

Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

Supplementary appendix

Supplement to: Dieussaert et al. RSV prefusion F maternal vaccine trial: preterm birth and other outcomes

Table of Contents

Author contributions	6
Supplementary methods	7
Randomization and blinding	7
Vaccines	7
Inclusion criteria	7
Exclusion criteria	10
Ethical considerations	16
Urgent safety measures	17
Gestational age assessment	18
Surveillance for respiratory tract illness	19
Case definitions of LRTD	20
Safety assessments	21
Laboratory assays.....	23
Statistical analyses	26
Supplementary results	28
Timeline of identification of safety signal and resulting actions	28
Additional information on preterm-born infants.....	28
Evaluation of neonatal death imbalance	30
COVID-19-related findings	31
Manufacturing, quality, and physical measurements of RSVPreF3-Mat	35
Other factors.....	36
Effect of fetal sex on preterm birth imbalance.....	36
Multivariable analysis.....	37
Supplementary tables	38

Table S1. List of pre-specified primary and secondary efficacy and safety objectives and endpoints	38
Table S2. Characteristics of maternal participants at baseline (exposed set) and infant participants at birth (infant cohort) in low- and middle-income and in high-income countries	44
Table S3. Representativeness of the trial population.....	50
Table S4. Pregnancy outcomes through 6 weeks post-delivery (exposed set)	52
Table S5. Serious adverse events ^a in maternal participants from RSVPreF3-Mat or placebo administration through 6 months post-delivery (exposed set)	53
Table S6. Serious adverse events ^a in infant participants from birth through 6 months of age (infant cohort)	58
Table S7. Preterm birth rates, overall and by different subgroups (infant cohort)	62
Table S8. Preterm birth rates in the RSV MAT-009 trial compared with background rates, by country	76
Table S9. Summary statistics for time between RSVPreF3-Mat or placebo administration and delivery among all infants (infant cohort) and preterm infants (infant cohort, preterm subgroup)	78
Table S10. Neonatal deaths (infant cohort)	79
Table S11. Summary of the seven neonatal deaths among preterm infants in the RSVPreF3-Mat group	80
Table S12. Stillbirths and infant deaths (exposed set or infant cohort)	81
Table S13. Monthly (non-cumulative) preterm birth rate throughout the trial (infant cohort)	82
Table S14. Preterm birth rate by vaccine lot used in the trial	83

Table S15. Seroconversion rates for SARS-CoV-2 N protein-binding antibodies in maternal participants (investigation cohort)	84
Table S16. Preterm birth rates with or without COVID-19 vaccine administered during pregnancy (infant cohort).....	86
Table S17. Preterm birth rates with or without suspected, probable, or confirmed COVID-19 case during pregnancy (infant cohort)	88
Table S18. Most common vaccines administered to maternal participants during the second and third trimester (infant cohort).....	90
Table S19. Preterm birth rates with or without additional vaccines administered during the second or third trimester of pregnancy (infant cohort)	92
Table S20. Percent reduction in preterm birth rates with versus without additional vaccines administered during the second or third trimester of pregnancy (infant cohort)	94
Table S21. Preterm birth rates by the number of active vaccine doses administered during pregnancy (infant cohort).....	95
Table S22. Summary statistics for time between any last vaccination during pregnancy (RSVPreF3-Mat, placebo, or other vaccines) and delivery among all infants (infant cohort) and preterm infants (infant cohort, preterm subgroup)	97
Table S23. RSV-A neutralizing titers and RSVPreF3-binding IgG concentrations in maternal participants and in infant cord blood (investigation cohort)	98
Table S24. Western blot profiles for RSV vaccination and RSV infection in maternal participants (investigation cohort, preterm group).....	100
Table S25. Multivariable analysis to identify possible risk factors of preterm birth.....	101
Supplementary figures.....	103
Figure S1. Maternal (A) and infant (B) participant flow diagram	103

Figure S2. Time between RSVPreF3-Mat or placebo administration and delivery among all infants (infant cohort) and preterm infants (infant cohort, preterm subgroup).....	105
Figure S3. Monthly preterm birth rates relative to monthly reported COVID-19 cases in the trial (infant cohort).....	106
Figure S4. Time between any vaccination during pregnancy and delivery among all infants (infant cohort) and preterm infants (infant cohort, preterm subgroup).....	107
Figure S5. Monthly preterm birth rates relative to monthly numbers of participants receiving additional vaccines during the second or third trimester of pregnancy (infant cohort).....	108
Figure S6. Annexin A5-binding IgG concentrations at Day 31 post-vaccination versus pre-vaccination (investigation cohort).....	110
Figure S7. Cytokine levels before and 1 month after RSVPreF3-Mat or placebo administration (investigation cohort).....	112
References	114

Author contributions

ID, JHK, CS, WP, GKS, PW, and PRD were involved in the conception and/or design of the study/investigation. PW contributed to the acquisition or generation of data. ID, JHK, SL, CS, WP, J-US, GKS, PW, and PRD were involved in the analysis and/or interpretation of the data.

Supplementary methods

Randomization and blinding

Randomization was done using an automated internet-based system. The randomization algorithm used a minimization procedure accounting for maternal age at the time of the trial intervention (18–34, 35–39, ≥ 40 years of age), gestational age at the time of the trial intervention ($24^{0/7}$ – $28^{0/7}$, $28^{1/7}$ – $34^{0/7}$), and center. Minimization factors had equal weight in the minimization algorithm.

The trial was set up and started with a double-blinded design, in which participants, investigators and their staff, and the laboratory in charge of sample testing were blinded to the assigned trial intervention throughout the trial. However, following the decision to stop enrollment and vaccination, the trial/site staff and participants were unblinded.

Vaccines

The investigational maternal respiratory syncytial virus (RSV) prefusion F protein-based vaccine (RSVPreF3-Mat) contained 120 μg RSVPreF3 antigen reconstituted in NaCl solution. Placebo contained sucrose reconstituted in NaCl solution. Both were injected in the deltoid muscle, preferably of the non-dominant arm.

Inclusion criteria

Maternal participants

Maternal participants had to satisfy all the following criteria at trial entry:

- Participants who, in the opinion of the investigator, could and would comply with the requirements of the protocol (e.g., completion of diaries, return for follow-up visits).
- Participants who gave written or witnessed/thumb printed informed consent after the trial had been explained according to local regulatory requirements, and before any

trial-specific procedures were performed. The informed consent given at screening had to (consistent with local regulations/guidelines) either:

- include consent for both the maternal participant's participation and the participation of the infant after the infant's birth, or
 - include consent for the maternal participant's participation and expressed willingness to consider permitting the infant to take part after the infant's birth (if local regulations/guidelines required parent(s) to provide an additional informed consent after the infant's birth).
 - Both mother and father had to consent if required by local regulations/guidelines.
- Age 18 to 49 years, inclusive, at the time of trial intervention.
- Pre-pregnancy body mass index (based on participant's report) 17.0 to 39.9 kg/m², inclusive.
- In good general maternal health as established by medical history and clinical examination before entering the trial.
- Singleton pregnancy (including instances where the singleton pregnancy derived from a vanishing twin syndrome).
- At 24^{0/7} to 34^{0/7} weeks of gestation at the time of trial vaccination (visit 1), as established by:
 - Last menstrual period (LMP) date corroborated by first- or second-trimester ultrasound examination, i.e., at or before 28 weeks of gestation.
 - First- or second-trimester ultrasound only, if LMP was unknown/uncertain.
 - Certain LMP, corroborated by an ultrasound performed after 28 weeks of gestation was also acceptable.

- If the pregnancy resulted from assisted reproductive technologies, the LMP date could be replaced by the intrauterine insemination (IUI) or embryo-transfer (ET) date.
 - If the LMP (or IUI or ET) and ultrasound performed before 28 weeks of gestation did not correlate, one had to default to ultrasound gestational age assessment.
 - If the first ultrasound was only performed after 28 weeks of gestation (i.e., third trimester) and there was no other basis for estimating gestational age, or if the only other basis was fundal height, then the gestational age calculation was uncertain, and the woman had to be excluded.
 - The level of diagnostic certainty of the gestational age had to be established by using the Global Alignment of Immunization safety Assessment in pregnancy (GAIA) gestation age assessment tool.
- No fetal genetic abnormalities (based on genetic testing, if performed).
 - No significant congenital malformations (such as abnormal fetal morphology, abnormal amniotic fluid levels, significant abnormalities in placenta or umbilical cord), as assessed by fetal anomaly ultrasound scan (also known as a level 2 ultrasound or fetal morphology assessment) conducted at or beyond 18 weeks of gestation.
 - Willing to provide cord blood.
 - Did not plan to give their child for adoption.
 - Planned to reside in the trial area for at least 1 year after delivery.
 - Willing to have the infant followed up after delivery for 12 months.

- Note: Women whose pregnancies resulted from assisted reproductive technologies could be enrolled if they met all inclusion criteria and none of the exclusion criteria.

Infant participants

Infant participants had to satisfy all the following criteria at trial entry:

- Live-born from the trial pregnancy.
- If required per local regulations/guidelines, re-signed (confirmed) written or witnessed/thumb printed informed consent for trial participation of the infant obtained from the infant's mother and/or father and/or legally acceptable representative (LAR), before performing any trial-specific procedure. To comply with respiratory tract infection surveillance and other protocol-required procedures that began immediately after birth: if written consent could not be provided by the parent(s)/LAR(s) readily post-birth, verbal consent—if permitted per local regulation—could be sought from the parent(s)/LAR(s) instead. Verbal consent had to be documented in the source data by the investigator or delegate. The parent(s)/LAR(s) provided additional, written informed consent by (or before) visit 2-newborn.

Exclusion criteria

The potential participant could not be included in the trial if any exclusion criterion applied.

Maternal participants

- History of allergic disease or reactions likely to be exacerbated by any component of the RSVPreF3-Mat vaccine.
- Hypersensitivity to latex.
- Significant (as per investigator's judgement) complications in the current pregnancy such as:

- Gestational hypertension (defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) at ≥ 20 weeks of gestation in the absence of proteinuria in a woman with a previously normal blood pressure. Women with gestational hypertension who maintained a blood pressure in the normal range (< 140 mmHg and < 90 mmHg) through diet and/or on antihypertensive medications were eligible.
- Gestational diabetes that was not controlled by medication, diet, and/or exercise (gestational diabetes was defined as absence of pre-gestational diabetes, and hyperglycemia during pregnancy that was not due to other known causes, confirmed based on positive oral glucose tolerance test or based on fasting plasma glucose levels in venous or capillary blood samples).
- Pre-eclampsia (defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure of ≥ 90 mmHg on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure and proteinuria or, in the absence of proteinuria, the new onset of thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or headache unresponsive to medication).
- Eclampsia (defined as occurrence of new-onset seizures in the absence of other causative conditions, in a woman with a hypertensive disorder of pregnancy).
- Intrauterine growth restriction/fetal growth restriction defined as a fetus with a sonographic estimation of fetal weight below the tenth percentile for a given gestational age with increasing specificity for adverse perinatal outcome below the third percentile.
- Placenta previa (unless there was documented sonographic evidence that the placenta had moved up before enrollment).

- Placental abruption, placenta accreta/percreta/increta, chorioamnionitis, or any abnormalities that in the opinion of the investigator could impair the maternal-fetal circulation.
- Polyhydramnios (defined as either a deepest vertical pocket of >8 cm or an amniotic fluid index >95th percentile for the corresponding gestational age).
- Oligohydramnios (defined as an amniotic fluid index <8 cm or a deepest vertical pocket <2 cm in the presence of intact membranes without concern for fetal anomalies contributing to its etiology).
- Preterm labor or history of preterm labor in the current pregnancy.
- Any intervention to prevent preterm delivery or medical treatment for suspected preterm delivery, including administration of systemic corticosteroids for fetal lung maturation.
 - Pregnant women under progesterone treatment beyond the first trimester of pregnancy, exclusively based on a prior pregnancy that resulted in preterm delivery/birth, but without any medical/clinical finding(s) that would lead to a suspicion that there was a risk of preterm delivery in the current pregnancy (e.g., shortened cervical length), were not considered as meeting this exclusion criterion.
- Cholestasis (defined as unexplained pruritus and/or abnormal liver function tests and/or raised bile acids, based on the investigator's clinical judgement).
- Other pregnancy-related complications that in the investigator's judgement would preclude participation in an investigational vaccine trial or might pose risk to the participant due to participation in the trial.
- Significant (as per investigator's judgement) structural abnormalities of the uterus or cervix.

- History of two or more prior stillbirths or neonatal deaths, or history of multiple (two or more) preterm births at ≤ 34 weeks' gestation, or multiple (three or more) consecutive spontaneous abortions.
 - Stillbirths, preterm births, and spontaneous abortions were counted per pregnancy (i.e., regardless of the number of fetuses in the concerned pregnancy).
- Known human immunodeficiency virus infection, as assessed by local standard-of-care serologic tests conducted during the current pregnancy and prior to enrollment.
- Known or suspected hepatitis B virus or hepatitis C virus infection, based on medical history and clinical presentation (no laboratory testing was required).
- Known or suspected infection during the current pregnancy with toxoplasma, parvovirus B19, syphilis, zika, rubella, varicella, cytomegalovirus, or primary genital herpes simplex, based on medical history and clinical presentation (no laboratory testing was required).
- Active infection with tuberculosis, based on medical history and clinical presentation (no laboratory testing was required).
- Known or suspected impairment of the immune system.
- Current autoimmune disorder (based on medical history and physical examination; no laboratory testing was required), for which the participant had received immune-modifying therapy within 6 months before trial vaccination or planned administration through delivery.
- Lymphoproliferative disorder or malignancy within 5 years before trial vaccination (excluding effectively treated non-melanoma skin cancer).
- Acute or chronic clinically significant abnormality or poorly controlled pre-existing comorbidities or any other clinical conditions, as determined by physical examination

or standard-of-care laboratory tests that, in the opinion of the investigator, could pose additional risks to the participant due to participation in the trial.

- Any conditions that, in the investigator's judgement, could interfere with the participant's ability to comply with trial procedures or receipt of prenatal care, such as behavioral or cognitive impairment or neuropsychiatric illness.
- Any condition that, in the investigator's opinion, would increase the risks of trial participation to the unborn infant.
- Prior receipt of an RSV vaccine in the current pregnancy.
- Use of any investigational or non-registered product other than the trial vaccine/product as described below, or planned use during the trial:
 - For a drug, vaccine, or medical device: 29 days before the dose of trial vaccine/product (Day -28 to Day 1).
 - For immunoglobulins: 3 months before the dose of trial vaccine/product.
 - The exception to this was investigational products (drugs/vaccines/immunoglobulins) administered in the setting of a pandemic. Administration in this case had to respect the same period outlined above prior to vaccination but could be allowed following delivery.
- (Planned) administration of any vaccine within 29 days before trial vaccine/product administration (Day -28 to Day 1) or planned administration through delivery (visit 3), except:
 - Seasonal influenza vaccines, tetanus vaccines, reduced-antigen diphtheria-tetanus-acellular pertussis (dTpa/Tdap) vaccines, dTpa/Tdap vaccines also containing other antigens and hepatitis B vaccines, all of which could be

administered according to standard of care ≥ 15 days before or after trial vaccination.

- If public health authorities organized an emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) outside the routine immunization program, then the intervals described above could be reduced if necessary for that mass vaccination vaccine, provided the vaccine was licensed and used according to its product information. COVID-19 vaccines were thus allowed when administered ≥ 15 days before or after trial vaccination.
- Administration of immunoglobulins (except anti-Rh0(D) Ig, which could be administered at any time), blood products, or plasma derivatives within 3 months before trial vaccination or planned administration through delivery (visit 3).
- Administration of immune-modifying therapy within 6 months before the trial vaccination or planned administration through delivery. This included but was not limited to:
 - Azathioprine, mycophenolate mofetil, 6-mercaptopurine, cyclosporine, tacrolimus, monoclonal or polyclonal antibodies.
 - Prednisone ≥ 5 mg/day or equivalent for ≥ 14 days. Inhaled, intra-articular/intrabursal, and topical steroids were allowed.
 - Corticosteroids administered for fetal lung maturation.
- Concurrently participating in another clinical trial, at any time during the trial period, in which the participant had been or would be exposed to an investigational or a non-investigational vaccine/product (drug or medical device).
- Alcoholism or substance use disorder within the past 24 months based on the presence of two or more of the following abuse criteria: hazardous use, social/interpersonal problems related to use, neglect of major roles to use, withdrawal, tolerance, use of

larger amounts or over a longer period, repeated attempts to quit or control use, much time spent using, physical or psychological problems related to use, activities given up to use, craving (based on the DSM-5 criteria¹).

- A local condition that in the opinion of the investigator precluded injection of the trial vaccine/product or precluded assessment of local (administration site) reactogenicity.
- Consanguinity of maternal participant and her partner (second-degree cousins or closer).
- Any trial personnel or their immediate dependents, family, or household members.

Infant participants

- Concurrently participating in another clinical trial, at any time during the trial, in which the participant had been or would be exposed to an investigational or a non-investigational vaccine/product (drug or medical device).
- Any condition that, in the investigator's opinion, would increase the risks of trial participation to the infant.
- Child in care.

Ethical considerations

This trial is conducted in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, the Council for International Organizations of Medical Sciences ethical guidelines, and local laws and regulations. The protocol, its amendments, and other trial documents were approved by the trial sites' institutional review boards or independent ethics committees.

During routine database cleaning at the end of the RSV MAT-009 study, we found that, for two infant participants born to mothers in the RSVPreF3-Mat group, the mother listed on the birth certificate provided a valid signature on the informed consent form, but the father listed

on the birth certificate did not. One infant was in Panama and one Mexico, and one was born preterm. In Panama and Mexico, local law requires that both parents sign the informed consent form. Therefore, these two participants were excluded from the analyses.

Urgent safety measures

After the identification of the safety signal, GSK informed the investigators that the following urgent safety measures had to be initiated as soon as possible. Some of the measures were implemented to reduce the burden on the participants.

Pregnant participants

- In addition to the monthly contacts between visit 2 (Day 31) and the delivery visit (visit 3), additional visits and contacts (not pre-specified, any desired frequency) could be made between visit 2 and the delivery visit, as per the investigator's or the participant's discretion. These visits had to be documented using the unscheduled-visit mechanism defined in the protocol.
- A blood sample at delivery had to be collected from all maternal participants. Maternal blood samples collected at visit 1 (Day 1), visit 2 (Day 31), and visit 3 (delivery), as well as the cord blood sample collected at delivery, were used for the assessment of the immune response. These samples could also be tested to support safety assessments.
- A placenta sample had to be collected from all participants, whenever feasible. These samples could be tested to support possible safety assessments, if necessary. This procedure did not replace local standards of practice.
- Medically attended respiratory tract infection surveillance for the maternal participants was no longer performed. Nasal swabs were no longer collected and respiratory tract

illness (RTI) assessment visits were no longer performed. However, medically attended adverse events (AEs) related to an RTI were still reported.

Infants

- A safety contact for infants was recommended approximately 7 days post-birth.
- Blood samples were no longer collected from infants at visit 2-newborn (Day 43 post-birth), visit 3-newborn (Day 121 post-birth) or visit 4-newborn (Day 181 post-birth). Cord blood was still collected. If a cord blood sample could not be obtained, a blood sample from the newborn was still to be collected within 72 hours after delivery.
- In the event of a stillbirth or neonatal death, GSK encouraged an autopsy to be performed to learn more about the reason of death, if supported by the participant. GSK covered the cost related to this examination if not covered otherwise.

Gestational age assessment

Gestational age at birth was determined based on the estimated delivery date, as explained in the inclusion criteria (see Appendix, p. 8–9). The level of diagnostic certainty of gestational age was established by using the GAIA gestational age assessment tool, as explained below.²

- **Level 1** (highest level of certainty): certain LMP, IUI, or ET date with confirmatory first-trimester U/S ($\leq 13^{6/7}$ weeks); or first-trimester U/S ($\leq 13^{6/7}$ weeks)
- **Level 2A**: certain LMP with second-trimester U/S ($14^{0/7}$ to $27^{6/7}$ weeks); or certain LMP with first-trimester physical examination
- **Level 2B**: uncertain LMP with second-trimester U/S ($14^{0/7}$ to $27^{6/7}$ weeks)
- **Level 3A**: certain LMP with third-trimester U/S ($\geq 28^{0/7}$ weeks); or certain LMP with confirmatory second-trimester fundal height; or certain LMP with birth weight; or uncertain LMP with first-trimester physical examination

- **Level 3B** (lowest level of certainty): uncertain LMP with fundal height; or uncertain LMP with neonatal physical assessment (New Ballard score); or uncertain LMP with birth weight

Note, underlined criteria are those that were applicable for enrollment in the RSV MAT-009 trial. Women with a level 3B diagnostic certainty of gestational age were not eligible for enrollment.

