Newborn combined respiratory syncytial virus (RSV)-A/RSV-B–neutralizing titer geometric mean ratios (GMRs) and geometric mean titers (GMTs) by subgroup. The GMTs and GMRs and the corresponding two-sided Student *t* distribution CIs were calculated by exponentiating the mean logarithm of the titers or the mean differences in the logarithms of the titers (RSV prefusion F protein vaccine [RSVpreF] group – placebo group), respectively. Assay results below the lower limit of quantitation were set to 0.5 times the lower limit of quantitation.

Simões. MATISSE Maternal Vaccination Final Analysis. Obstet Gynecol 2025.

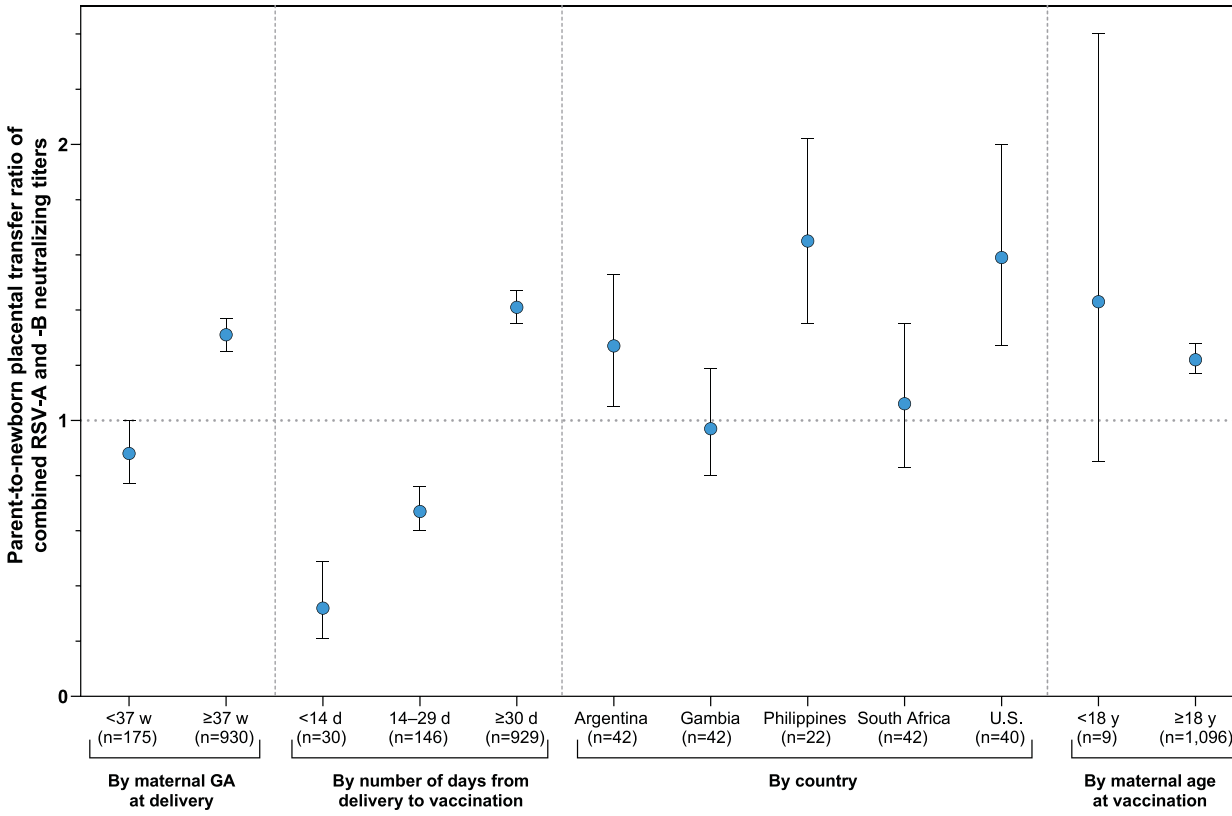


Fig. 4. Parent-to-newborn placental transfer ratio of combined respiratory syncytial virus (RSV)-A/RSV-B–neutralizing titers by subgroup: RSV prefusion F protein vaccine (RSVpreF) group. For each parent–newborn dyad, the transfer ratio was calculated as the ratio of the newborn's RSV-neutralizing titer to the pregnant individual's with back-transformed Student *t* distribution CIs. *Error bars* are 95% CIs. Assay results below the lower limit of quantitation were set to 0.5 times the lower limit of quantitation. GA, gestational age (weeks).