Surveillance for respiratory tract illness

Active and passive surveillance for RTI symptoms (runny nose, blocked nose, cough, difficulty breathing, and wheezing) started at birth and ended at 12 months of age. As part of the active surveillance, the site staff contacted the parents/LARs weekly during the RSV season and monthly outside the RSV season in regions with seasonal RSV transmission, and every 2 weeks in regions with year-round transmission. During the COVID-19 pandemic, social distancing and confinement measures impacted RSV seasonality. Therefore, the frequency of the active contacts was adapted to match the altered seasonality in the different countries. Passive surveillance involved the infants' parents/LARs contacting the study site staff if the infants showed any RTI symptoms.

The site staff used information gathered during each active or passive surveillance contact to decide whether a visit to assess a potential lower respiratory tract disease (LRTD) had to be scheduled, i.e., if an infant had difficulty breathing, wheezing, or if its parent(s)/LAR(s) intended to seek medical care because of concerns about the infant's health related to the RTI. An LRTD assessment visit had to take place as soon as possible, ideally within 3 calendar days. During the assessment visit, the study staff clinically evaluated the infant and recorded all signs and symptoms, respiratory rate, blood oxygen saturation, and healthcare utilization. They also collected at least one nasal swab for each potential LRTD. Nasal swabs were used

for quantitative reverse transcriptase-polymerase chain reaction to detect the presence of RSV-A and/or RSV-B.

Case definitions of LRTD

A medically assessed LRTD implied that the infant was evaluated by a healthcare professional (e.g., physician, nurse) for the LRTD.

An RSV-LRTD was defined as:

- a history of cough or difficulty breathing (reported by parents/LARs; this included signs of wheezing or stridor, tachypnea, flaring of nostrils, chest in-drawing, and apnea)
- and oxygen saturation <95% or increased respiratory rate
- and confirmed RSV infection

A severe RSV-LRTD was defined as:

- meeting the case definition of RSV-LRTD
- and oxygen saturation <93% or lower chest wall in-drawing or inability to feed or failure to respond/being unconscious

RSV infection was confirmed if the nasal swab sample collected at the assessment visit tested positive for RSV-A or RSV-B by quantitative reverse transcriptase-polymerase chain reaction performed at the sponsor's laboratory.

For oxygen saturation, the lowest value monitored was used. At high altitudes (>2500 m), an oxygen saturation <92% was applicable for LRTD and <90% for severe LRTD.

An increased respiratory rate was defined as a respiratory rate >60/minute (<2 months of age), >50/minute (2–11 months of age), or >40/minute (12–24 months of age).

Safety assessments

Solicited and unsolicited AEs in maternal participants were collected for 7 and 30 days post-vaccination, respectively. Results for these outcomes will be reported separately. Serious AEs (SAEs) were collected from vaccination until 6 months post-delivery in maternal participants and are being collected until 1 year post-birth for infant participants. Pregnancy outcomes, pregnancy-related AEs of special interest (AESIs), and neonatal AESIs were collected from vaccination until Day 43 post-delivery/birth. Pregnancy outcomes and maternal and neonatal AESIs were based on GAIA definitions when applicable.³

Maternal and infant COVID-19 cases identified during the study (as per standard of care) were captured and reported using standard AE, medically attended AE, or SAE criteria. COVID-19 cases had to be reported in the eCRF according to the World Health Organization case definition, using one of the following terms: “Suspected COVID-19 infection”, “Probable COVID-19 infection”, “Confirmed COVID-19 infection”.

Pregnancy outcomes include:

- Live birth
 - Without congenital anomalies
 - With minor congenital anomalies only
 - With at least one major congenital anomaly
- Fetal death/stillbirth, defined as a fetal death occurring before birth and after 20 to 28 weeks of gestation (variation due to country-specific definitions), either antepartum (before evidence of labor) or intrapartum (during labor)⁴
 - Without congenital anomalies
 - With minor congenital anomalies only
 - With at least one major congenital anomaly

- Elective/therapeutic termination
 - Without congenital anomalies
 - With minor congenital anomalies only
 - With at least one major congenital anomaly

Pregnancy-related AESIs (newly occurring) include:

- Maternal death, defined a death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes⁵
- Hypertensive disorders of pregnancy, defined as described by Rouse et al.⁶
 - Gestational hypertension
 - Pre-eclampsia
 - Pre-eclampsia with severe features including eclampsia
- Fetal growth restriction, defined as a fetus with a sonographic estimation of fetal weight below the tenth percentile for a given gestational age, with increasing specificity for adverse perinatal outcomes below the third percentile⁷
- Pathways to preterm birth, with preterm being <37 gestation-completed weeks (<259 days), as defined by Harrison et al.⁸, including:
 - Premature preterm rupture of membranes
 - Preterm labor
 - Provider-initiated preterm birth
- Gestational diabetes mellitus, defined as a clinical syndrome characterized by the absence of pre-gestational diabetes diagnosis and identification of sustained hyperglycemia during pregnancy not due to other known causes⁹

- Chorioamnionitis, encompassing a broad spectrum of diseases during pregnancy, characterized by inflammation and/or infection of intrauterine structures (e.g., placenta, chorion, amnion), defined as described by Kachikis et al.¹⁰

Neonatal AESIs include:

- Small for gestational age, defined as a weight below the tenth percentile for gestational age as assessed against validated global, regional, or local standards¹¹
- Low birth weight (<2500 g) including very low (<1500 g) and extremely low (<1000 g) birth weight, regardless of gestational age¹²
- Congenital anomalies, i.e., major congenital anomalies, defined as events of prenatal origin that present at birth, potentially impacting an infant's health, development, and/or survival¹³, including:
 - Major external structural defects
 - Internal structural defects
 - Functional defects
- Neonatal death, defined as death of a live-born infant regardless of gestational age at birth, within the first 28 completed days of life¹⁴:
 - In an extremely preterm birth (22 weeks ≤ gestational age <28 weeks)
 - In a preterm live birth (28 weeks ≤ gestational age <37 weeks)
 - In a term live birth
- Preterm birth, defined as birth at <37 gestation-completed weeks (<259 days)²

Laboratory assays

RSV-A neutralizing titers and RSVPreF3-binding immunoglobulin G (IgG)

To investigate whether the humoral immune response elicited by RSVPreF3-Mat had an impact on preterm delivery, we compared RSV-A neutralizing titers and RSVPreF3-binding

IgG concentrations between cases (mothers and infants with preterm birth) and controls (matched mothers and infants with term birth) in the investigation cohort (see “Statistical analyses” section below) in the RSVPreF3-Mat group. The RSV-A neutralization assay and RSVPreF3-binding enzyme-linked immunosorbent assay (ELISA) were performed as previously described¹⁵ on serum samples collected from maternal participants pre-vaccination, Day 31 post-vaccination, and at delivery, and from infant cord blood.

Western blot for RSV infection

To investigate whether infection with RSV could have contributed to the imbalance in preterm births between the RSVPreF3-Mat and placebo groups, we compared western blot profiles between serum samples taken before vaccine or placebo administration and those taken at delivery (from the mother or cord blood). Only samples for the preterm group in the investigation cohort were analyzed (see “Statistical analyses” section below); samples from 241 participants were analyzed. Proteins from sucrose-purified RSV/Bernett were separated by polyacrylamide gel electrophoresis and transferred onto a nitrocellulose membrane, which was incubated with serum samples. Serum antibodies binding to surface (G protein, F1 protein) and internal (nucleoprotein [N], phosphoprotein [P], matrix protein [M]) RSV proteins were visualized by use of labeled anti-human IgG and a color reaction. Color development of bands with molecular weights of 76 kDa, 50 kDa, 42 kDa, 35 kDa, and 28 kDa corresponded to the proteins G, F1, N, P, and M, respectively. The apparent molecular weights of the G, F1, N, and P proteins were confirmed by use of monoclonal antibodies (Wyeth-Lederle Vaccines, Rochester, NY), and the 28 kDa protein was inferred as the M protein based on published data.^{16,17} A western blot “vaccine profile” was characterized by an increase in band intensity or appearance of new bands that corresponded to the F protein between the pre-vaccination and delivery samples, and no change in intensity of bands corresponding to G or internal RSV proteins. A western blot “infection profile” was

characterized by an increase in band intensity or appearance of new bands that corresponded to one or more internal RSV proteins, or to surface protein(s) and internal protein(s) between the pre-vaccination and delivery samples.

SARS-CoV-2 N-binding antibodies

To investigate whether infection with SARS-CoV-2 could have contributed to the imbalance in preterm births between the RSVPreF3-Mat and placebo groups, we compared seroconversion rates for SARS-CoV-2 N protein-binding antibodies between cases and controls in the investigation cohort (see “Statistical analyses” section below) in the RSVPreF3-Mat and placebo groups. Seroconversion was defined as seronegative for SARS-CoV-2 N protein-binding antibodies pre-vaccination and seropositive at Day 31 post-vaccination or at delivery. The N protein is present in SARS-CoV-2 but is not expressed by COVID-19 mRNA or adenovirus-vectored vaccines and is not present in recombinant subunit COVID-19 vaccines. COVID-19 testing was not part of the trial procedures. Therefore, mild COVID-19 cases or asymptomatic SARS-CoV-2 infections might have been missed, and reported COVID-19 rates may not have reflected the true exposure rates in the trial population. N-binding antibodies were therefore measured to allow detection of asymptomatic SARS-CoV-2 infections and mild COVID-19 cases. The *Elecsys* Anti-SARS-CoV-2 immunoassay (Roche) was used.¹⁸

Annexin A5-binding antibodies

The RSVPreF3 antigen is produced in Chinese hamster ovary cells (a routine expression system for recombinant proteins), and traces of host-cell proteins have been detected in the purified RSVPreF3 antigen used for clinical trials.¹⁹ We therefore analyzed whether low levels of one of the most abundant host-cell proteins (annexin A5) induced an immune

response and whether any detected response correlated with the increased risk of preterm birth observed after RSVPreF3-Mat vaccination in the trial.

Annexin A5-binding IgG was measured in samples taken pre-vaccination and on Day 31 post-vaccination from maternal participants in the investigation cohort (see “Statistical analyses” section below) using a commercial kit (DRG International, BioCheck, Inc.) for which minimum assay qualification was performed.

Inflammatory markers

To evaluate whether RSVPreF3-Mat vaccination induced an inflammatory response that was associated with preterm birth, we measured inflammatory markers (48 cytokines) in samples taken pre-vaccination and on Day 31 post-vaccination from maternal participants in the investigation cohort (see “Statistical analyses” section below). Participants with missing samples were excluded together with their matched samples to reduce bias; 218 matched pairs were considered in the analyses. Inflammatory markers were detected and quantified using the Olink Target 48 Cytokine kit.²⁰

Statistical analyses

Investigation cohort

The investigation cohort was set up using a matched (1:1) case-cohort design, in which cases were preterm births and controls were term births with the following matching variables:

- Maternal age at vaccination: <35 years versus ≥ 35 years
- Gestational age at vaccination: <28 weeks versus ≥ 28 weeks
- Smoking during pregnancy: yes versus no
- History of preterm delivery: yes versus no
- Economic region: low- and middle-income country (LMIC) versus high-income country (HIC)

To start investigating the safety signal immediately after its identification, the investigation cohort was set up before all infants were born. It included 618 participants, originally 309 with preterm delivery/birth and 309 with term delivery/birth. Upon data cleaning, 11 preterm participants were reclassified as term, resulting in a preterm group with 298 participants and a term group with 320 participants in the investigation cohort.

Univariate and multivariable analyses

Univariate analyses were conducted post-hoc to examine the association between risk factors and preterm birth via logistic regression. Unadjusted odds ratios and their 95% Wald confidence intervals were calculated to evaluate potential risk factors. A multivariable logistic regression analysis was performed to further assess the potential risk factors of preterm birth. The final multiple covariates model was developed through a combination of covariate selection methods and validated using resampling techniques.

Number needed to harm

The number needed to harm (analyzed post-hoc) indicates how many persons on average need to be exposed to a risk factor over a specific period to cause harm in an average of one person who would not otherwise have been harmed. It is defined as the inverse of the absolute risk increase and was calculated as: $1/(I_e - I_u)$, where I_e was the incidence of preterm birth in the RSVPreF3-Mat group and I_u the incidence of preterm birth in the placebo group. Newcombe confidence limits for absolute risk increase were used to calculate the confidence limits for number needed to harm estimates.²¹

Supplementary results

Timeline of identification of safety signal and resulting actions

The imbalance in preterm births in the RSV MAT-009 trial was initially noted by the Independent Data Monitoring Committee (IDMC) overseeing the trial during a pre-scheduled review of trial data and was discussed by the IDMC during a closed ad-hoc meeting on February 14, 2022. The IDMC notified GSK of the imbalance immediately after. Following verification of the imbalance in preterm births, GSK paused enrollment and vaccination in the RSV MAT-009 trial and all other ongoing trials in pregnant women. GSK subsequently stopped enrollment and vaccination in all RSVPreF3-Mat trials in pregnant women on February 25, 2022 and in all RSVPreF3-Mat trials in non-pregnant women on March 1, 2022. Trials in pregnant women were unblinded, so that participants could be informed and monitored closely to ensure the best possible care.

Additional information on preterm-born infants

Adjudication Committee evaluation

All preterm births were positively adjudicated by the Adjudication Committee, except one. For this infant, information on the LMP date was missing at the time of the review by the Adjudication Committee. This information became available later and, together with the infant's date of birth, confirmed that the infant was preterm.

Level of diagnostic certainty of gestational age

Of the 323 preterm births in our trial:

- 177 had level 1 certainty (RSVPreF3-Mat: 128; placebo: 49)
- 88 had level 2A certainty (RSVPreF3-Mat: 66; placebo: 22)
- 43 had level 2B certainty (RSVPreF3-Mat: 35; placebo: 8)

- 14 had level 3A certainty (RSVPreF3-Mat: 7; placebo: 7)
- 1 had level 3B certainty (with level 3B certainty, this maternal participant should not have been enrolled per eligibility criteria [see Appendix p. 9, p. 19], but ineligibility was only declared retrospectively) (RSVPreF3-Mat: 1)

See Appendix p. 18–19 for definitions of diagnostic certainty.

Birth weight

Of the 308 infants who were born at a gestational age of 32 to <37 weeks (RSVPreF3-Mat: 224; placebo: 84), 133 had a low birth weight (<2500 g; RSVPreF3-Mat: 98; placebo: 35).

Underlying cause of preterm birth

Of the total 323 preterm births, the precipitating cause was:

- preterm labor for 191 births (RSVPreF3-Mat: 136; placebo: 55)
- premature preterm rupture of membranes for 69 births (RSVPreF3-Mat: 52; placebo: 17)
- provider-initiated preterm birth for 63 births (RSVPreF3-Mat: 49; placebo: 14)

Among the provider-initiated preterm births, the most common reason was hypertensive disorders of pregnancy, with or without fetal growth restriction or other medical conditions (38 cases; RSVPreF3-Mat: 29; placebo: 9). Other reasons included fetal growth restriction not secondary to pre-eclampsia (n=2), chorioamnionitis (n=1), COVID-19 pneumonia (n=2), oligohydramnios (n=1), placental abruption/placenta previa (n=3), risk factors (n=4), non-reassuring fetal status/heart rate/fetal distress (n=4), and other reasons (n=8, e.g., elective C-section after incorrect calculation of gestational age when scheduling delivery).

Evaluation of neonatal death imbalance

The imbalance between the RSVPreF3-Mat and placebo groups in the rates of neonatal death was likely attributable to the imbalance in the rates of preterm birth and is not an independent safety signal. This conclusion was based on the following considerations:

- The relative risk of neonatal death in the full cohort of infants in the vaccine group versus the full cohort of infants in the placebo group (2.16, 95% CI 0.62–7.56) was not statistically significantly different from 1, meaning that the observed numerical imbalance between the RSVPreF3-Mat group and the placebo group may have occurred by chance alone (**Table S10**).
- No numerical imbalance in neonatal deaths was observed among infants born at term (**Table S10**).
- A numerical imbalance in neonatal deaths was only observed among preterm-born infants (**Table S10**).
- There were more preterm births in the vaccine group than in the placebo group. The risk of neonatal mortality is expected to increase with decreasing gestational age and is especially high in extremely (<28 weeks' gestation) and very (28–<32 weeks' gestation) preterm-born infants.^{22,23} In this trial, there were more extremely and very preterm-born infants in the RSVPreF3-Mat group than in the placebo group (**Table 4** – main manuscript).
- There were no neonatal deaths among preterm-born infants in the placebo group (**Table S10**). Based on background neonatal mortality rates, an incidence of 2.13% (95% CI, 0.44–6.09) would be expected in this group. The absence of any neonatal death observed in the placebo group may be due to the relatively small number of preterm births in this group overall (n=86) and may not accurately reflect the underlying risk of neonatal death in the placebo group.

- An in-depth qualitative review of the individual cases of neonatal death in preterm-born infants, which were all considered unrelated to vaccination by the investigators, concluded that the events most likely leading to neonatal death were in line with those expected in preterm-born infants, and that there was no consistent temporal pattern of events from birth or from vaccination (**Table S11**).
- No imbalance was observed in the occurrence of stillbirth, and no statistically significant imbalance was observed in the occurrence of infant death (birth to 365 days) in this trial at the time of the Day-43 post-birth analysis (**Table S12**). No neonatal death was observed in RSV MAT-004 (NCT04126213, phase 2 trial in pregnant women),¹⁵ and no imbalance was observed in RSV MAT-012 (NCT04980391, high-risk pregnancy trial in which one case in the vaccine group and one in the placebo group were recorded; unpublished data).

COVID-19-related findings

SARS-CoV-2 infection during pregnancy—particularly with the Delta variant—has been associated with an increased risk of preterm birth.^{24,25} Given the distinctive temporal pattern of the preterm birth imbalance observed in our trial (peaking from August to December 2021), we assessed whether it could be associated with COVID-19.

1. Temporal association of preterm birth imbalance with Delta variant circulation.

- Overall, the months when the imbalance in preterm births was observed did not match the months when most COVID-19 cases were reported in the trial, which was in the period when the Omicron variant was dominant. However, the peak in the preterm birth imbalance did show an overlap with the COVID-19 wave that occurred when the Delta variant was dominant (**Figure S3**). The numbers of preterm births for each country were too low overall to reveal any

clear and conclusive patterns in the timing of COVID-19 spread compared to the temporal distribution of preterm births at a country-specific level. For some countries, the period when the preterm birth imbalance was observed overlapped with a COVID-19 wave, but this was not the case for all countries.

2. The number of COVID-19 cases or SARS-CoV-2 infections during pregnancy among women who delivered preterm was too low for COVID-19 to drive the preterm birth imbalance between the RSVPreF3-Mat and placebo groups.

- Among all preterm births, only 15/237 (6.3%) in the RSVPreF3-Mat group and 5/86 (5.8%) in the placebo group were from women with a suspected, probable, or confirmed COVID-19 case during pregnancy.
- In the preterm subgroup of the matched case-control investigation cohort, only 17/222 (7.7%) women in the RSVPreF3-Mat group and 7/75 (9.3%) in the placebo group seroconverted for SARS-CoV-2 N protein-binding antibodies between trial vaccination and delivery.

3. The imbalance in preterm birth rates between the RSVPreF3-Mat and placebo groups was unlikely to be explained by an association with COVID-19 cases during pregnancy.

- Preterm birth rates in our trial tended to be higher among women who reported a suspected, probable, or confirmed COVID-19 case during pregnancy than among those who did not, but this was observed both among women in the vaccine group (8.43% with COVID-19 versus 6.69% without COVID-19) and women in the placebo group (6.02% versus 4.89%). As a result, the preterm birth imbalance between the vaccine and placebo groups was of a similar magnitude among women who reported a suspected, probable, or confirmed

COVID-19 case during pregnancy (RR: 1.40, 95% CI: 0.53–3.72) and among those who did not (RR: 1.37, 95% CI: 1.07–1.75) (**Table S17**).

- The Delta variant of SARS-CoV-2 has been associated with a greater incidence of preterm birth than other SARS-CoV-2 variants.^{24,25} We also found higher rates of preterm birth (regardless of RSVPreF3-Mat immunization status) among participants with versus without COVID-19 during pregnancy when Delta was the dominant SARS-CoV-2 variant (defined as July–December 2021 based on data from <https://ourworldindata.org/> for the five countries with highest enrollment in our trial). Preterm birth rates during the Delta wave in the RSVPreF3-Mat group were 13.11% among women with COVID-19 versus 8.22% without; in the placebo group, preterm birth rates with versus without COVID-19 were 9.52% versus 4.91%. Hence, the imbalance in preterm births associated with RSVPreF3-Mat immunization among those with COVID-19 was not magnified during the Delta wave (RR: 1.38, 95% CI: 0.32–5.98), and the RR point estimate was actually higher among those without COVID-19 (RR: 1.68, 95% CI: 1.20–2.34).
- The rates of suspected, probable, or confirmed COVID-19 cases reported among maternal participants during pregnancy were similar in the RSVPreF3-Mat group (178/3494 [5.1%]) and the placebo group (83/1739 [4.8%]).
- The rate of COVID-19 cases reported as medically attended AEs between vaccination and delivery tended to be higher in RSVPreF3-Mat than in placebo recipients (78/3494 [2.2%] versus 32/1739 [1.8%]; RR: 1.21). However, only a small number of women who delivered preterm reported COVID-19 as medically attended AE (8/237 in RSVPreF3-Mat and 1/86 in placebo).

- Therefore, different rates of COVID-19 cannot explain the observed imbalance in preterm births between the RSVPreF3-Mat and placebo groups during the trial.

4. The imbalance in preterm birth rates between the RSVPreF3-Mat and placebo groups was unlikely to be explained by an association with SARS-CoV-2 infection.

- Seroconversion rates for SARS-CoV-2 N protein-binding antibodies between trial vaccination and delivery were comparable between RSVPreF3-Mat and placebo recipients and between mothers of preterm-born infants and mothers of term-born infants (**Table S15**).
- Among women who delivered during the period when Delta was the dominant SARS-CoV-2 variant, seroconversion rates were not higher in RSVPreF3-Mat recipients who delivered preterm (8.39%) than in placebo recipients who delivered preterm (9.52%) or than in RSVPreF3-Mat recipients who delivered at term (10.00%) (**Table S15**). However, sample sizes in the different subgroups were too small to be able to draw sound conclusions.

5. The imbalance in preterm births between the RSVPreF3-Mat and placebo groups was not specifically associated with COVID-19 immunization during pregnancy.

- The numbers of participants immunized with any particular vaccine were too small for robust determinations of associations between the preterm birth imbalance and any particular other vaccine. Nevertheless, the imbalance was present both among women who did and among those who did not receive any COVID-19 vaccines during pregnancy. In women who did receive a COVID-

19 vaccine during pregnancy, preterm birth rates were 4.88% in the RSVPreF3-Mat group versus 3.47% in the placebo group (RR: 1.41, 95% CI: 0.89–2.22). In women who did not receive any COVID-19 vaccine during pregnancy, preterm birth rates were 8.05% in the RSVPreF3-Mat group versus 5.92% in the placebo group (RR: 1.36, 95% CI: 1.03–1.80) (**Table S16**).

- The same was observed for women who delivered when Delta was the dominant SARS-CoV-2 variant. In women who did receive a COVID-19 vaccine during pregnancy and who delivered when Delta was dominant, preterm birth rates were 6.77% in the RSVPreF3-Mat group versus 3.82% in the placebo group (RR: 1.77, 95% CI: 0.97–3.23). Among women who did not receive any COVID-19 vaccines during pregnancy and who delivered when Delta was dominant, preterm birth rates were 9.48% in the RSVPreF3-Mat group and 5.77% in the placebo group (RR: 1.64, 95% CI: 1.11–2.43) (**Table S16**).

In conclusion, although we cannot exclude that COVID-19 might have contributed to the observed imbalance in preterm births between the RSVPreF3-Mat and placebo groups in our trial, the evidence we gathered indicates that the observed preterm birth imbalance cannot be explained primarily by an association with COVID-19 cases, SARS-CoV-2 infection, or COVID-19 vaccination during pregnancy.

Manufacturing, quality, and physical measurements of RSVPreF3-Mat

Sequence and structural in silico analyses did not predict substantial molecular mimicry between the vaccine antigen and human proteins (data not shown). The purity of the main RSVPreF3-Mat batch used in the trial was 98.5%. The quality characteristics of all the vaccine batches administered in the trial were within pre-specified limits, and procedures for

preparation and use were standardized across trial sites. The preterm birth imbalance was not differentially associated with any batch of vaccine administered (**Table S14**). Preclinical toxicology studies, including reproductive and developmental toxicity studies in rats and rabbits produced no concerning findings.²⁶ Two independent toxicologists re-reviewed all generated toxicology data and concluded that RSVPreF3-Mat was well tolerated and that there were no findings concerning vaccine safety. Among maternal participants, antibodies recognizing the most abundant residual host-cell (Chinese hamster ovary) protein in the vaccine, Annexin A5, were rare and not associated with preterm birth (**Figure S6**). In addition, we tested serum samples from participants in a phase 1 trial with the RSVPreF3-Mat vaccine candidate (RSV MAT-001, NCT03674177) for the presence of antibodies binding to glucose-regulated protein 78 (GRP78), another residual host-cell protein. We found that none of the 105 tested post-vaccination samples was positive GRP78-binding IgG (data not shown).

Other factors

The imbalance was observed regardless of various maternal characteristics, medical conditions, and risk factors for preterm birth (**Table S7**). No association was found between preterm birth and the magnitude of the vaccine-induced humoral immune response (**Table S23**) or elevated serum inflammatory markers 1 month post-vaccination (**Figure S7** and data not shown). The preterm birth imbalance was not associated with maternal participants reporting infectious illnesses during pregnancy (**Table S7**), nor with RSV infection detected through western blot analyses (**Table S24**).

Effect of fetal sex on preterm birth imbalance

It has been shown previously that background preterm birth rates are higher for male than for female fetuses.²⁷ In both groups in our trial, the proportions of girls and boys born from maternal participants were similar (49.8% girls and 50.1% boys, **Table 1**). The relative risk of

preterm birth in the RSVPreF3-Mat versus the placebo group was 1.58 (95% CI: 1.12–2.23) for boys and 1.19 (0.85–1.66) for girls (**Table S7**).

Multivariable analysis

As shown in **Table S25**, multivariable analysis to identify possible risk factors of preterm birth indicated that:

- The risk of preterm birth was increased in participants from LMICs receiving RSVPreF3-Mat (versus placebo) with or without additional vaccines administered during pregnancy.
- The risk of preterm birth tended to be higher among participants from LMICs than among participants from HICs.
- The risk of preterm birth tended to be lower among participants receiving additional vaccines during pregnancy than among those not receiving additional vaccines, which was seen across study groups and economic regions.
- Other risk factors for preterm birth included pre-eclampsia, smoking or living with a smoker, and preterm birth in a previous pregnancy.

Supplementary tables

Table S1. List of pre-specified primary and secondary efficacy and safety objectives and endpoints

Primary objectives	Primary endpoints
To assess the efficacy of a single dose of RSVPreF3-Mat administered to maternal participants in preventing medically assessed ^a , RSV-associated severe LRTDs in their infant ^b participants up to 6 months of age	From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of medically assessed ^a , RSV-associated severe LRTDs according to the case definitions ^c
OR	
To assess the efficacy of a single dose of RSVPreF3-Mat administered to maternal participants in preventing medically assessed ^a , RSV-associated LRTDs of any severity in their infant ^b participants up to 6 months of age	From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of any medically assessed ^a , RSV-associated LRTDs according to the case definitions ^c
AND	
To evaluate the safety of RSVPreF3-Mat in infant ^b participants born to mothers who were vaccinated with a single dose of study vaccine, up to 12 months after birth	Occurrence of SAEs, AEs leading to study termination, and medically attended AEs from birth up to 6 months after birth ^d Occurrence of SAEs, AEs leading to study termination, and medically attended AEs from birth up to 12 months after birth ^d
Secondary efficacy objectives^e	Secondary efficacy endpoints
To assess the efficacy of a single dose of RSVPreF3-Mat administered to maternal participants in preventing RSV-associated	From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of RSV-associated

hospitalization in their infant ^b participants up to 6 months of age	hospitalizations according to the case definitions ^c
To assess the efficacy of a single dose of RSVPreF3-Mat administered to maternal participants in preventing, in their infant ^b participants up to 6 months of age, all-cause LRTD	From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of all-cause LRTD
To assess the efficacy of a single dose of RSVPreF3-Mat administered to maternal participants in preventing, in their infant ^b participants up to 6 months of age, all-cause LRTD with hospitalization	From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of all-cause LRTD with hospitalization
To assess the efficacy of a single dose of RSVPreF3-Mat administered to maternal participants in preventing medically assessed ^a , RSV-associated severe LRTDs in their infant ^b participants up to 12 months of age	From birth (Visit 1-NB) to 12 months (Visit 5-NB), occurrences of medically assessed ^a , RSV-associated severe LRTDs according to the case definitions ^c
Secondary efficacy objectives^c	Secondary efficacy endpoints
To assess the efficacy of a single dose of RSVPreF3-Mat administered to maternal participants in preventing medically assessed ^a , RSV-associated LRTDs of any severity in their infant ^b participants up to 12 months of age	From birth (Visit 1-NB) to 12 months (Visit 5-NB), occurrences of any medically assessed ^a , RSV-associated LRTDs according to the case definitions ^c
To assess the efficacy of a single dose of RSVPreF3-Mat administered to maternal participants in preventing severe medically assessed ^a , RSV-associated LRTDs for each RSV	From birth (Visit 1-NB) to 6 months (Visit 4-NB), occurrences of severe medically assessed ^a , RSV-associated LRTDs according to the case

subtype (A and B) separately in their infant ^b participants up to 6 months of age	definition ^c , for RSV subtype A and RSV subtype B separately
To assess the efficacy of a single dose of RSVPreF3-Mat administered to maternal participants in preventing medically assessed ^a , RSV-associated LRTDs of any severity, for each RSV subtype (A and B) separately in their infant ^b participants up to 6 months of age	From birth (Visit 1-NB) to 6 months (Visit 4- NB), occurrences of any medically assessed ^a , RSV-associated LRTDs according to the case definition ^c , for RSV subtype A and RSV subtype B separately
To assess the efficacy of a single dose of RSVPreF3-Mat administered to maternal participants in preventing medically assessed ^a , RSV-associated severe LRTDs in their infant ^b participants up to 4 months of age	From birth (Visit 1-NB) to 4 months (Visit 3- NB), occurrences of severe medically assessed ^a , RSV-associated LRTDs according to the case definition ^c
To assess the efficacy of a single dose of RSVPreF3-Mat administered to maternal participants in preventing medically assessed ^a , RSV-associated LRTDs of any severity in their infant ^b participants up to 4 months of age	From birth (Visit 1-NB) to 4 months (Visit 3- NB), occurrences of any medically assessed ^a , RSV-associated LRTDs according to the case definition ^c
To assess the efficacy of a single dose of RSVPreF3-Mat administered to maternal participants in preventing, in their infant ^b participants up to 6 months of age, all-cause pneumonia	From birth (Visit 1-NB) to 6 months (Visit 4- NB), occurrences of all-cause pneumonia
To assess the efficacy of a single dose of RSVPreF3-Mat administered to maternal participants in preventing RSV-associated	From birth (Visit 1-NB) to 12 months (Visit 5- NB), occurrences of RSV-associated hospitalizations according to the case definition ^c

hospitalization in their infant ^b participants up to 12 months of age	
To assess the efficacy of a single dose of RSVPreF3-Mat administrated to maternal participants in preventing, in all vaccinated maternal participants up to 6 months post-delivery, RSV-associated medically attended RTIs	From study intervention administration (Visit 1) to 6 months post-delivery (Contact 1), occurrence of RSV-associated medically attended RTIs ²
Secondary safety objectives	Secondary safety endpoints
To evaluate reactogenicity of a single dose of RSVPreF3-Mat in stage A maternal participants, during a 7-day follow-up period after the study intervention	Occurrence of solicited administration site and systemic events in stage A maternal participants, during a 7-day follow-up period after the study intervention (i.e., the day of the intervention and 6 subsequent days)
To evaluate the safety of a single dose of RSVPreF3-Mat in all maternal participants, during a 30-day follow-up period after the study intervention	Occurrence of unsolicited AEs in all maternal participants during a 30-day follow-up period after the study intervention (i.e., the day of the intervention and 29 subsequent days)
To evaluate the safety of a single dose of RSVPreF3-Mat in all maternal participants, from Visit 1 up to 6 months after delivery	Occurrence of SAEs, AEs leading to study termination, and medically attended RTIs in all maternal participants from Visit 1 (Day 1) up to 6 months after delivery Occurrence of all other medically attended AEs in all maternal participants from Visit 1 (Day 1) up to Day 42 after delivery
To evaluate pregnancy outcomes and pregnancy-related AESIs after a single dose of	Pregnancy outcomes from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery,

RSVPreF3-Mat administered to maternal participants, from Visit 1 up to 6 weeks after delivery (Visit 4)	Visit 4). These include live birth with no congenital anomalies, live birth with minor congenital anomaly(ies) only; live birth with at least one major congenital anomaly, fetal death/still birth (antepartum or intrapartum) with no congenital anomalies, fetal death/still birth (antepartum or intrapartum) with only minor congenital anomalies, fetal death/still birth (antepartum or intrapartum) with at least one major congenital anomaly; elective/therapeutic termination with no congenital anomalies; elective/therapeutic termination with only minor congenital anomalies, and elective/therapeutic termination with at least one major congenital anomaly^d Pregnancy-related AESIs from Day 1 (Visit 1) up to 6 weeks after delivery (Day 43 post-delivery, Visit 4). These include maternal death, hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, pre-eclampsia with severe features including eclampsia), fetal growth restriction, pathways to preterm birth (premature preterm rupture of membranes, preterm labor, provider-initiated preterm birth), gestational diabetes mellitus, chorioamnionitis^d
To evaluate the occurrence of neonatal AESIs (reported up to 6 weeks after birth), in infant^b	The occurrence of neonatal AESIs (reported up to 6 weeks after birth). These include small for

participants born to mothers who were vaccinated with a single dose of RSVPreF3-Mat	gestational age, low birth weight including very low and extremely low birth weight (<2500 g, <1500 g, <1000 g), congenital anomalies (major external structural defects, internal structural defects, functional defects), neonatal death (in an extremely preterm birth [22≤GA<28 weeks], in a preterm live birth [28≤GA<37 weeks], or in a term live birth), preterm birth ^d
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List of objectives and endpoints based on Protocol amendment 5, amended in February 2023.

^a“Medically assessed” means that the infant was evaluated by a healthcare professional (physician, nurse, etc.) for the LRTD.

^bAn infant is defined as a child <1 year old; a neonate is defined as an infant ≤28 days old.

^cCase definitions for RSV-associated LRTDs and surveillance for potential LRTDs are summarized in this Appendix (sections “Surveillance for respiratory tract illness” and “Case definitions of LRTD”).

^dMaternal and neonatal AESIs and pregnancy outcomes had to be recorded in the electronic case report form along with an assessment of level of diagnostic certainty by GAIA definitions when applicable. Of note, not all AEs listed by GAIA as events of special interest were reported as AESIs in this trial.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; RSV, respiratory syncytial virus; LRTD, lower respiratory tract disease; NB, newborn; SAE, serious adverse event; AE, adverse event; RTI, respiratory tract illness; AESI, adverse event of special interest; GA, gestational age; GAIA, Global Alignment of Immunization safety Assessment in pregnancy.

^eSecondary efficacy objective results are not included in the present report.

Table S2. Characteristics of maternal participants at baseline (exposed set) and infant participants at birth (infant cohort) in low- and middle-income and in high-income countries

Characteristic	LMIC		HIC	
	RSVPreF3-Mat	Placebo	RSVPreF3-Mat	Placebo
Maternal participants	N=1808	N=898	N=1749	N=873
Mean age ± SD at vaccination, years	26.6 ± 5.6	26.6 ± 5.6	31.5 ± 5.2	31.6 ± 5.4
Age category at vaccination, n (%)				
18–34 years	1623 (89.8)	806 (89.8)	1243 (71.1)	602 (69.0)
35–39 years	158 (8.7)	78 (8.7)	423 (24.2)	222 (25.4)
≥40 years	27 (1.5)	14 (1.6)	83 (4.7)	49 (5.6)
Gestational age at vaccination, n (%)				
<24 ^{0/7} weeks	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)
24 ^{0/7} –28 ^{6/7} weeks	956 (52.9)	452 (50.3)	513 (29.3)	275 (31.5)
29 ^{0/7} –34 ^{0/7} weeks	845 (46.7)	442 (49.2)	1234 (70.6)	594 (68.0)
>34 ^{0/7} weeks	6 (0.3)	2 (0.2)	2 (0.1)	4 (0.5)
Ethnicity, n (%)				
Hispanic or Latino	919 (50.8)	452 (50.3)	277 (15.8)	130 (14.9)
Not Hispanic or Latino	889 (49.2)	446 (49.7)	1471 (84.1)	743 (85.1)

Characteristic	LMIC		HIC	
	RSVPreF3-Mat	Placebo	RSVPreF3-Mat	Placebo
Missing, n	0	0	1	0
Race, n (%)				
Asian	522 (28.9)	260 (29.0)	141 (8.1)	66 (7.6)
Black	434 (24.0)	210 (23.4)	83 (4.7)	41 (4.7)
White	217 (12.0)	102 (11.4)	1452 (83.0)	736 (84.3)
Other ^a	635 (35.1)	326 (36.3)	72 (4.1)	30 (3.4)
Missing, n	0	0	1	0
Time between vaccination and delivery, days				
Mean ± SD	69.7 ± 22.9	69.7 ± 22.9	62.0 ± 21.2	63.1 ± 21.4
Min–max	3–125	3–121	2–126	6–122
Missing, n	37	19	6	4
Parity, n (%)				
Multiparous with a history of preterm birth	122 (6.7)	55 (6.1)	75 (4.3)	45 (5.2)
Multiparous without history of preterm birth	987 (54.6)	482 (53.7)	863 (49.3)	430 (49.3)
Nulliparous	699 (38.7)	361 (40.2)	811 (46.4)	398 (45.6)
Highest maternal education, n (%)				
Less than primary education	36 (2.0)	17 (1.9)	6 (0.3)	5 (0.6)

Characteristic	LMIC		HIC	
	RSVPreF3-Mat	Placebo	RSVPreF3-Mat	Placebo
Primary education	110 (6.1)	46 (5.1)	71 (4.1)	37 (4.2)
Lower secondary education	269 (14.9)	132 (14.7)	72 (4.1)	33 (3.8)
Upper secondary education	835 (46.2)	413 (46.0)	255 (14.6)	137 (15.7)
Post-secondary non-tertiary education	167 (9.2)	87 (9.7)	144 (8.2)	67 (7.7)
Short-cycle tertiary education	128 (7.1)	54 (6.0)	163 (9.3)	69 (7.9)
Bachelor's degree or equivalent level	237 (13.1)	129 (14.4)	603 (34.5)	309 (35.4)
Master's degree or equivalent level	15 (0.8)	10 (1.1)	336 (19.2)	168 (19.2)
Doctorate or equivalent level	3 (0.2)	0 (0.0)	80 (4.6)	36 (4.1)
Not elsewhere classified	7 (0.4)	9 (1.0)	19 (1.1)	12 (1.4)
Missing, n	1	1	0	0
Pre-pregnancy BMI group, n (%)				
<18.5 kg/m ²	19 (1.1)	13 (1.4)	19 (1.1)	17 (1.9)
18.5–24.9 kg/m ²	899 (49.7)	476 (53.0)	890 (50.9)	448 (51.3)
25–29.9 kg/m ²	532 (29.4)	230 (25.6)	496 (28.4)	244 (27.9)
≥30 kg/m ²	357 (19.7)	179 (19.9)	344 (19.7)	163 (18.7)
Missing, n	1	0	0	1

Characteristic	LMIC		HIC	
	RSVPreF3-Mat	Placebo	RSVPreF3-Mat	Placebo
Smoking status, n (%)				
Yes	18 (1.0)	7 (0.8)	84 (4.8)	55 (6.3)
No	1789 (98.9)	889 (99.0)	1665 (95.2)	818 (93.7)
Missing, n	1	2	0	0
Smoking status during pregnancy or smoke in surrounding, n (%)				
Yes	275 (15.2)	141 (15.7)	207 (11.8)	106 (12.1)
No	1532 (84.7)	755 (84.1)	1541 (88.1)	767 (87.9)
Missing, n	1	2	1	0
Alcohol consumption during pregnancy, n (%)				
Yes	58 (3.2)	32 (3.6)	64 (3.7)	30 (3.4)
No	1749 (96.7)	865 (96.3)	1685 (96.3)	842 (96.4)
Missing, n	1	1	0	1
Infant participants	N=1753	N=875	N=1741	N=864
Mean gestational age $\pm$ SD, weeks	38.8 $\pm$ 1.7	38.9 $\pm$ 1.4	39.3 $\pm$ 1.4	39.4 $\pm$ 1.3
Gestational age category, n (%)				

Characteristic	LMIC		HIC	
	RSVPreF3-Mat	Placebo	RSVPreF3-Mat	Placebo
<37 weeks	172 (9.8)	55 (6.3)	65 (3.7)	31 (3.6)
≥37 weeks	1581 (90.2)	820 (93.7)	1676 (96.3)	833 (96.4)
Sex, n (%)				
Female	886 (50.5)	445 (50.9)	855 (49.1)	421 (48.7)
Male	866 (49.4)	429 (49.0)	885 (50.8)	443 (51.3)
Missing, n	1	1	1	0
Mean length ± SD, cm	49.3 ± 2.7	49.2 ± 2.5	50.3 ± 2.4	50.3 ± 2.4
Missing, n	19	5	33	10
Mean weight ± SD, g	3097.5 ± 482.6	3105.1 ± 475.4	3350.2 ± 467.3	3340.9 ± 485.8
Missing, n	5	5	11	3
Mean head circumference ± SD, cm	34.1 ± 1.6	34.1 ± 1.6	34.6 ± 1.6	34.5 ± 1.6
Missing, n	25	5	82	44
Apgar score at 1 min, n (%)				
0–3	12 (0.7)	11 (1.3)	16 (0.9)	6 (0.7)
4–6	85 (4.8)	49 (5.6)	65 (3.7)	39 (4.5)
7–10	1611 (91.9)	795 (90.9)	1635 (93.9)	803 (92.9)
Missing, n	45	20	25	16

Characteristic	LMIC		HIC	
	RSVPreF3-Mat	Placebo	RSVPreF3-Mat	Placebo
Apgar score at 5 min, n (%)				
0–3	3 (0.2)	1 (0.1)	3 (0.2)	1 (0.1)
4–6	16 (0.9)	6 (0.7)	14 (0.8)	6 (0.7)
7–10	1690 (96.4)	846 (96.7)	1691 (97.1)	839 (97.1)
Missing, n	44	22	33	18

Analysis based on October 4, 2022 data lock point. The exposed set included women who received a single dose of an investigational maternal respiratory syncytial virus prefusion F protein-based vaccine (RSVPreF3-Mat) or placebo. The infant cohort included their (enrolled) infants.