Simões. MATISSE Maternal Vaccination Final Analysis. Obstet Gynecol 2025.

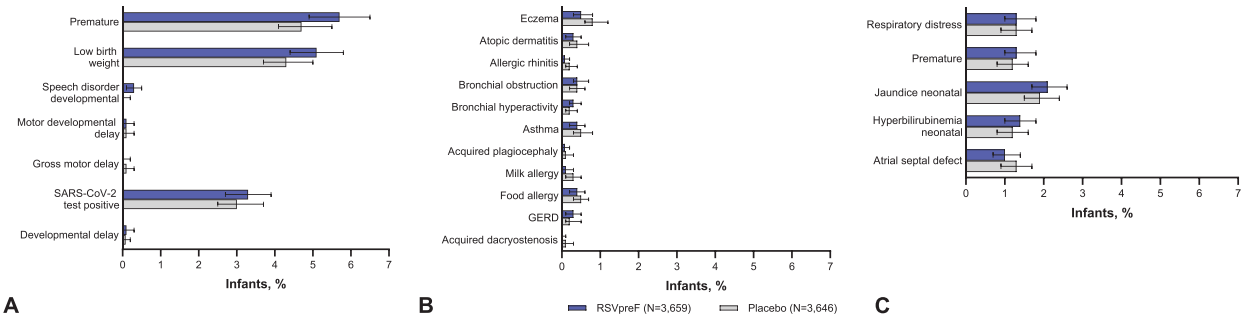


Fig. 5. Safety in children from birth to age 24 months. **A** and **B**. Adverse events of special-interest and newly diagnosed chronic medical conditions, respectively, occurring in 0.1% or more of pediatric participants in either study group. **C**. Serious adverse events occurring in 1% or more of pediatric participants in either study group. *Error bars* are two-sided 95% CIs. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; GERD, gastroesophageal reflux disease; RSVpreF, respiratory syncytial virus prefusion F protein vaccine.

Simões. MATISSE Maternal Vaccination Final Analysis. Obstet Gynecol 2025.

hyperbilirubinemia, premature birth, and respiratory distress, which occurred at similar rates in the RSVpreF and placebo groups (Fig. 5C). No serious adverse events in newborns and infants were considered related to maternal vaccination. Congenital abnormalities occurred at similar frequencies in both groups (RSVpreF 5.6%, placebo 6.7%).

Twenty-two deaths were reported from birth to 24 months (RSVpreF n=8, placebo n=14) (Appendix 22, available online at http://links.lww.com/AOG/D942). One death in a 120-day-old full-term infant in the placebo group was later classified by the Endpoint Adjudication Committee as caused by RSV-associated acute respiratory illness.

DISCUSSION

In this final analysis of the global phase 3 MATISSE study, consistent with the primary analysis, maternal vaccination with RSVpreF was efficacious in preventing RSV-associated lower respiratory tract illness in infants through 180 days after birth and appeared safe in pregnant individuals and newborns and infants.[7] Protection was evident from birth as shown by cases prevented in the first month of life. Maternal RSVpreF vaccination also elicited robust immune responses in pregnant participants, and newborns achieved correspondingly high RSV-neutralizing titers.