LMIC, low- and middle-income country (includes Argentina, Bangladesh, Brazil, Colombia, Dominican Republic, Honduras, India, Mexico, Panama, the Philippines, South Africa, Thailand); HIC, high-income country (includes Australia, Belgium, Canada, Finland, France, Italy, New Zealand, Republic of Korea, Spain, Taiwan, United Kingdom, United States); N, total number of participants; SD, standard deviation; n (%), number (percentage) of participants in the indicated category; BMI, body mass index.

^aIncludes American Indian or Alaska Native (n=8 vs 2 in LMIC and n=6 vs 5 in HIC), Native Hawaiian or other Pacific Islander (n=8 vs 4 in HIC), and other (n=627 vs 324 in LMIC and n=58 vs 21 in HIC); the latter were mostly mixed race.

Table S3. Representativeness of the trial population

Disease, problem, or condition under investigation	Respiratory syncytial virus (RSV)-associated lower respiratory tract disease (LRTD) in infants up to 6 months of age.
Special considerations related to:	
Sex and gender	RSV-associated LRTD affects both sexes. Studies have shown that boys are at higher risk of RSV-associated LRTD, severe disease, and hospitalization than girls. ²⁸⁻³¹
Age	RSV infects most children at least once by their second birthday. Most RSV-associated LRTDs occur during infancy, and infants younger than 6 months are at highest risk of severe disease and hospitalization due to RSV. ^{29,32-34}
Comorbidities and other risk factors	Infants/children at high risk of severe RSV disease include preterm infants and infants or young children with chronic lung disease (bronchopulmonary dysplasia), congenital heart disease, Down syndrome, cystic fibrosis, anatomic pulmonary anomalies, neuromuscular disease, and immunodeficiency. ^{31,35-41} Other risk factors include low birth weight, maternal smoking during pregnancy, not being breastfed, proximity of birth to the RSV season, having school-aged siblings, day care attendance. ^{29,31,35,38}
Race or ethnic group	RSV-associated LRTDs affect all racial and ethnic groups. Some studies have shown racial or ethnic disparities in the rate of RSV infections and

	hospitalizations, for instance, higher hospitalization rates were reported in children of Māori or Pacific ethnicity and in Black, Hispanic, American Indian, and Alaska Native children.^{29,42-45} Differences in sociodemographic factors and healthcare utilization may contribute to these disparities.
Geography	RSV-associated LRTDs affect infants and children across the globe. The RSV burden is highest in low- and middle-income countries.³⁴
Other considerations	RSV is a seasonal virus with a peak prevalence during autumn and winter months in temperate regions and more variable patterns in tropical regions.^{32,46} During the first years of the COVID-19 pandemic, RSV circulation decreased and seasonal patterns were altered as a result of implementation of non-pharmaceutical interventions.⁴⁷⁻⁵⁰
Overall representativeness of this trial	Our trial enrolled pregnant women and their infants in 24 countries across six continents, with approximately 50% of the trial population enrolled in low- and middle-income countries. Infants are followed up for the occurrence of RSV-associated LRTDs until 12 months of age. Participants of various racial and ethnic groups were included, and boys and girls were equally represented among the enrolled infant cohort. Mothers were not included in the trial if their fetuses showed genetic abnormalities or significant congenital malformations. Prematurely born infants were included.

Table S4. Pregnancy outcomes through 6 weeks post-delivery (exposed set)

Outcome	RSVPreF3-Mat		Placebo		RSVPreF3-Mat/Placebo
	N=3557		N=1771		
	n	% (95% CI)	n	% (95% CI)	
Live birth with no congenital anomalies	3118	87.7 (86.5–88.7)	1555	87.8 (86.2–89.3)	1.00 (0.98–1.02)
Live birth with only minor congenital anomalies	317	8.9 (8.0–9.9)	143	8.1 (6.8–9.4)	1.10 (0.91–1.33)
Live birth with ≥1 major congenital anomaly	61	1.7 (1.3–2.2)	43	2.4 (1.8–3.3)	0.71 (0.48–1.04)
Fetal death/stillbirth with no congenital anomalies	9	0.3 (0.1–0.5)	6	0.3 (0.1–0.7)	0.75 (0.27–2.09)
Fetal death/stillbirth with ≥1 major congenital anomaly	2	0.1 (0.0–0.2)	0	0.0 (0.0–0.2)	NE
Unknown ^a	50	1.4 (1.0–1.8)	24	1.4 (0.9–2.0)	1.04 (0.64–1.68)

Analysis based on October 5, 2023 data lock point, in women who received a single dose of the investigational maternal respiratory syncytial virus prefusion F protein-based vaccine (RSVPreF3-Mat) or placebo. Definitions for pregnancy outcomes are provided in the **Supplementary methods**. There was no adjustment for multiplicity for these analyses.

N, number of maternal participants analyzed; n/%, number/percentage of participants in the indicated category; CI, confidence interval; RR, relative risk; NE, could not be estimated.

^aIncludes participants withdrawn before or at delivery with no available data on pregnancy outcomes.

Table S5. Serious adverse events^a in maternal participants from RSVPreF3-Mat or placebo administration through 6 months post-delivery (exposed set)

Primary System Organ Class	RSVPreF3-Mat				Placebo				Relative risk (95% CI)
	N=3557				N=1771				
	95% CI				95% CI				
Preferred Term	n	%	LL	UL	n	%	LL	UL	
At least one serious unsolicited AE	827	23.2	21.9	24.7	395	22.3	20.4	24.3	1.04 (0.94–1.16)
Blood and lymphatic system disorders	13	0.4	0.2	0.6	6	0.3	0.1	0.7	1.08 (0.41–2.83)
Anemia	11	0.3	0.2	0.6	3	0.2	0.0	0.5	1.83 (0.51–6.54)
Cardiac disorders	49	1.4	1.0	1.8	19	1.1	0.6	1.7	1.28 (0.76–2.17)
Bradycardia fetal	10	0.3	0.1	0.5	4	0.2	0.1	0.6	1.24 (0.39–3.96)
Fetal heart rate deceleration abnormality	11	0.3	0.2	0.6	5	0.3	0.1	0.7	1.10 (0.38–3.15)
Non-reassuring fetal heart rate pattern	19	0.5	0.3	0.8	7	0.4	0.2	0.8	1.35 (0.57–3.21)
Tachycardia fetal	5	0.1	0.0	0.3	3	0.2	0.0	0.5	0.83 (0.20–3.47)
Gastrointestinal disorders	17	0.5	0.3	0.8	5	0.3	0.1	0.7	1.69 (0.63–4.58)
Abdominal pain lower	5	0.1	0.0	0.3	3	0.2	0.0	0.5	0.83 (0.20–3.47)
General disorders and administration site conditions	2	0.1	0.0	0.2	5	0.3	0.1	0.7	0.20 (0.04–1.03)
Pyrexia	0	0.0	0.0	0.1	3	0.2	0.0	0.5	NE
Hepatobiliary disorders	15	0.4	0.2	0.7	5	0.3	0.1	0.7	1.49 (0.54–4.10)

Primary System Organ Class	RSVPreF3-Mat				Placebo				Relative risk (95% CI)
	N=3557				N=1771				
	95% CI				95% CI				
Preferred Term	n	%	LL	UL	n	%	LL	UL	
Cholestasis of pregnancy	4	0.1	0.0	0.3	3	0.2	0.0	0.5	0.66 (0.15–2.96)
Infections and infestations	85	2.4	1.9	2.9	47	2.7	2.0	3.5	0.90 (0.63–1.28)
Amniotic cavity infection	12	0.3	0.2	0.6	11	0.6	0.3	1.1	0.54 (0.24–1.23)
COVID-19	8	0.2	0.1	0.4	2	0.1	0.0	0.4	1.99 (0.42–9.37)
Endometritis	5	0.1	0.0	0.3	3	0.2	0.0	0.5	0.83 (0.20–3.47)
Mastitis	6	0.2	0.1	0.4	1	0.1	0.0	0.3	2.99 (0.36–24.79)
Postoperative wound infection	7	0.2	0.1	0.4	1	0.1	0.0	0.3	3.49 (0.43–28.31)
Pyelonephritis acute	1	0.0	0.0	0.2	3	0.2	0.0	0.5	0.17 (0.02–1.59)
Urinary tract infection	14	0.4	0.2	0.7	11	0.6	0.3	1.1	0.63 (0.29–1.39)
Pregnancy, puerperium, and perinatal conditions	678	19.1	17.8	20.4	327	18.5	16.7	20.4	1.03 (0.92–1.16)
Arrested labor	21	0.6	0.4	0.9	9	0.5	0.2	1.0	1.16 (0.53–2.53)
Breech presentation	20	0.6	0.3	0.9	5	0.3	0.1	0.7	1.99 (0.75–5.30)
Cephalo-pelvic disproportion	23	0.6	0.4	1.0	16	0.9	0.5	1.5	0.72 (0.38–1.35)
Cervix dystocia	7	0.2	0.1	0.4	4	0.2	0.1	0.6	0.87 (0.26–2.97)
Failed induction of labor	27	0.8	0.5	1.1	12	0.7	0.4	1.2	1.12 (0.57–2.21)
Fetal damage	5	0.1	0.0	0.3	5	0.3	0.1	0.7	0.50 (0.14–1.72)

Primary System Organ Class	RSVPreF3-Mat				Placebo				Relative risk (95% CI)
	N=3557				N=1771				
	95% CI				95% CI				
Preferred Term	n	%	LL	UL	n	%	LL	UL	
Fetal distress syndrome	125	3.5	2.9	4.2	69	3.9	3.0	4.9	0.90 (0.68–1.20)
Fetal growth restriction	17	0.5	0.3	0.8	13	0.7	0.4	1.3	0.65 (0.32–1.34)
Fetal hypokinesia	9	0.3	0.1	0.5	2	0.1	0.0	0.4	2.24 (0.48–10.36)
Fetal macrosomia	9	0.3	0.1	0.5	3	0.2	0.0	0.5	1.49 (0.40–5.51)
Gestational diabetes	10	0.3	0.1	0.5	2	0.1	0.0	0.4	2.49 (0.55–11.35)
Gestational hypertension	46	1.3	0.9	1.7	22	1.2	0.8	1.9	1.04 (0.63–1.72)
Hemorrhage in pregnancy	6	0.2	0.1	0.4	2	0.1	0.0	0.4	1.49 (0.30–7.39)
Meconium in amniotic fluid	15	0.4	0.2	0.7	6	0.3	0.1	0.7	1.24 (0.48–3.20)
Obstructed labor	9	0.3	0.1	0.5	2	0.1	0.0	0.4	2.24 (0.48–10.36)
Oligohydramnios	19	0.5	0.3	0.8	14	0.8	0.4	1.3	0.68 (0.34–1.34)
Postpartum hemorrhage	46	1.3	0.9	1.7	26	1.5	1.0	2.1	0.88 (0.55–1.42)
Pre-eclampsia	105	3.0	2.4	3.6	51	2.9	2.2	3.8	1.03 (0.74–1.43)
Premature labor	56	1.6	1.2	2.0	15	0.8	0.5	1.4	1.86 (1.05–3.28)
Premature rupture of membranes	11	0.3	0.2	0.6	5	0.3	0.1	0.7	1.10 (0.38–3.15)
Premature separation of placenta	9	0.3	0.1	0.5	8	0.5	0.2	0.9	0.56 (0.22–1.45)
Preterm premature rupture of membranes	37	1.0	0.7	1.4	14	0.8	0.4	1.3	1.32 (0.71–2.43)

Primary System Organ Class	RSVPreF3-Mat				Placebo				Relative risk (95% CI)
	N=3557				N=1771				
	95% CI				95% CI				
Preferred Term	n	%	LL	UL	n	%	LL	UL	
Prolonged labor	66	1.9	1.4	2.4	43	2.4	1.8	3.3	0.76 (0.52–1.12)
Prolonged pregnancy	8	0.2	0.1	0.4	7	0.4	0.2	0.8	0.57 (0.21–1.57)
Prolonged rupture of membranes	11	0.3	0.2	0.6	3	0.2	0.0	0.5	1.83 (0.51–6.54)
Retained placenta or membranes	9	0.3	0.1	0.5	3	0.2	0.0	0.5	1.49 (0.40–5.51)
Stillbirth	11	0.3	0.2	0.6	6	0.3	0.1	0.7	0.91 (0.34–2.46)
Threatened labor	28	0.8	0.5	1.1	15	0.8	0.5	1.4	0.93 (0.50–1.74)
Umbilical cord compression	6	0.2	0.1	0.4	0	0.0	0.0	0.2	NE
Surgical and medical procedures	37	1.0	0.7	1.4	12	0.7	0.4	1.2	1.54 (0.80–2.94)
Medically induced preterm birth	37	1.0	0.7	1.4	12	0.7	0.4	1.2	1.54 (0.80–2.94)

Analysis based on October 5, 2023 data lock point. The exposed set included women who received a single dose of an investigational maternal respiratory syncytial virus prefusion F protein-based vaccine (RSVPreF3-Mat) or placebo. Most of the reported serious adverse events in maternal participants occurred up to 6 weeks post-delivery (Day 43). Six serious adverse events, reported by five women, were considered by the investigator as related to vaccine/placebo administration: fetal hypokinesia and oligohydramnios (reported by one women), premature labor (reported by two women), and medically induced preterm birth in the RSVPreF3-Mat group and fetal growth restriction in the placebo group. There was no adjustment for multiplicity for these analyses.

N, total number of participants in the exposed set; CI, confidence interval; n/%, number/percentage of participants in the indicated category; LL, lower limit of the 95% CI; UL, upper limit of the 95% CI; AE, adverse event; NE, could not be estimated.

^aTable shows serious adverse events by preferred term reported in $\geq 0.2\%$ of participants in either group and the associated system organ classes.

Table S6. Serious adverse events^a in infant participants from birth through 6 months of age (infant cohort)

Primary System Organ Class	RSVPreF3-Mat				Placebo				Relative Risk (95% CI)
	N=3494				N=1741				
	95% CI				95% CI				
Preferred Term	n	%	LL	UL	n	%	LL	UL	
At least one serious unsolicited AE	640	18.3	17.0	19.6	323	18.6	16.8	20.5	0.99 (0.87–1.11)
Congenital, familial, and genetic disorders	149	4.3	3.6	5.0	77	4.4	3.5	5.5	0.96 (0.74–1.26)
Ankyloglossia congenital	9	0.3	0.1	0.5	7	0.4	0.2	0.8	0.64 (0.24–1.72)
Atrial septal defect	22	0.6	0.4	1.0	10	0.6	0.3	1.1	1.10 (0.52–2.31)
Congenital pneumonia	4	0.1	0.0	0.3	5	0.3	0.1	0.7	0.40 (0.11–1.48)
Cryptorchism	13	0.4	0.2	0.6	4	0.2	0.1	0.6	1.62 (0.53–4.96)
Developmental hip dysplasia	9	0.3	0.1	0.5	8	0.5	0.2	0.9	0.56 (0.22–1.45)
Hypospadias	9	0.3	0.1	0.5	6	0.3	0.1	0.7	0.75 (0.27–2.10)
Patent ductus arteriosus	3	0.1	0.0	0.3	8	0.5	0.2	0.9	0.19 (0.05–0.70)
Pectus excavatum	7	0.2	0.1	0.4	2	0.1	0.0	0.4	1.74 (0.36–8.39)
Polydactyly	5	0.1	0.0	0.3	4	0.2	0.1	0.6	0.62 (0.17–2.32)
Talipes	7	0.2	0.1	0.4	1	0.1	0.0	0.3	3.49 (0.43–28.33)
Ventricular septal defect	12	0.3	0.2	0.6	5	0.3	0.1	0.7	1.20 (0.42–3.39)
Gastrointestinal disorders	24	0.7	0.4	1.0	7	0.4	0.2	0.8	1.71 (0.74–3.96)
Diarrhea	1	0.0	0.0	0.2	3	0.2	0.0	0.5	0.17 (0.02–1.60)

RSVPreF3-Mat					Placebo				Relative Risk (95% CI)
Primary System Organ Class	N=3494				N=1741				
	95% CI				95% CI				
Preferred Term	n	%	LL	UL	n	%	LL	UL	
General disorders and administration site conditions	31	0.9	0.6	1.3	14	0.8	0.4	1.3	1.10 (0.59–2.07)
Death neonatal	13	0.4	0.2	0.6	3	0.2	0.0	0.5	2.16 (0.62–7.57)
Pyrexia	6	0.2	0.1	0.4	4	0.2	0.1	0.6	0.75 (0.21–2.65)
Hepatobiliary disorders	28	0.8	0.5	1.2	16	0.9	0.5	1.5	0.87 (0.47–1.61)
Hyperbilirubinemia neonatal	26	0.7	0.5	1.1	14	0.8	0.4	1.3	0.93 (0.48–1.77)
Immune system disorders	10	0.3	0.1	0.5	6	0.3	0.1	0.7	0.83 (0.30–2.28)
ABO incompatibility	7	0.2	0.1	0.4	1	0.1	0.0	0.3	3.49 (0.43–28.33)
Blood type incompatibility	1	0.0	0.0	0.2	3	0.2	0.0	0.5	0.17 (0.02–1.60)
Infections and infestations	191	5.5	4.7	6.3	95	5.5	4.4	6.6	1.00 (0.79–1.27)
Bronchiolitis	34	1.0	0.7	1.4	12	0.7	0.4	1.2	1.41 (0.73–2.72)
COVID-19	15	0.4	0.2	0.7	7	0.4	0.2	0.8	1.07 (0.44–2.61)
Neonatal infection	2	0.1	0.0	0.2	3	0.2	0.0	0.5	0.33 (0.06–1.99)
Neonatal pneumonia	5	0.1	0.0	0.3	3	0.2	0.0	0.5	0.83 (0.20–3.47)
Pneumonia	24	0.7	0.4	1.0	9	0.5	0.2	1.0	1.33 (0.62–2.85)
Respiratory syncytial virus bronchiolitis	11	0.3	0.2	0.6	10	0.6	0.3	1.1	0.55 (0.23–1.29)
Sepsis neonatal	46	1.3	1.0	1.8	18	1.0	0.6	1.6	1.27 (0.74–2.19)

RSVPreF3-Mat					Placebo				Relative Risk (95% CI)
Primary System Organ Class	N=3494				N=1741				
	95% CI				95% CI				
	Preferred Term	n	%	LL	UL	n	%	LL	
Upper respiratory tract infection	3	0.1	0.0	0.3	3	0.2	0.0	0.5	0.50 (0.10–2.47)
Urinary tract infection	16	0.5	0.3	0.7	1	0.1	0.0	0.3	7.97 (1.06–60.07)
Investigations	13	0.4	0.2	0.6	5	0.3	0.1	0.7	1.30 (0.46–3.63)
Medical observation	6	0.2	0.1	0.4	3	0.2	0.0	0.5	1.00 (0.25–3.98)
Metabolism and nutrition disorders	43	1.2	0.9	1.7	23	1.3	0.8	2.0	0.93 (0.56–1.54)
Dehydration	6	0.2	0.1	0.4	6	0.3	0.1	0.7	0.50 (0.16–1.54)
Hypoglycemia	2	0.1	0.0	0.2	5	0.3	0.1	0.7	0.20 (0.04–1.03)
Hypoglycemia neonatal	27	0.8	0.5	1.1	9	0.5	0.2	1.0	1.49 (0.70–3.17)
Nervous system disorders	24	0.7	0.4	1.0	12	0.7	0.4	1.2	1.00 (0.50–1.99)
Hypoxic-ischemic encephalopathy	2	0.1	0.0	0.2	3	0.2	0.0	0.5	0.33 (0.06–1.99)
Pregnancy, puerperium, and perinatal conditions	190	5.4	4.7	6.2	97	5.6	4.5	6.8	0.98 (0.77–1.24)
Jaundice neonatal	89	2.5	2.1	3.1	51	2.9	2.2	3.8	0.87 (0.62–1.22)
Large for dates baby	3	0.1	0.0	0.3	3	0.2	0.0	0.5	0.50 (0.10–2.47)
Low birth weight baby	53	1.5	1.1	2.0	21	1.2	0.7	1.8	1.26 (0.76–2.08)
Premature baby	84	2.4	1.9	3.0	30	1.7	1.2	2.5	1.40 (0.92–2.11)
Small for dates baby	21	0.6	0.4	0.9	15	0.9	0.5	1.4	0.70 (0.36–1.35)

RSVPreF3-Mat					Placebo				Relative Risk (95% CI)
N=3494					N=1741				
95% CI					95% CI				
Primary System Organ Class									
Preferred Term	n	%	LL	UL	n	%	LL	UL	
Respiratory, thoracic, and mediastinal disorders	160	4.6	3.9	5.3	74	4.3	3.4	5.3	1.08 (0.82–1.41)
Meconium aspiration syndrome	10	0.3	0.1	0.5	8	0.5	0.2	0.9	0.62 (0.25–1.58)
Neonatal asphyxia	4	0.1	0.0	0.3	3	0.2	0.0	0.5	0.66 (0.15–2.97)
Neonatal respiratory distress	66	1.9	1.5	2.4	31	1.8	1.2	2.5	1.06 (0.70–1.62)
Neonatal respiratory distress syndrome	23	0.7	0.4	1.0	7	0.4	0.2	0.8	1.64 (0.70–3.81)
Pneumothorax	4	0.1	0.0	0.3	3	0.2	0.0	0.5	0.66 (0.15–2.97)
Pulmonary hypertension	4	0.1	0.0	0.3	3	0.2	0.0	0.5	0.66 (0.15–2.97)
Transient tachypnoea of the newborn	37	1.1	0.7	1.5	16	0.9	0.5	1.5	1.15 (0.64–2.07)

Analysis based on October 5, 2023 data lock point. The infant cohort included infants whose mothers received a single dose of an investigational maternal respiratory syncytial virus prefusion F protein-based vaccine (RSVPreF3-Mat) or placebo. Five serious adverse events, reported for five infants were considered by the investigator as related to vaccine/placebo administration: low birth weight, premature baby, craniosynostosis, and neonatal respiratory distress (in two infants), all in the RSVPreF3-Mat group. There was no adjustment for multiplicity for these analyses.

N, total number of participants in the exposed set; CI, confidence interval; n/%, number/percentage of participants in the indicated category; LL, lower limit of the 95% CI; UL, upper limit of the 95% CI; AE, adverse event; NE, could not be estimated.

^aTable shows serious adverse events by preferred term reported in $\geq 0.2\%$ of participants in either group and the associated system organ classes.

Table S7. Preterm birth rates, overall and by different subgroups (infant cohort)

Overall/subgroup	Categories	RSVPreF3-Mat				Placebo				RSVPreF3-
		N=3494				N=1739				Mat/Placebo
		n/N	%	95%CI		n/N	%	95%CI		RR (95% CI)
				LL	UL			LL	UL	
Overall	Overall	237/3494	6.78	5.97	7.67	86/1739	4.95	3.97	6.07	1.37 (1.08–1.74)
Age group at vaccination	18–24 years	85/901	9.43	7.61	11.53	31/450	6.89	4.73	9.64	1.37 (0.92–2.03)
	25–34 years	119/1908	6.24	5.19	7.42	40/929	4.31	3.09	5.82	1.45 (1.02–2.05)
	≥35 years	33/685	4.82	3.34	6.70	15/360	4.17	2.35	6.78	1.16 (0.64–2.10)
Race	Black	42/495	8.48	6.18	11.30	17/240	7.08	4.18	11.10	1.20 (0.70–2.06)
	Asian	71/649	10.94	8.64	13.60	27/321	8.41	5.62	12.00	1.30 (0.85–1.98)
	White	65/1654	3.93	3.05	4.98	27/830	3.25	2.15	4.70	1.21 (0.78–1.88)
	Other	59/695	8.49	6.53	10.81	15/348	4.31	2.43	7.01	1.97 (1.13–3.42)
	Missing	0/1	0.00	-	-	0/0	-	-	-	NE
Ethnicity	Hispanic or Latino	89/1172	7.59	6.14	9.26	25/572	4.37	2.85	6.38	1.74 (1.13–2.68)
	Not Hispanic or Latino	148/2321	6.38	5.42	7.45	61/1167	5.23	4.02	6.66	1.22 (0.91–1.63)
Highest education attainment	Less than or equal to secondary	150/1615	9.29	7.92	10.81	51/802	6.36	4.77	8.28	1.46 (1.08–1.98)
	Higher than secondary	86/1852	4.64	3.73	5.70	34/915	3.72	2.59	5.15	1.25 (0.85–1.84)

Overall/subgroup	Categories	RSVPreF3-Mat				Placebo				RSVPreF3-
		N=3494				N=1739				Mat/Placebo
		n/N	%	95%CI		n/N	%	95%CI		RR (95% CI)
				LL	UL			LL	UL	
	Missing/unknown	1/27	3.70	0.09	18.97	1/22	4.55	0.12	22.84	0.81 (0.05–12.30)
Household environment	Urban	157/2256	6.96	5.94	8.09	56/1140	4.91	3.73	6.33	1.42 (1.05–1.91)
	Suburban	52/829	6.27	4.72	8.14	20/388	5.15	3.18	7.85	1.22 (0.74–2.01)
	Rural	28/408	6.86	4.61	9.77	10/210	4.76	2.31	8.58	1.44 (0.71–2.91)
	Missing	0/1	0.00	-	-	0/1	0.00	-	-	NE
Economic region	LMIC	172/1753	9.81	8.46	11.30	55/875	6.29	4.77	8.10	1.56 (1.17–2.09)
	HIC	65/1741	3.73	2.89	4.73	31/864	3.59	2.45	5.05	1.04 (0.68–1.58)
Country	Argentina	14/187	7.49	4.15	12.24	5/90	5.56	1.83	12.49	1.35 (0.50–3.63)
	Australia	0/27	0.00	0.00	12.77	1/14	7.14	0.18	33.87	NE
	Bangladesh	31/211	14.69	10.21	20.20	11/106	10.38	5.30	17.81	1.42 (0.74–2.70)
	Belgium	3/41	7.32	1.54	19.92	0/18	0.00	0.00	18.53	NE
	Brazil	1/50	2.00	0.05	10.65	1/25	4.00	0.10	20.35	0.50 (0.03–7.67)
	Canada	1/31	3.23	0.08	16.70	0/13	0.00	0.00	24.71	NE
	Colombia	18/167	10.78	6.51	16.50	4/82	4.88	1.34	12.02	2.21 (0.77–6.32)
	Dominican Republic	1/16	6.25	0.16	30.23	1/7	14.29	0.36	57.87	0.44 (0.03–6.04)

Overall/subgroup	Categories	RSVPreF3-Mat				Placebo				RSVPreF3-
		N=3494				N=1739				Mat/Placebo
		n/N	%	95%CI		n/N	%	95%CI		RR (95% CI)
				LL	UL			LL	UL	
	Finland	2/126	1.59	0.19	5.62	1/65	1.54	0.04	8.28	1.03 (0.10–11.17)
	France	0/21	0.00	-	-	0/13	0.00	-	-	NE
	Honduras	2/15	13.33	1.66	40.46	0/7	0.00	0.00	40.96	NE
	India	1/35	2.86	0.07	14.92	0/21	0.00	0.00	16.11	NE
	Italy	0/38	0.00	-	-	0/25	0.00	-	-	NE
	Mexico	3/24	12.50	2.66	32.36	0/16	0.00	0.00	20.59	NE
	New Zealand	5/140	3.57	1.17	8.14	4/63	6.35	1.76	15.47	0.56 (0.16–2.02)
	Panama	36/440	8.18	5.80	11.15	9/216	4.17	1.92	7.76	1.96 (0.96–4.00)
	Philippines	29/226	12.83	8.76	17.91	11/108	10.19	5.20	17.49	1.26 (0.65–2.43)
	Republic of Korea	0/9	0.00	-	-	0/4	0.00	-	-	NE
	South Africa	33/347	9.51	6.64	13.10	12/177	6.78	3.55	11.54	1.40 (0.74–2.65)
	Spain	18/507	3.55	2.12	5.55	8/251	3.19	1.39	6.18	1.11 (0.49–2.53)
	Taiwan	4/76	5.26	1.45	12.93	4/33	12.12	3.40	28.20	0.43 (0.12–1.63)
	Thailand	3/35	8.57	1.80	23.06	1/20	5.00	0.13	24.87	1.71 (0.19–15.40)
	United Kingdom	0/1	0.00	-	-	-	-	-	-	NE

Overall/subgroup	Categories	RSVPreF3-Mat				Placebo				RSVPreF3-
		N=3494				N=1739				Mat/Placebo
		n/N	%	95%CI		n/N	%	95%CI		RR (95% CI)
				LL	UL			LL	UL	
	United States	32/724	4.42	3.04	6.18	13/365	3.56	1.91	6.01	1.24 (0.66–2.34)
Climate region	Temperate	144/2505	5.75	4.87	6.73	60/1249	4.80	3.69	6.14	1.20 (0.89–1.60)
	Tropical	93/989	9.40	7.66	11.40	26/490	5.31	3.50	7.68	1.77 (1.16–2.70)
Gestational age group at vaccination	≤28 ^{6/7} weeks	127/1428	8.89	7.47	10.49	49/714	6.86	5.12	8.97	1.30 (0.94–1.78)
	≥29 ^{0/7} weeks	110/2066	5.32	4.40	6.38	37/1025	3.61	2.55	4.94	1.47 (1.02–2.12)
Cumulative gestational age group at vaccination	≥23 weeks	237/3494	6.78	5.97	7.67	86/1738	4.95	3.98	6.08	1.37 (1.08–1.74)
	≥24 weeks	237/3494	6.78	5.97	7.67	85/1737	4.89	3.93	6.02	1.39 (1.09–1.76)
	≥25 weeks	208/3230	6.44	5.62	7.34	78/1609	4.85	3.85	6.01	1.33 (1.03–1.71)
	≥26 weeks	176/2937	5.99	5.16	6.91	69/1470	4.69	3.67	5.90	1.28 (0.97–1.67)
	≥27 weeks	156/2659	5.87	5.00	6.83	53/1317	4.02	3.03	5.23	1.46 (1.08–1.98)
	≥28 weeks	137/2370	5.78	4.88	6.80	43/1169	3.68	2.67	4.92	1.57 (1.12–2.20)
	≥29 weeks	110/2066	5.32	4.40	6.38	37/1025	3.61	2.55	4.94	1.47 (1.02–2.12)
	≥30 weeks	88/1781	4.94	3.98	6.05	30/891	3.37	2.28	4.77	1.47 (0.98–2.20)
	≥31 weeks	59/1450	4.07	3.11	5.22	21/739	2.84	1.77	4.31	1.43 (0.88–2.34)
	≥32 weeks	40/1081	3.70	2.66	5.00	14/563	2.49	1.37	4.14	1.49 (0.82–2.71)

Overall/subgroup	Categories	RSVPreF3-Mat				Placebo				RSVPreF3-
		N=3494				N=1739				Mat/Placebo
		n/N	%	95%CI		n/N	%	95%CI		RR (95% CI)
				LL	UL			LL	UL	
Sex of infant	Male	127/1751	7.25	6.08	8.57	40/872	4.59	3.30	6.19	1.58 (1.12–2.23)
	Female	110/1741	6.32	5.22	7.57	46/866	5.31	3.91	7.02	1.19 (0.85–1.66)
	Missing	0/2	0.00	-	-	0/1	0.00	-	-	NE
Pre-pregnancy BMI group	<18.5 kg/m ² : underweight	3/38	7.89	1.66	21.38	2/29	6.90	0.85	22.77	1.14 (0.20–6.41)
	18.5–<25 kg/m ² : normal	125/1754	7.13	5.97	8.43	46/910	5.05	3.72	6.69	1.41 (1.02–1.96)
	25–<30 kg/m ² : overweight	65/1011	6.43	5.00	8.12	21/464	4.53	2.82	6.84	1.42 (0.88–2.29)
	≥30 kg/m ² : obesity	44/690	6.38	4.67	8.47	17/335	5.07	2.98	8.00	1.26 (0.73–2.17)
	Missing	0/1	0.00	-	-	0/1	0.00	-	-	NE
Smoking during pregnancy	Yes	44/471	9.34	6.87	12.34	17/242	7.02	4.15	11.01	1.33 (0.78–2.28)
	No	193/3022	6.39	5.54	7.32	69/1495	4.62	3.61	5.81	1.38 (1.06–1.81)
	Missing	0/1	0.00	-	-	0/2	0.00	-	-	NE
Alcohol consumption during pregnancy	Yes	11/120	9.17	4.67	15.81	1/62	1.61	0.04	8.66	5.68 (0.75–43.02)
	No	226/3373	6.70	5.88	7.60	85/1675	5.07	4.07	6.24	1.32 (1.04–1.68)
	Missing	0/1	0.00	-	-	0/2	0.00	-	-	NE
Parity	Multiparous	150/2066	7.26	6.18	8.47	51/1024	4.98	3.73	6.50	1.46 (1.07–1.99)

		RSVPreF3-Mat				Placebo				RSVPreF3-
		N=3494				N=1739				Mat/Placebo
		95%CI				95%CI				
Overall/subgroup	Categories	n/N	%	LL	UL	n/N	%	LL	UL	RR (95% CI)
	Nulliparous	87/1428	6.09	4.91	7.46	34/713	4.77	3.32	6.60	1.28 (0.87–1.88)
	Missing	0/0	-	-	-	1/2	50.00	1.26	98.74	NE
Interval between previous	<12 months	29/437	6.64	4.49	9.39	10/220	4.55	2.20	8.20	1.46 (0.72–2.94)
delivery/abortion and current	≥12 months or no previous	205/2989	6.86	5.98	7.82	76/1497	5.08	4.02	6.31	1.35 (1.05–1.74)
pregnancy	pregnancy									
	Missing	3/68	4.41	0.92	12.36	0/22	0.00	-	-	NE
History of preterm birth	≥1 preterm delivery	36/213	16.90	12.13	22.62	9/103	8.74	4.07	15.94	1.93 (0.97–3.86)
	None	201/3281	6.13	5.33	7.00	76/1634	4.65	3.68	5.79	1.32 (1.02–1.70)
	Missing	0/0	-	-	-	1/2	50.00	1.26	98.74	NE
Number of previous preterm	0 (no previous pregnancy)	72/1172	6.14	4.84	7.67	33/602	5.48	3.80	7.61	1.12 (0.75–1.67)
birth	0 (≥1 delivery but no preterm)	114/1853	6.15	5.10	7.34	42/921	4.56	3.31	6.11	1.35 (0.96–1.90)
	0 (all fetuses aborted)	15/256	5.86	3.32	9.48	1/111	0.90	0.02	4.92	6.50 (0.87–48.64)
	1	31/195	15.90	11.06	21.80	9/91	9.89	4.62	17.95	1.61 (0.80–3.23)
	2	5/18	27.78	9.69	53.48	0/11	0.00	-	-	NE
	3	0/0	-	-	-	0/1	0.00	-	-	NE

Overall/subgroup	Categories	RSVPreF3-Mat				Placebo				RSVPreF3-
		N=3494				N=1739				Mat/Placebo
		n/N	%	95%CI		n/N	%	95%CI		RR (95% CI)
				LL	UL			LL	UL	
	Missing	0/0	-	-	-	1/2	50.00	1.26	98.74	NE
History of abortion	Yes (≥ 1 spontaneous abortion)	47/624	7.53	5.59	9.89	9/276	3.26	1.50	6.10	2.31 (1.15–4.65)
	Yes (≥ 1 abortion but no spontaneous)	6/139	4.32	1.60	9.16	2/97	2.06	0.25	7.25	2.09 (0.43–10.16)
	No	184/2731	6.74	5.83	7.74	74/1364	5.43	4.28	6.76	1.24 (0.96–1.61)
	Missing	0/0	-	-	-	1/2	50.00	1.26	98.74	NE
Number of previous abortions	0	184/2731	6.74	5.83	7.74	74/1364	5.43	4.28	6.76	1.24 (0.96–1.61)
	1	43/614	7.00	5.11	9.32	9/298	3.02	1.39	5.66	2.32 (1.15–4.69)
	≥ 2	10/149	6.71	3.27	12.00	2/75	2.67	0.32	9.30	2.52 (0.57–11.20)
	Missing	0/0	-	-	-	1/2	50.00	1.26	98.74	NE
Provider-initiated preterm birth	Preterm, Yes	46/46	100.0	92.29	100.0	14/14	100.0	76.84	100.0	NE
	Preterm, No	191/191	100.0	98.09	100.0	72/72	100.0	95.01	100.0	NE
Psychological disorders	Yes	5/240	2.08	0.68	4.79	3/97	3.09	0.64	8.77	0.67 (0.16–2.76)
	No	232/3254	7.13	6.27	8.07	83/1642	5.05	4.05	6.23	1.41 (1.11–1.80)
	Yes	7/109	6.42	2.62	12.78	2/44	4.55	0.56	15.47	1.41 (0.31–6.54)

Overall/subgroup	Categories	RSVPreF3-Mat				Placebo				RSVPreF3-
		N=3494				N=1739				Mat/Placebo
		n/N	%	95%CI		n/N	%	95%CI		RR (95% CI)
				LL	UL			LL	UL	
Gestational diabetes in current pregnancy	No	230/3385	6.79	5.97	7.70	84/1695	4.96	3.97	6.10	1.37 (1.08–1.75)
Gestational hypertension in current pregnancy	Yes	5/82	6.10	2.01	13.66	5/37	13.51	4.54	28.77	0.45 (0.14–1.46)
	No	232/3412	6.80	5.98	7.70	81/1702	4.76	3.80	5.88	1.43 (1.12–1.83)
Gestational hypertension in current pregnancy (including pre-eclampsia)	Yes	32/194	16.49	11.56	22.48	10/92	10.87	5.34	19.08	1.52 (0.78–2.95)
	No	205/3300	6.21	5.41	7.09	76/1647	4.61	3.65	5.74	1.35 (1.04–1.74)
Pre-eclampsia in current pregnancy	Yes	29/117	24.79	17.27	33.62	7/58	12.07	4.99	23.30	2.05 (0.96–4.40)
	No	208/3377	6.16	5.37	7.02	79/1681	4.70	3.74	5.82	1.31 (1.02–1.69)
Intensity of pre-eclampsia in current pregnancy	Pre-eclampsia with severe features including eclampsia	18/42	42.86	27.72	59.04	4/18	22.22	6.41	47.64	1.93 (0.76–4.90)
	Pre-eclampsia	11/75	14.67	7.56	24.73	3/40	7.50	1.57	20.39	1.96 (0.58–6.61)
	None	208/3377	6.16	5.37	7.02	79/1681	4.70	3.74	5.82	1.31 (1.02–1.69)
Pre-existing hypertension	Yes	7/43	16.28	6.81	30.70	2/22	9.09	1.12	29.16	1.79 (0.41–7.91)
	No	230/3451	6.66	5.86	7.55	84/1717	4.89	3.92	6.02	1.36 (1.07–1.74)

Overall/subgroup	Categories	RSVPreF3-Mat				Placebo				RSVPreF3-
		N=3494				N=1739				Mat/Placebo
		n/N	%	95%CI		n/N	%	95%CI		RR (95% CI)
				LL	UL			LL	UL	
Pre-existing diabetes	Yes	1/3	33.33	0.84	90.57	0/1	0.00	-	-	NE
	No	236/3491	6.76	5.95	7.64	86/1738	4.95	3.98	6.08	1.37 (1.07–1.74)
Vaginal bleeding during pregnancy	Yes	1/15	6.67	0.17	31.95	0/4	0.00	-	-	NE
	No	236/3479	6.78	5.97	7.67	86/1735	4.96	3.98	6.09	1.37 (1.08–1.74)
Polyhydramnios or oligohydramnios during pregnancy	Yes	3/52	5.77	1.21	15.95	4/30	13.33	3.76	30.72	0.43 (0.10–1.80)
	No	234/3442	6.80	5.98	7.69	82/1709	4.80	3.83	5.92	1.42 (1.11–1.81)
MedDRA SOC Infections and Infestations during pregnancy (medical history, AE, SAE)	Yes	53/618	8.58	6.49	11.07	18/304	5.92	3.55	9.20	1.45 (0.86–2.43)
	No	184/2876	6.40	5.53	7.35	68/1435	4.74	3.70	5.97	1.35 (1.03–1.77)
MedDRA SOC Infections and Infestations during pregnancy (AE, SAE)	Yes	43/531	8.10	5.92	10.75	14/260	5.38	2.97	8.87	1.50 (0.84–2.70)
	No	194/2963	6.55	5.68	7.50	72/1479	4.87	3.83	6.09	1.34 (1.03–1.75)
	Yes	38/493	7.71	5.51	10.43	13/235	5.53	2.98	9.27	1.39 (0.76–2.57)