Consistent with the primary analysis,[7] RSVpreF did not prevent all-cause lower respiratory tract illness; it is important to note that this study was conducted during the coronavirus disease 2019 (COVID-19) pandemic, during which reductions in all-cause lower respiratory tract illness and all-cause lower respiratory tract illness hospitalizations and RSV-associated lower respiratory tract illnesses relative to other etiologies occurred.[11]

Whole-viral-genome sequencing was performed given the previous observation of RSV F protein mutations in monoclonal antibody studies.[12,13] Overall, the number of F protein sequence differences was higher in RSV-B cases compared with RSV-A cases, including in antigenic site Ø (a major neutralizing antibody target of RSV F protein[14]), which is consistent with general findings across RSV genomic surveillance studies.[15] F sequence differences in antigenic site Ø were not detected in any RSV-A cases. I206M/Q209R/S211N was the most common combination of sequence differences occurring in site Ø followed by I206M/Q209R. These sequence differences localize to the nirsevimab binding site (amino acids 62–69 and 196–212)[16]; nirsevimab is an antigenic site Ø prefusion-specific monoclonal antibody. Differences at each of these positions have previously been reported in RSV-B clinical isolates[17]; S211N has been shown to result in a modest reduction in nirsevimab in vitro neutralization potency.[18] LS172QL, found in antigenic site V,[19] was another common sequence difference in RSV-B cases in this study and is in the binding site of the RSV prefusion-specific monoclonal antibody suptavumab.[12] In a phase 3 clinical trial, suptavumab did not reduce overall RSV hospitalizations or outpatient lower respiratory tract illness because all RSV-B isolates contain the LS172QL amino acid change, which led to subgroup-specific loss of monoclonal antibody binding and neutralization activity.[12] The high frequency of RSV-B cases with which these sequence differences occurred is therefore consistent with previous studies and suggests that these are stably found in circulating RSV-B strains. It is important to note that the case sequencing data presented here suggest no differences between the relative case numbers containing the LS172QL or S211N sequence

differences in the RSVpreF compared with placebo group and highlight potential of maternal bivalent RSVpreF vaccination, offering the possibility of a polyclonal immune response potentially less susceptible to immune escape observed with some monoclonal antibodies.

This study found that RSVpreF elicited robust immune responses in pregnant participants compared with placebo across all subgroups (days from vaccination to delivery, gestational age at delivery, country, maternal age at vaccination). Newborns achieved robust combined RSV-A/RSV-B–neutralizing titers in the majority of subgroups. GMTs in newborns in the RSVpreF group born 14–29 days or 30 or more days after vaccination were high (neutralizing titer geometric mean ratios compared with placebo 10.2 and 12.2, respectively), suggesting that 14 days or more after vaccination is sufficient time to allow transplacental transfer of antibodies to the newborns. As expected, neutralizing geometric mean ratios for those born less than 14 days after maternal vaccination were lower but were 4.1-fold above titers in those born of placebo participants. Combined RSV-A/RSV-B–neutralizing titer parent-to-newborn placental transfer ratios in the RSVpreF group were generally above 1 or approached 1, except for those in newborns born less than 14 days or 14–29 days after maternal vaccination (0.32 and 0.67, respectively). Newborn titers in all RSVpreF subgroups were substantially higher compared with placebo.

Final RSVpreF safety and tolerability results in pregnant participants were consistent with the primary analysis.[7] Adverse event and serious adverse event rates and profiles were similar to those in the primary analyses and in the maternal RSVpreF and placebo groups.[7] No new safety concerns were detected in children after maternal RSVpreF vaccination, with adverse events reported being generally common occurrences during the neonatal period and throughout the first 12–24 months of life. Adverse event, serious adverse event, newly diagnosed chronic medical condition, and special-interest adverse event rates were generally similar between the RSVpreF and placebo groups. Preterm birth rates (RSVpreF 5.7%, placebo 4.7%) have been described further separately.[20]

Study limitations include the exclusion of individuals with high-risk pregnancies and limited data outside of high-income countries where RSVpreF may have the greatest effects on newborn or infant mortality.[7] In addition, exploratory immunogenicity analyses were conducted in pregnant and newborn participant subsets from the evaluable immunogenicity population who were compared with a control group based on maternal characteristics (ie, not randomized comparisons) and were therefore descriptive in nature.

In summary, this final analysis of MATISSE trial data confirms the conclusions of the primary analysis: maternal vaccination with RSVpreF has a favorable safety profile in both pregnant and newborn and infant participants and demonstrates efficacy against RSV-associated lower respiratory tract illness in newborns and infants through age 6 months. In addition, RSVpreF induces robust immune responses in pregnant individuals and associated high RSV-neutralizing titers in their newborns.

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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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