Overall/subgroup	Categories	RSVPreF3-Mat				Placebo				RSVPreF3-
		N=3494				N=1739				Mat/Placebo
		n/N	%	95%CI		n/N	%	95%CI		RR (95% CI)
				LL	UL			LL	UL	
MedDRA SOC Infections and Infestations during pregnancy (AE)	No	199/3001	6.63	5.77	7.58	73/1504	4.85	3.82	6.06	1.37 (1.05–1.77)
MedDRA SOC Infections and	Yes	7/48	14.58	6.07	27.76	4/29	13.79	3.89	31.66	1.06 (0.34–3.30)
Infestations during pregnancy (SAE)	No	230/3446	6.67	5.86	7.56	82/1710	4.80	3.83	5.92	1.39 (1.09–1.78)
MedDRA SOC Infections and	Yes	34/392	8.67	6.08	11.91	10/186	5.38	2.61	9.66	1.61 (0.81–3.19)
Infestations during pregnancy (medically attended AE or SAE)	No	203/3102	6.54	5.70	7.47	76/1553	4.89	3.87	6.09	1.34 (1.03–1.73)
Urinary tract infections during pregnancy	Yes	14/128	10.94	6.11	17.67	3/63	4.76	0.99	13.29	2.30 (0.68–7.70)
	No	223/3366	6.63	5.81	7.52	83/1676	4.95	3.96	6.10	1.34 (1.05–1.71)
Asymptomatic bacteriuria	Yes	0/7	0.00	-	-	0/3	0.00	-	-	NE
during pregnancy	No	237/3487	6.80	5.98	7.68	86/1736	4.95	3.98	6.08	1.37 (1.08–1.74)
	Yes	2/29	6.90	0.85	22.77	1/12	8.33	0.21	38.48	0.83 (0.08–8.29)

Overall/subgroup	Categories	RSVPreF3-Mat				Placebo				RSVPreF3-
		N=3494				N=1739				Mat/Placebo
		n/N	%	95%CI		n/N	%	95%CI		RR (95% CI)
				LL	UL			LL	UL	
Amniotic cavity infections during pregnancy	No	235/3465	6.78	5.97	7.67	85/1727	4.92	3.95	6.05	1.38 (1.08–1.75)
Female reproductive tract infections during pregnancy	Yes	6/50	12.00	4.53	24.31	2/20	10.00	1.23	31.70	1.20 (0.26–5.45)
	No	231/3444	6.71	5.89	7.59	84/1719	4.89	3.92	6.01	1.37 (1.08–1.75)
Syphilis during pregnancy	Yes	1/1	100.0	2.50	100.0	0/2	0.00	-	-	NE
	No	236/3493	6.76	5.95	7.64	86/1737	4.95	3.98	6.08	1.36 (1.07–1.73)
COVID-19 during pregnancy (suspected COVID-19 included)	Yes	15/178	8.43	4.79	13.52	5/83	6.02	1.98	13.50	1.40 (0.53–3.72)
	No	222/3316	6.69	5.87	7.60	81/1656	4.89	3.90	6.04	1.37 (1.07–1.75)
COVID-19 during pregnancy (suspected COVID-19 excluded)	Yes	14/170	8.24	4.58	13.43	5/81	6.17	2.03	13.82	1.33 (0.50–3.58)
	No	223/3324	6.71	5.88	7.61	81/1658	4.89	3.90	6.04	1.37 (1.07–1.76)
Flu infection during pregnancy	Yes	0/7	0.00	-	-	2/6	33.33	4.33	77.72	1.50 (0.85–2.64)
	No	237/3487	6.80	5.98	7.68	84/1733	4.85	3.88	5.97	1.40 (1.10–1.79)
Tdap during pregnancy	Yes	120/1920	6.25	5.21	7.43	39/964	4.05	2.89	5.49	1.54 (1.09–2.20)

		RSVPreF3-Mat				Placebo				RSVPreF3-
		N=3494				N=1739				Mat/Placebo
Overall/subgroup	Categories	n/N	%	95%CI		n/N	%	95%CI		RR (95% CI)
				LL	UL			LL	UL	
	No	117/1574	7.43	6.19	8.84	47/775	6.06	4.49	7.98	1.23 (0.88–1.70)
Number of Tdap doses during pregnancy	1	92/1606	5.73	4.64	6.98	28/793	3.53	2.36	5.06	1.62 (1.07–2.46)
	2	24/292	8.22	5.34	11.98	10/156	6.41	3.12	11.47	1.28 (0.63–2.61)
	3	3/21	14.29	3.05	36.34	1/15	6.67	0.17	31.95	2.14 (0.25–18.66)
	4	1/1	100.0	2.50	100.0	0/0	-	-	-	NE
Study vaccine administered with additional vaccine(s) during pregnancy	No additional vaccine (RSVPreF3-Mat only or placebo only)	80/849	9.42	7.54	11.59	34/435	7.82	5.47	10.75	1.21 (0.82–1.77)
	With additional vaccine(s)	157/2645	5.94	5.07	6.90	52/1304	3.99	2.99	5.20	1.49 (1.10–2.02)
Study vaccine administered with additional vaccine(s) during 2 nd and 3 rd trimesters	No additional vaccine (RSVPreF3-Mat only or placebo only)	101/1082	9.33	7.67	11.23	41/523	7.84	5.68	10.48	1.19 (0.84–1.69)
	With additional vaccine(s)	136/2412	5.64	4.75	6.63	45/1216	3.70	2.71	4.92	1.52 (1.10–2.12)
Study vaccine administered with additional vaccine(s) during 3 rd trimester	No additional vaccine (RSVPreF3-Mat only or placebo only)	101/1289	7.84	6.43	9.44	30/623	4.82	3.27	6.80	1.63 (1.09–2.42)
	With additional vaccine(s)	53/1422	3.73	2.80	4.85	22/709	3.10	1.95	4.66	1.20 (0.74–1.96)

Overall/subgroup	Categories	RSVPreF3-Mat				Placebo				RSVPreF3-Mat/Placebo	
		N=3494				N=1739					
		n/N	%	95%CI		n/N	%	95%CI		RR (95% CI)	
				LL	UL			LL	UL		
	No vaccine administered	83/783	10.60	8.53	12.97	34/407	8.35	5.85	11.48	1.27 (0.87–1.86)	
Study vaccine administered	RSVPreF3-Mat only or placebo only	231/3412	6.77	5.95	7.67	83/1690	4.91	3.93	6.05	1.38 (1.08–1.76)	
with additional vaccine(s)	Additional vaccine(s) administered	6/82	7.32	2.73	15.25	3/49	6.12	1.28	16.87	1.20 (0.31–4.56)	
within 2 weeks	within 2 weeks of RSVPreF3-Mat or placebo										
Number of additional	0	231/3412	6.77	5.95	7.67	83/1690	4.91	3.93	6.05	1.38 (1.08–1.76)	
vaccine(s) within 2 weeks	1	6/78	7.69	2.88	15.99	3/44	6.82	1.43	18.66	1.13 (0.30–4.29)	
	2	0/4	0.00	-	-	0/4	0.00	-	-	NE	
	3	0/0	-	-	-	0/1	0.00	-	-	NE	
Pre-eclampsia and eclampsia in	Yes	29/119	24.37	16.97	33.09	8/59	13.56	6.04	24.98	1.80 (0.88–3.68)	
current pregnancy	No	208/3375	6.16	5.38	7.03	78/1680	4.64	3.69	5.76	1.33 (1.03–1.71)	
Gestational hypertension in	Yes	32/196	16.33	11.44	22.26	11/93	11.83	6.05	20.18	1.38 (0.73–2.62)	
current pregnancy (including	No	205/3298	6.22	5.42	7.09	75/1646	4.56	3.60	5.68	1.36 (1.05–1.77)	
pre-eclampsia and eclampsia)											
Fetal growth restriction	Yes	5/34	14.71	4.95	31.06	4/28	14.29	4.03	32.67	1.03 (0.31–3.47)	

Overall/subgroup	Categories	RSVPreF3-Mat				Placebo		RSVPreF3-		
		N=3494				N=1739		Mat/Placebo		
		n/N	%	95% CI		n/N	%	95% CI		RR (95% CI)
				LL	UL			LL	UL	
	No	232/3460	6.71	5.89	7.59	82/1711	4.79	3.83	5.91	1.40 (1.10–1.79)

Post-hoc analysis based on October 4, 2022 data lock point. There was no adjustment for multiplicity for these analyses. The following infections during pregnancy were also evaluated but were not reported by any of the participants: genitourinary tract infections and inflammations NEC, bladder infections and inflammations, urethral infections and inflammations, urine culture positive, intrauterine infection, amniotic infection syndrome of Blane, reproductive tract infections and inflammations NEC, Trichomonas infections, cervix infections and inflammations, vaginal and vulval infections and inflammations, uterine infections and inflammations excluding cervix, fallopian tube and ovary infections and inflammations, pelvic and site unspecified infections and inflammations, culture cervix positive, and infections and infestations congenital.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; N, number of participants in the corresponding category; n/%, number/percentage of preterm births in the corresponding category; LL, lower limit of the 95% confidence interval; UL, upper limit of the 95% confidence interval; RR, relative risk, calculated by dividing the event rate in the RSVPreF3-Mat group by the event rate in the placebo group (CIs calculated using the Wald method); CI, confidence interval; NE, could not be estimated; LMIC, low- and middle-income country (includes Argentina, Bangladesh, Brazil, Colombia, Dominican Republic, Honduras, India, Mexico, Panama, the Philippines, South Africa, Thailand); HIC, high-income country (includes Australia, Belgium, Canada, Finland, France, Italy, New Zealand, Republic of Korea, Spain, Taiwan, United Kingdom, United States); BMI, body mass index; MedDRA SOC, Medical Dictionary for Regulatory Activities System Organ Class; AE, adverse event; SAE, serious adverse event; NEC, not elsewhere classified; Tdap, tetanus-diphtheria-acellular pertussis vaccine.

Table S8. Preterm birth rates in the RSV MAT-009 trial compared with background rates, by country

Country	Preterm birth rate in RSV MAT-009		Preterm birth background rates		
	RSVPreF3-Mat	Placebo	Latest	2014 ⁵¹	GSK studies
	% (95% CI)	% (95% CI)	%	% (UR)	% (95% CI)
Argentina	7.49 (4.15–12.24)	5.56 (1.83–12.49)	2019: 8.99 ⁵²	8.4	5.7 (3.3–9.0) ^b
Australia	0.00 (0.00–12.77)	7.14 (0.18–33.87)	2019: 8.7 ⁵³	8.6	
Bangladesh	14.69 (10.21–20.20)	10.38 (5.30–17.81)		19.1 (13.2–26.2) ^a	12.6 (8.3–18.2) ^b
Belgium	7.32 (1.54–19.92)	0.00 (0.00–18.53)		10.1 (7.7–12.9) ^a	
Brazil	2.00 (0.05–10.65)	4.00 (0.10–20.35)	2021: 12.19 ⁵⁴	11.2	4.9 (2.3–9.1) ^b
Canada	3.23 (0.08–16.70)	0.00 (0.00–24.71)	2017: 8.2 ⁵⁵	8.2 (6.8–9.7) ^a	6.3 ^c
Colombia	10.78 (6.51–16.50)	4.88 (1.34–12.02)		14.5 (11.4–18.2) ^a	5.1 (2.7–8.6) ^b
Dominican Republic	6.25 (0.16–30.23)	14.29 (0.36–57.87)		9.8 (8.6–11.3) ^d	
Finland	1.59 (0.19–5.62)	1.54 (0.04–8.28)	2020: 5.6 ⁵⁶	5.8	1.8 ^c
France	0.00	0.00	2019: 6.9 ⁵⁷	8.4 (6.0–11.4) ^a	
Honduras	13.33 (1.66–40.46)	0.00 (0.00–40.96)		9.8 (8.6–11.3) ^d	2.3 ^c
India	2.86 (0.07–14.92)	0.00 (0.00–16.11)		13.6 (11.1–16.1) ^a	
Italy	0.00	0.00	2020: 6.4 ⁵⁸	7.8 (6.6–9.1) ^a	
Mexico	12.50 (2.66–32.36)	0.00 (0.00–20.59)		7.0 (5.6–8.7) ^a	5.3 (1.7–11.9) ^b
New Zealand	3.57 (1.17–8.14)	6.35 (1.76–15.47)	2018: 7.49 ⁵⁹	7.5	

Panama	8.18 (5.80–11.15)	4.17 (1.92–7.76)		9.8 (8.6–11.3) ^d	8.2 (2.7–18.1) ^b
Philippines	12.83 (8.76–17.91)	10.19 (5.20–17.49)		13.3 (9.1–18.5) ^a	4.6 (2.3–8.1) ^b
Republic of Korea	0.00	0.00		6.7	
South Africa	9.51 (6.64–13.10)	6.78 (3.55–11.54)		12.4 (8.6–17.1) ^a	8.3 (5.7–11.6) ^b
Spain	3.55 (2.12–5.55)	3.19 (1.39–6.18)	2020: 6.76 ⁶⁰	6.5	
Taiwan	5.26 (1.45–12.93)	12.12 (3.40–28.20)	2009: 7.1 ⁶¹		
Thailand	8.57 (1.80–23.06)	5.00 (0.13–24.87)		12.7 (10.1–15.6) ^a	5.5 (3.0–9.0) ^b
United Kingdom	0.00	-		7.0 (6.4–7.8) ^a	6.8 ^e
United States	4.42 (3.04–6.18)	3.56 (1.91–6.01)	2020: 8.42 ⁶²	9.6	1.8 ^c

There was no adjustment for multiplicity for these analyses. RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; CI, confidence interval; UR, uncertainty range (lower UR: 2%, upper UR: 98%).

^aBased on modeled national estimates (with uncertainty interval) and not directly reported rates.

^bRate from EPI RSV-008 study (Aurpibul et al.⁶³ and unpublished data).

^cRate from EPI RSV-005 study⁶⁴; likely an underestimate as infants born at a gestational age of <28 weeks were excluded from this study.

^dRegional preterm birth rate for Latin America and the Caribbean.

^eRate from EPI RSV-015 study⁶⁵; low-risk pregnancies in the United Kingdom.

Table S9. Summary statistics for time between RSVPreF3-Mat or placebo administration and delivery among all infants (infant cohort) and preterm infants (infant cohort, preterm subgroup)

Summary statistics	All infants		Preterm infants	
	RSVPreF3-Mat	Placebo	RSVPreF3-Mat	Placebo
	N=3494	N=1739	N=237	N=86
Any GA at vaccination				
Mean $\pm$ SD, days	67.0 $\pm$ 22.3	67.5 $\pm$ 22.3	48.5 $\pm$ 21.9	50.2 $\pm$ 21.9
Median (IQR), days	64.5 (49–85)	64 (50–86)	48 (30–67)	53 (34–68)
<29 weeks GA at vaccination				
Mean $\pm$ SD, days	87.8 $\pm$ 15.5	88.9 $\pm$ 13.8	62.2 $\pm$ 19.2	65.0 $\pm$ 13.6
Median (IQR), days	89 (79–98)	90 (80–99)	64 (51–77)	65 (57–73)
$\geq$29 weeks GA at vaccination				
Mean $\pm$ SD, days	52.6 $\pm$ 13.1	52.6 $\pm$ 13.1	32.7 $\pm$ 11.9	30.6 $\pm$ 13.9
Median (IQR), days	52 (44–62)	52 (44–62)	31 (24–42)	30 (19–41)

Post-hoc analysis based on October 4, 2022 data lock point.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; N, number of participants; GA, gestational age; SD, standard deviation; IQR, interquartile range.

Table S10. Neonatal deaths (infant cohort)

Category	RSVPreF3-Mat		Placebo		RSVPreF3-Mat/ Placebo
	N=3494		N=1739		Placebo
	n	% (95% CI)	n	% (95% CI)	RR (95% CI)
Total neonatal deaths	13	0.37 (0.20–0.64)	3	0.17 (0.04–0.50)	2.16 (0.62–7.56)
Among term births (≥ 37 weeks)	6	0.17 (0.06–0.37)	3	0.17 (0.04–0.50)	1.00 (0.25–3.98)
Among extremely preterm births (22–<28 weeks)	2	0.06 (0.01–0.21)	0	0.00 (0.00–0.21)	(0.26–inf)
Among other preterm births (28–<37 weeks)	5	0.14 (0.05–0.33)	0	0.00 (0.00–0.21)	(0.65–inf)

Analysis based on October 4, 2022 data lock point. Neonatal death was defined as death of a live-born infant within the first 28 completed days of life regardless of gestational age at birth. There was no adjustment for multiplicity for these analyses.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; N, number of participants; n/%, number/percentage of neonatal deaths in the indicated category; CI, confidence interval; RR, relative risk, calculated by dividing the event rate in the RSVPreF3-Mat group by the event rate in the placebo group (CIs calculated using the Wald method, except for the CIs for the RRs of neonatal death among extremely and other preterm births, for which a Wilson-type of CI was constructed⁶⁶); inf, infinity.

Table S11. Summary of the seven neonatal deaths among preterm infants in the RSVPreF3-Mat group

Gestational age category at birth	Economic region	GBD category of death ^a	Possible contributing risk factors
Extremely preterm (<28 weeks)	LMIC	Preterm birth complication	Extremely preterm, extremely or very low birth weight, disseminated congenital viral infection ^b
	HIC	Neonatal sepsis & infections	
Very preterm (28–<32 weeks)	LMIC	Other neonatal conditions	Very preterm, low birth weight, hypervolemic fetal condition
Moderate to late preterm (32–<37 weeks)	LMIC	Neonatal sepsis & infections	Low birth weight, bacterial sepsis, septic shock, anemia, seizure, neonatal pneumonia, pulmonary hypertension, genetic disorder, cardiac anomaly, necrotizing colitis ^c
	LMIC	Neonatal sepsis & infections	
	LMIC	Preterm birth complication	
	LMIC	Preterm birth complication	

Analysis based on October 4, 2022 data lock point.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; GBD, Global Burden of Disease; LMIC, low- and middle-income country; HIC, high-income country.

^aPer GSK assessment following GBD 2017 data resources (<https://ghdx.healthdata.org/gbd-2017>).

^bCombined risk factors for the two neonatal death cases among extremely preterm infants.

^cCombined risk factors for the four neonatal death cases among moderate-to-late preterm infants.

Table S12. Stillbirths and infant deaths (exposed set or infant cohort)

Category	RSVPreF3-Mat		Placebo		RSVPreF3-Mat/Placebo
	n/N	% (95% CI)	n/N	% (95% CI)	RR (95% CI)
Stillbirth	11/3557	0.31 (0.15–0.55)	6/1771	0.34 (0.12–0.74)	0.91 (0.34–2.46)
Infant death	18/3494	0.52 (0.31–0.81)	4/1739	0.23 (0.06–0.59)	2.24 (0.76–6.61)

Analysis based on October 4, 2022 data lock point. Stillbirth was a fetal death occurring before birth and after 20–28 weeks of gestation (depending on the country).⁴ Infant death was a death from birth up to 1 year (including the 13 neonatal deaths in the RSVPreF3-Mat and 3 in the placebo group) based on data up to the data lock point of October 4, 2022 (when not all infants had reached 1 year of follow-up). After the October 4 database freeze, 2 additional infant deaths were reported in the RSVPreF3-Mat group (data lock point of October 5, 2023). Of the 20 infant deaths (13 neonatal, 7 post-neonatal) in the RSVPreF3-Mat group, 9 deaths (7 neonatal, 2 post-neonatal) were in preterm infants. There was no adjustment for multiplicity for these analyses.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; N, number of maternal (for stillbirth) or infant (for infant death) participants; n/%, number/percentage of participants in the indicated category; CI, confidence interval; RR, relative risk, calculated by dividing the event rate in the RSVPreF3-Mat group by the event rate in the placebo group (CIs calculated using the Wald method).

Table S13. Monthly (non-cumulative) preterm birth rate throughout the trial (infant cohort)

Month of delivery	Preterm birth rate, % (n/N)		RR (80% CI)	Probability of RR ≥ 1
	RSVPreF3-Mat	Placebo		
March 2021	8.70% (4/46)	4.17% (1/24)	2.09 (0.52–8.43)	0.750
April 2021	2.56% (2/78)	2.56% (1/39)	1.00 (0.21–4.71)	0.500
May 2021	4.35% (5/115)	2.04% (1/49)	2.13 (0.53–8.53)	0.758
June 2021	6.29% (10/159)	4.35% (3/69)	1.46 (0.64–3.32)	0.717
July 2021	5.91% (11/186)	5.26% (6/114)	1.12 (0.60–2.12)	0.593
August 2021	9.24% (23/249)	4.20% (5/119)	2.20 (1.19–4.07)	0.949
September 2021	7.31% (22/301)	3.68% (5/136)	1.99 (1.07–3.70)	0.922
October 2021	9.93% (30/302)	3.33% (5/150)	2.98 (1.63–5.46)	0.990
November 2021	8.31% (29/349)	6.32% (11/174)	1.31 (0.85–2.04)	0.788
December 2021	8.80% (30/341)	6.52% (12/184)	1.35 (0.89–2.06)	0.818
January 2022	4.53% (16/353)	8.02% (15/187)	0.56 (0.36–0.88)	0.050
February 2022	6.05% (19/314)	5.67% (8/141)	1.07 (0.63–1.80)	0.563
March 2022	6.69% (24/359)	3.30% (6/182)	2.03 (1.14–3.60)	0.943
April 2022	3.03% (7/231)	4.92% (6/122)	0.62 (0.31–1.24)	0.187
May 2022	1.20% (1/83)	2.56% (1/39)	0.47 (0.08–2.83)	0.295

Post-hoc analysis based on October 4, 2022 data lock point. The probability of the relative risk of preterm birth to be 1 or higher in August, September, and October 2021 and in March 2022 is very high and is thus not likely to be random variation. There was no adjustment for multiplicity for these analyses.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; n, number of preterm births in the indicated month; N, number of infants born in the indicated month; RR, relative risk; CI, confidence interval.

Table S14. Preterm birth rate by vaccine lot used in the trial

Lot number (intervention)	Economic region	Number of deliveries	Number of preterm infants	Preterm rate among deliveries, % (95% CI)
DRSVA032B	Overall	2700	187	6.93 (6.00–7.95)
(RSVPreF3-Mat)	LMIC	1253	131	10.45 (8.82–12.28)
	HIC	1447	56	3.87 (2.94–5.00)
DRSVA036A	Overall	261	17	6.51 (3.84–10.22)
(RSVPreF3-Mat)	LMIC	106	12	11.32 (5.99–18.94)
	HIC	155	5	3.23 (1.06–7.37)
DRSVA037A	Overall	362	18	4.97 (2.97–7.74)
(RSVPreF3-Mat)	LMIC	224	14	6.25 (3.46–10.26)
	HIC	138	4	2.90 (0.80–7.26)
DRSVA038A	Overall	171	15	8.77 (4.99–14.06)
(RSVPreF3-Mat)	LMIC	170	15	8.82 (5.02–14.14)
	HIC	1	0	0.00 (0.00–97.50)
PVZVA016A	Overall	1345	62	4.61 (3.55–5.87)
(placebo)	LMIC	633	38	6.00 (4.28–8.15)
	HIC	712	24	3.37 (2.17–4.97)
PVZVA020A	Overall	394	24	6.09 (3.94–8.93)
(placebo)	LMIC	242	17	7.03 (4.15–11.01)
	HIC	152	7	4.61 (1.87–9.26)

Post-hoc analysis based on October 4, 2022 data lock point. There was no adjustment for multiplicity for these analyses.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; CI, confidence interval; LMIC, low- and middle-income country; HIC, high-income country.

Table S15. Seroconversion rates for SARS-CoV-2 N protein-binding antibodies in maternal participants (investigation cohort)

Category	RSVPreF3-Mat		Placebo		RSVPreF3-Mat/Placebo
	n/N	% (95% CI)	n/N	% (95% CI)	RR (95% CI)
Delivery throughout trial					
Preterm group	17/222	7.66 (4.52–11.98)	7/75	9.33 (3.84–18.29)	0.82 (0.35–1.90)
Term group	24/222	10.81 (7.05–15.66)	10/98	10.20 (5.00–17.97)	1.06 (0.53–2.13)
Delivery during Delta wave					
Preterm group	12/143	8.39 (4.41–14.20)	4/42	9.52 (2.66–22.62)	0.88 (0.30–2.59)
Term group	12/120	10.00 (5.27–16.82)	3/56	5.36 (1.12–14.87)	1.87 (0.55–6.35)
Delivery outside Delta wave					
Preterm group	5/79	6.33 (2.09–14.16)	3/33	9.09 (1.92–24.33)	0.70 (0.18–2.75)
Term group	12/102	11.76 (6.23–19.65)	7/42	16.67 (6.97–31.36)	0.71 (0.30–1.67)

Post-hoc analysis based on October 4, 2022 data lock point. These analyses were done on the investigation cohort, set up using a matched (1:1) case-cohort design, in which cases were women with preterm births and controls were women with term births (see this Appendix, “Statistical analyses” section). Analyses were done on maternal serum samples collected pre-vaccination, Day 31 post-vaccination, and at delivery (maternal serum or cord blood samples). Seroconversion was defined as seronegative for SARS-CoV-2 N protein-binding antibodies pre-vaccination and seropositive at any of the subsequent visits. The sensitivity of the assay depends on the timing after infection.¹⁸ False negatives are possible. Delivery during Delta wave refers to women who delivered when Delta was the dominant SARS-CoV-2 variant; this period (July–December 2021) was defined as the period when >50% of the isolated SARS-CoV-2 variants were Delta (based on <https://ourworldindata.org/>) in the five countries that enrolled the most participants in the RSV MAT-009 trial (Panama, Philippines, South Africa, Spain, United States). There was no adjustment for multiplicity for these analyses.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; n/%, number/percentage of participants who seroconverted; N, number of participants in the investigation cohort; CI, confidence interval; RR, relative risk, calculated by dividing the event rate in the RSVPreF3-Mat group by the event rate in the placebo group (CIs calculated using the Wald method).

Table S16. Preterm birth rates with or without COVID-19 vaccine administered during pregnancy (infant cohort)

Category	RSVPreF3-Mat		Placebo		RSVPreF3-Mat/Placebo
	n/N	% (95% CI)	n/N	% (95% CI)	RR (95% CI)
Delivery throughout trial					
With COVID-19 vaccine(s)	68/1394	4.88 (3.81–6.14)	24/692	3.47 (2.23–5.12)	1.41 (0.89–2.22)
No COVID-19 vaccine(s)	169/2100	8.05 (6.92–9.29)	62/1047	5.92 (4.57–7.53)	1.36 (1.03–1.80)
Delivery during Delta wave					
With COVID-19 vaccine(s)	47/694	6.77 (5.02–8.90)	13/340	3.82 (2.05–6.45)	1.77 (0.97–3.23)
No COVID-19 vaccine(s)	98/1034	9.48 (7.76–11.43)	31/537	5.77 (3.96–8.09)	1.64 (1.11–2.43)
Delivery outside Delta wave					
With COVID-19 vaccine(s)	21/700	3.00 (1.87–4.55)	11/352	3.13 (1.57–5.52)	0.96 (0.47–1.97)
No COVID-19 vaccine(s)	71/1066	6.66 (5.24–8.33)	31/510	6.08 (4.17–8.52)	1.10 (0.73–1.65)

Post-hoc analysis based on October 4, 2022 data lock point. Delivery during Delta wave refers to infants whose mothers delivered when Delta was the dominant SARS-CoV-2 variant; this period (July–December 2021) was defined as the period when >50% of the isolated SARS-CoV-2 variants were Delta (based on <https://ourworldindata.org/>) in the five countries that enrolled the most participants in the RSV MAT-009 trial (Panama, Philippines, South Africa, Spain, United States). With or without COVID-19 vaccine(s) refers to infants whose mothers received a COVID-19 vaccine or no COVID-19 vaccine during pregnancy. There was no adjustment for multiplicity for these analyses.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; n/%, number/percentage of preterm infants in the indicated category; N, total number of infants in the indicated category; CI, confidence interval; RR, relative risk, calculated by dividing the event rate in the RSVPreF3-Mat group by the event rate in the placebo group (CIs calculated using the Wald method).

Table S17. Preterm birth rates with or without suspected, probable, or confirmed COVID-19 case during pregnancy (infant cohort)

Category	RSVPreF3-Mat		Placebo		RSVPreF3-Mat/Placebo
	n/N	% (95% CI)	n/N	% (95% CI)	RR (95% CI)
Delivery throughout trial					
With COVID-19 case	15/178	8.43 (4.79–13.52)	5/83	6.02 (1.98–13.50)	1.40 (0.53–3.72)
No COVID-19 case	222/3316	6.69 (5.87–7.60)	81/1656	4.89 (3.90–6.04)	1.37 (1.07–1.75)
Delivery during Delta wave					
With COVID-19 case	8/61	13.11 (5.84–24.22)	2/21	9.52 (1.17–30.38)	1.38 (0.32–5.98)
No COVID-19 case	137/1667	8.22 (6.94–9.64)	42/856	4.91 (3.56–6.57)	1.68 (1.20–2.34)
Delivery outside Delta wave					
With COVID-19 case	7/117	5.98 (2.44–11.94)	3/62	4.84 (1.01–13.50)	1.24 (0.33–4.61)
No COVID-19 case	85/1649	5.15 (4.14–6.33)	39/800	4.88 (3.49–6.60)	1.06 (0.73–1.53)

Post-hoc analysis based on October 4, 2022 data lock point. Delivery during Delta wave refers to infants whose mothers delivered when Delta was the dominant SARS-CoV-2 variant; this period (July–December 2021) was defined as the period when >50% of the isolated SARS-CoV-2 variants were Delta (based on <https://ourworldindata.org/>) in the five countries that enrolled the most participants in the RSV MAT-009 trial (Panama, Philippines, South Africa, Spain, United States). With or without COVID-19 case refers to infants whose mothers did or did not report a suspected, probable, or confirmed COVID-19 case during pregnancy. There was no adjustment for multiplicity for these analyses.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; n/%, number/percentage of preterm infants in the indicated category; N, total number of infants in the indicated category; CI, confidence interval; RR, relative risk, calculated by dividing the event rate in the RSVPreF3-Mat group by the event rate in the placebo group (CIs calculated using the Wald method).

Table S18. Most common vaccines administered to maternal participants during the second and third trimester (infant cohort)

Vaccine	Setting	Number (%) receiving additional vaccine	
		RSVPreF3-Mat	Placebo
		N=3494	N=1739
		(LMIC: N=1753; HIC: N=1741)	(LMIC: N=875; HIC: N=864)
Any additional vaccine	All countries	2412 (69.0)	1216 (69.9)
	LMIC	1128 (64.3)	577 (65.9)
	HIC	1284 (73.8)	639 (74.0)
Pertussis-containing vaccine	All countries	1449 (41.5)	728 (41.9)
	LMIC	479 (27.3)	243 (27.8)
	HIC	970 (55.7)	485 (56.1)
COVID-19 mRNA vaccine	All countries	1067 (30.5)	520 (29.9)
	LMIC	350 (20.0)	168 (19.2)
	HIC	717 (41.2)	352 (40.7)
Influenza vaccine	All countries	955 (27.3)	518 (29.8)
	LMIC	432 (24.6)	235 (26.9)
	HIC	523 (30.0)	283 (32.8)
Tetanus vaccine	All countries	317 (9.1)	176 (10.1)
	LMIC	316 (18.0)	176 (20.1)

	HIC	1 (0.1)	0 (0.0)
Tetanus, diphtheria vaccine	All countries	181 (5.2)	107 (6.2)
	LMIC	181 (10.3)	106 (12.1)
	HIC	0 (0.0)	1 (0.1)
COVID-19 adenoviral vaccine	All countries	84 (2.4)	35 (2.0)
	LMIC	71 (4.1)	29 (3.3)
	HIC	13 (0.7)	6 (0.7)
Hepatitis B vaccine	All countries	65 (1.9)	35 (2.0)
	LMIC	64 (3.7)	35 (4.0)
	HIC	1 (0.1)	0 (0.0)
COVID-19 inactivated vaccine	All countries	42 (1.2)	22 (1.3)
	LMIC	42 (2.4)	22 (2.5)
	HIC	0 (0.0)	0 (0.0)
COVID-19 unspecified vaccine	All countries	18 (0.5)	11 (0.6)
	LMIC	2 (0.1)	0 (0.0)
	HIC	16 (0.9)	11 (1.3)

Post-hoc analysis based on October 4, 2022 data lock point. Table shows the number (percentage) of infants for whom the mothers received the indicated vaccine(s). Vaccines are those other than the study vaccine administered during the second or third trimester of pregnancy.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; N, number of participants; LMIC, low- and middle-income country; HIC, high-income country.

Table S19. Preterm birth rates with or without additional vaccines administered during the second or third trimester of pregnancy (infant cohort)

Category	RSVPreF3-Mat		Placebo		RSVPreF3-Mat/Placebo
	n/N	% (95% CI)	n/N	% (95% CI)	RR (95% CI)
Overall (all countries)					
No additional vaccine(s)	101/1082	9.33 (7.67–11.23)	41/523	7.84 (5.68–10.48)	1.19 (0.84–1.69)
With additional vaccine(s)	136/2412	5.64 (4.75–6.63)	45/1216	3.70 (2.71–4.92)	1.52 (1.10–2.12)
Pertussis-containing	68/1449	4.69 (3.66–5.91)	26/728	3.57 (2.35–5.19)	1.31 (0.84–2.05)
COVID-19 mRNA	55/1067	5.15 (3.91–6.66)	17/520	3.27 (1.92–5.18)	1.58 (0.92–2.69)
Influenza	47/955	4.92 (3.64–6.49)	17/518	3.28 (1.92–5.20)	1.50 (0.87–2.58)
Tetanus ^a	26/317	8.20 (5.43–11.79)	7/176	3.98 (1.61–8.02)	2.06 (0.91–4.65)
Tetanus-diphtheria ^a	14/181	7.73 (4.29–12.64)	5/107	4.67 (1.53–10.57)	1.66 (0.61–4.47)
LMIC					
No additional vaccine(s)	80/625	12.80 (10.28–15.68)	30/298	10.07 (6.90–14.06)	1.27 (0.86–1.89)
With additional vaccine(s)	92/1128	8.16 (6.63–9.91)	25/577	4.33 (2.82–6.33)	1.88 (1.22–2.90)
Pertussis-containing	34/479	7.10 (4.97–9.78)	12/243	4.94 (2.58–8.47)	1.44 (0.76–2.73)
COVID-19 mRNA	31/350	8.86 (6.10–12.34)	7/168	4.17 (1.69–8.40)	2.13 (0.96–4.73)
Influenza	34/432	7.87 (5.51–10.82)	8/235	3.40 (1.48–6.60)	2.31 (1.09–4.91)

Tetanus	26/316	8.23 (5.45–11.82)	7/176	3.98 (1.61–8.02)	2.07 (0.92–4.67)
Tetanus-diphtheria	14/181	7.73 (4.29–12.64)	5/106	4.72 (1.55–10.67)	1.64 (0.61–4.42)
HIC					
No additional vaccine(s)	21/457	4.60 (2.87–6.94)	11/225	4.89 (2.47–8.58)	0.94 (0.46–1.92)
With additional vaccine(s)	44/1284	3.43 (2.50–4.57)	20/639	3.13 (1.92–4.79)	1.09 (0.65–1.84)
Pertussis-containing	34/970	3.51 (2.44–4.86)	14/485	2.89 (1.59–4.80)	1.21 (0.66–2.24)
COVID-19 mRNA	24/717	3.35 (2.16–4.94)	10/352	2.84 (1.37–5.16)	1.18 (0.57–2.44)
Influenza	13/523	2.49 (1.33–4.21)	9/283	3.18 (1.46–5.95)	0.78 (0.34–1.81)

Post-hoc analysis based on October 4, 2022 data lock point. Additional vaccines are vaccines other than the study vaccine administered to maternal participants during the second or third trimester of pregnancy; the most common vaccines were pertussis-containing, COVID-19 mRNA, influenza, tetanus (in LMIC), and tetanus-diphtheria (in LMIC) vaccines. Analyses by vaccine were done for infants whose mothers had received at least the indicated vaccine; they may have received any of the other vaccines as well. There was no adjustment for multiplicity for these analyses.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; n/%, number/percentage of preterm infants in the indicated category; N, total number of infants in the indicated category; CI, confidence interval; RR, relative risk, calculated by dividing the event rate in the RSVPreF3-Mat group by the event rate in the placebo group (CIs calculated using the Wald method); LMIC, low- and middle-income country; HIC, high-income country.

^aTetanus and tetanus-diphtheria vaccines were given almost exclusively in LMIC.

Table S20. Percent reduction in preterm birth rates with versus without additional vaccines administered during the second or third trimester of pregnancy (infant cohort)

	RSVPreF3-Mat	Placebo
Overall		
No additional vaccine(s), preterm birth rate	9.33	7.84
With additional vaccine(s), preterm birth rate	5.64	3.70
% reduction with additional vs no additional vaccines	39.55	52.81
LMIC		
No additional vaccine(s), preterm birth rate	12.80	10.07
With additional vaccine(s), preterm birth rate	8.16	4.33
% reduction with additional vs no additional vaccines	36.25	57.00
HIC		
No additional vaccine(s), preterm birth rate	4.60	4.89
With additional vaccine(s), preterm birth rate	3.43	3.13
% reduction with additional vs no additional vaccines	25.43	35.99

Post-hoc analysis based on October 4, 2022 data lock point. Additional vaccines are vaccines other than the study vaccine administered to maternal participants during the second or third trimester of pregnancy. Percent reduction was calculated as: $100 \times (\text{preterm birth rate with additional vaccines} - \text{preterm birth rate no additional vaccines}) / \text{preterm birth rate no additional vaccines}$.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; LMIC, low- and middle-income country; HIC, high-income country.

Table S21. Preterm birth rates by the number of active vaccine doses administered during pregnancy (infant cohort)

Number of active vaccine doses ^a	RSVPreF3-Mat		Placebo		RSVPreF3-Mat/ Placebo
	N=3494		N=1739		Placebo
	n/N	% (95% CI)	n/N	% (95% CI)	RR (95% CI)
0	0/0	-	41/523	7.84 (5.68–10.48)	NE
1	101/1082	9.33 (7.67–11.23)	18/461	3.90 (2.33–6.10)	2.39 (1.47–3.90)
2	56/948	5.91 (4.49–7.60)	14/371	3.77 (2.08–6.25)	1.57 (0.88–2.78)
3	45/720	6.25 (4.59–8.27)	9/258	3.49 (1.61–6.52)	1.79 (0.89–3.61)
4	24/541	4.44 (2.86–6.53)	2/105	1.90 (0.23–6.71)	2.33 (0.56–9.71)
5	9/166	5.42 (2.51–10.04)	2/16	12.50 (1.55–38.35)	0.43 (0.10–1.84)
6	1/30	3.33 (0.08–17.22)	0/5	0.00	NE
7	1/5	20.00 (0.51–71.64)	0/0	-	NE
8	0/1	0.00	0/0	-	NE
9	0/1	0.00	0/0	-	NE

Post-hoc analysis based on October 4, 2022 data lock point. There was no adjustment for multiplicity for these analyses.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; n/%, number/percentage of preterm infants in the indicated category; N, total number of infants in the indicated category; CI, confidence interval; RR, relative risk, calculated by dividing the event rate in the RSVPreF3-Mat group by the event rate in the placebo group (CIs calculated using the Wald method); NE, could not be estimated.

^aActive vaccines included RSVPreF3-Mat and any other vaccines administered during the second or third trimester of pregnancy; placebo was not counted as an active vaccine. Zero active vaccine doses therefore means participants who received no RSVPreF3-Mat and no other vaccine in the RSVPreF3-Mat group, and placebo without any other vaccine in the placebo group; one active vaccine dose means participants who received RSVPreF3-Mat without any other vaccine in the RSVPreF3-Mat group and placebo with one other vaccine in the placebo group; two active vaccine doses means participants who received RSVPreF3-Mat and one other vaccine in the RSVPreF3-Mat group and placebo with two other vaccines in the placebo group.

Table S22. Summary statistics for time between any last vaccination during pregnancy (RSVPreF3-Mat, placebo, or other vaccines) and delivery among all infants (infant cohort) and preterm infants (infant cohort, preterm subgroup)

Summary statistics	All infants		Preterm infants	
	RSVPreF3-Mat	Placebo	RSVPreF3-Mat	Placebo
	N=3494	N=1739	N=237	N=86
Any GA at vaccination				
Mean $\pm$ SD, days	57.9 $\pm$ 24.7	58.6 $\pm$ 25.0	44.1 $\pm$ 22.5	44.6 $\pm$ 21.8
Median (IQR), days	56 (41–76)	56 (41–78)	42 (26–60)	46 (26–61)
<29 weeks GA at vaccination				
Mean $\pm$ SD, days	74.2 $\pm$ 25.7	75.8 $\pm$ 25.2	55.9 $\pm$ 22.7	55.9 $\pm$ 20.0
Median (IQR), days	80 (62–92)	82 (63–93)	59 (41–74)	58 (48–69)
$\geq$29 weeks GA at vaccination				
Mean $\pm$ SD, days	46.7 $\pm$ 16.2	46.6 $\pm$ 16.5	30.6 $\pm$ 12.5	29.5 $\pm$ 13.6
Median (IQR), days	48 (37–58)	47 (37–58)	30 (22–39)	28 (19–40)

Post-hoc analysis based on October 4, 2022 data lock point.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; N, number of participants; GA, gestational age; SD, standard deviation; IQR, interquartile range.

Table S23. RSV-A neutralizing titers and RSVPreF3-binding IgG concentrations in maternal participants and in infant cord blood (investigation cohort)

Timepoint	Preterm group (RSVPreF3-Mat)		Full-term group (RSVPreF3-Mat)	
	N	Value (95% CI)	N	Value (95% CI)
RSV-A neutralizing titers				
GMT, ED60				
Pre-vaccination	222	737.0 (657.9–825.7)	222	738.0 (658.1–827.5)
Day 31 post-vaccination	160	10,277.2 (9072.4–11,642.0)	216	9706.5 (8737.5–10,783.0)
Delivery	54	7253.1 (5534.2–9505.8)	69	6058.4 (4825.7 –7606.0)
Cord blood	194	7192.5 (6351.1–8145.3)	214	8510.7 (7464.4–9703.7)
GMR				
Day 31 post/pre-vaccination	160	13.5 (11.6–15.8)	216	13.3 (11.7–15.3)
Delivery/pre-vaccination	54	11.4 (8.4–15.4)	69	8.3 (6.6–10.5)
RSVPreF3-binding IgG (ELISA)				
GMC, EU/mL				
Pre-vaccination	222	6698.3 (6128.0–7321.6)	222	6463.0 (5896.0–7084.6)
Day 31 post-vaccination	161	126,130.8 (113,144.4–140,607.7)	215	114,688.0 (106,303.8–123,733.4)
Delivery	55	88,568.8 (71,259.7–110,082.4)	70	69,853.7 (56,755.1–85,975.4)

Cord blood	190	82,102.7 (73,672.6–91,497.3)	214	96,068.6 (87,942.6–104,945.4)
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GMR

Day 31 post/pre-vaccination	161	17.8 (15.5–20.4)	215	17.9 (16.0–19.9)
Delivery/pre-vaccination	55	13.9 (11.0–17.6)	70	12.0 (9.9–14.4)

Post-hoc analysis based on October 4, 2022 data lock point. These analyses were done on the investigation cohort, set up using a matched (1:1) case-cohort design, in which cases were women or infants with preterm births and controls were women or infants with term births (see this Appendix, “Statistical analyses” section). Analyses were done on maternal serum samples collected pre-vaccination, Day 31 post-vaccination, and at delivery, and on infant cord blood at birth. The similar GMRs on Day 31 indicated that humoral immune responses induced by RSVPreF3-Mat vaccination were in the same range in women who delivered preterm and in those who delivered at term, both in terms of RSV-A serum neutralizing titers and RSVPreF3-binding IgG levels. There was no adjustment for multiplicity for these analyses.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; N, number of participants in the investigation cohort with available results at the indicated timepoint (for GMRs, at the indicated post-vaccination timepoint and at baseline); CI, confidence interval; GMT, geometric mean titer; ED60, estimated dilution 60; GMR, geometric mean of individual ratios of titers or concentrations at the indicated post-vaccination timepoint over baseline; IgG, immunoglobulin G; ELISA, enzyme-linked immunosorbent assay; GMC, geometric mean concentration; EU, ELISA units.

Table S24. Western blot profiles for RSV vaccination and RSV infection in maternal participants (investigation cohort, preterm group)

Timepoint	Group	Tested samples	Vaccine profile	Infection profile	No change
		N	n (%)	n (%)	n (%)
Delivery	RSVPreF3-Mat	55	42 (76.4)	7 (12.7)	6 (10.9)
	Placebo	22	0 (0.0)	5 (22.7)	17 (77.3)
Cord blood	RSVPreF3-Mat	122	100 (82.0)	5 (4.1)	17 (13.9)
	Placebo	42	6 (14.3)	5 (11.9)	31 (73.8)
Delivery and cord blood	RSVPreF3-Mat	177	142 (80.2)	12 (6.8)	23 (13.0)
	Placebo	64	6 (9.4)	10 (15.6)	48 (75.0)

Post-hoc analysis based on February 6, 2023 data lock point. These analyses were done on the investigation cohort, set up using a matched (1:1) case-cohort design, in which cases were women with preterm births and controls were women with term births (see this Appendix, “Statistical analyses” section).

“Vaccine profile” was characterized by an increase in band intensity or identification of new bands that corresponded to the F surface protein between the pre-vaccination and delivery samples, and no change in intensity of bands corresponding to G or internal RSV proteins. “Infection profile” was characterized by an increase in band intensity or identification of new bands that corresponded to one or more internal RSV proteins, or to surface protein(s) and internal protein(s) between the pre-vaccination and delivery samples. “No change” was characterized by no change in RSV western blot pattern between the pre-vaccination and delivery samples. RSV infection between vaccination and delivery was observed more often in the placebo (15.6%) than in the RSVPreF3-Mat group (6.8%). Most delivery samples in the RSVPreF3-Mat group showed the “Vaccine profile”, while most samples in the placebo group showed “No change”. The western blot was not 100% sensitive or specific for a post-immunization response.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; N, number of tested samples; n (%), number (percentage) of samples with the indicated western blot profile.

Table S25. Multivariable analysis to identify possible risk factors of preterm birth

Risk factor	Odds ratio (95% CI)
RSVPreF3-Mat vs placebo	
RSVPreF3-Mat vs placebo for LMIC and no additional vaccine(s)	1.22 (0.74–1.99)
RSVPreF3-Mat vs placebo for LMIC and with additional vaccine(s)	1.96 (1.29–2.99)
RSVPreF3-Mat vs placebo for HIC and no additional vaccine(s)	1.03 (0.45–2.33)
RSVPreF3-Mat vs placebo for HIC and with additional vaccine(s)	1.03 (0.61–1.71)
Race	
Other ^a vs White	1.15 (0.76–1.75)
Asian vs White	1.70 (1.11–2.60)
Black vs White	1.44 (0.94–2.20)
Smoking/living with a smoker during current pregnancy	
Yes vs no	1.46 (1.08–1.97)
Interval between previous delivery/abortion and current pregnancy	
At least 12 months vs less than 12 months	0.92 (0.65–1.31)
History of preterm birth	
At least one preterm delivery vs none	2.74 (1.92–3.91)
Pre-eclampsia in current pregnancy	
Yes vs no	5.07 (3.38–7.59)
Study vaccine administered with additional vaccine(s) during pregnancy	
No additional vaccines vs with additional vaccine(s) for LMIC and placebo	2.30 (1.24–4.25)
No additional vaccines vs with additional vaccine(s) for LMIC and RSVPreF3-Mat	1.42 (0.93–2.19)
No additional vaccines vs with additional vaccines for HIC and placebo	1.30 (0.59–2.86)
No additional vaccines vs with additional vaccine(s) for HIC and RSVPreF3-Mat	1.30 (0.74–2.27)
Economic region	
LMIC vs HIC for placebo and no additional vaccines	1.86 (0.79–4.36)
LMIC vs HIC for RSVPreF3-Mat and no additional vaccines	2.20 (1.16–4.15)
LMIC vs HIC for placebo and with additional vaccines	1.05 (0.56–1.96)

Post-hoc analysis based on October 4, 2022 data lock point. Additional vaccines are vaccines other than the study vaccine administered any time during pregnancy.

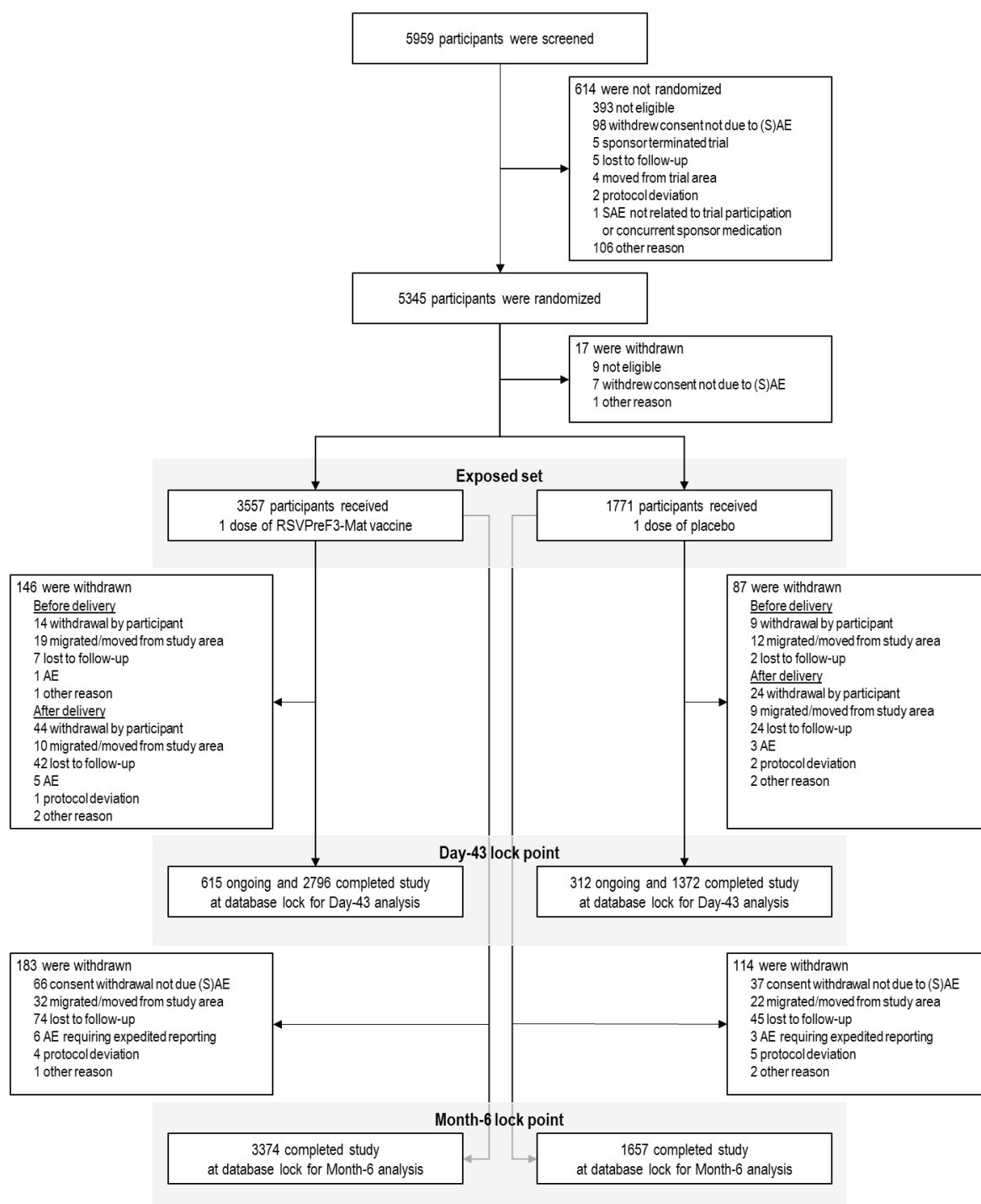
CI, confidence interval; RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; LMIC, low- and middle-income country; HIC, high-income country.

^aOther race includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and other; the latter were mostly mixed race.

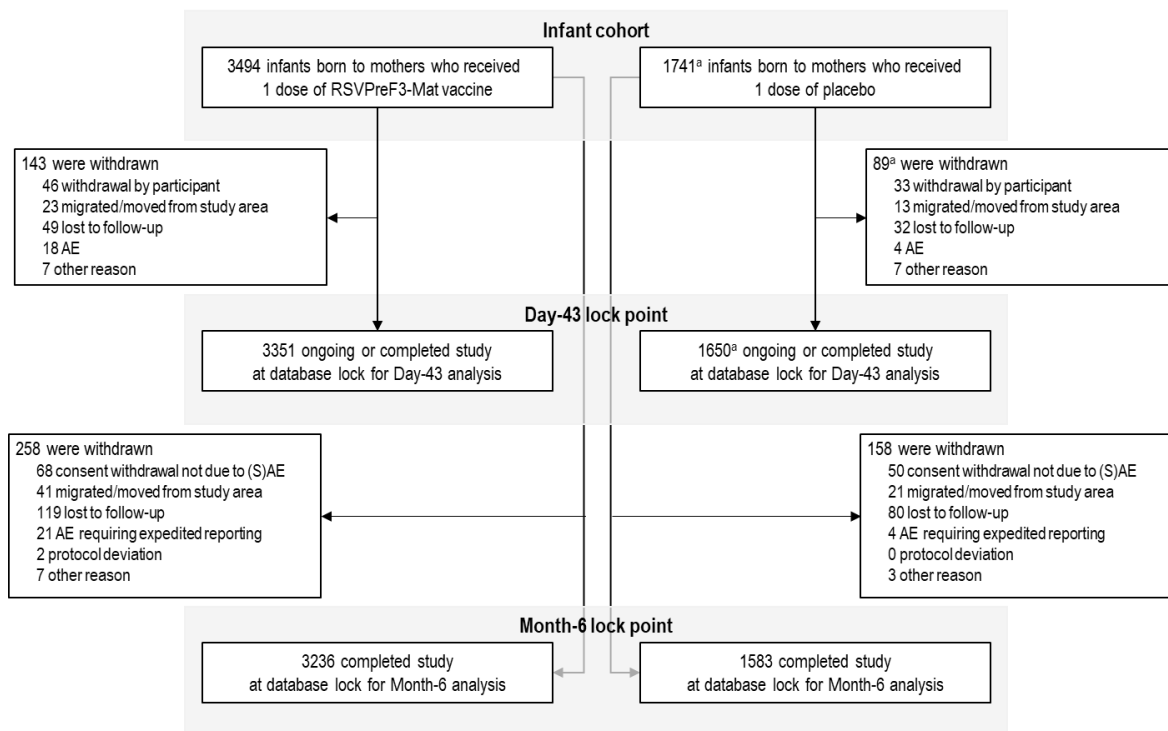
Supplementary figures

Figure S1. Maternal (A) and infant (B) participant flow diagram

A. Maternal participants



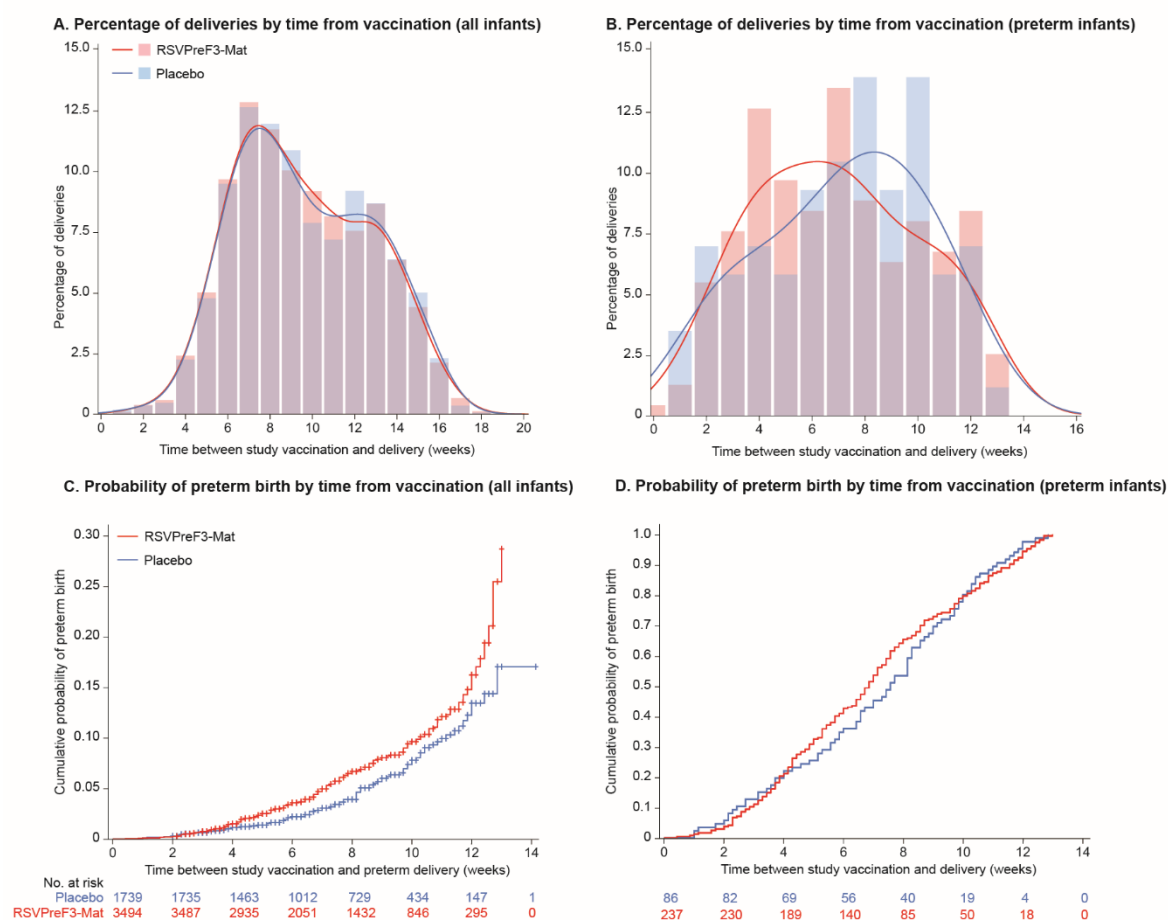
B. Infant participants



Database lock points were October 4, 2022 for the Day-43 post-birth analysis and October 5, 2023 for the Month-6 post-birth analysis. (S)AE, (serious) adverse event; RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine.

^aAt the time of the database lock for the Day-43 post-birth analysis, two infants in the placebo group were not yet included in the infant cohort due to missing information. The Day-43 post-birth analysis was therefore based on an infant cohort with 1739 infants in the placebo group instead of 1741.

Figure S2. Time between RSVPreF3-Mat or placebo administration and delivery among all infants (infant cohort) and preterm infants (infant cohort, preterm subgroup)

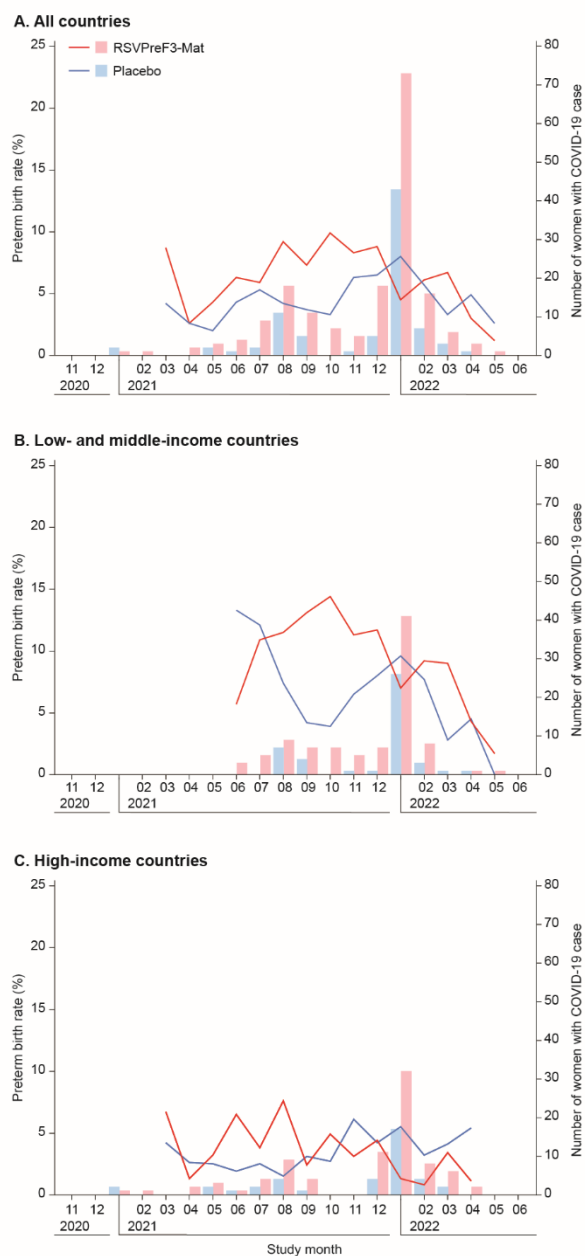


Post-hoc analysis based on October 4, 2022 data lock point. In panels A and B, bars (pink for RSVPreF3-Mat and blue for placebo) show the percentages of infants born by time interval (in weeks) between RSVPreF3-Mat or placebo administration and delivery among all infants (A) and among preterm infants (B); lines (red for RSVPreF3-Mat and blue for placebo) are corresponding smoothed density curves.

Panels C and D show the cumulative probability of preterm birth by time from vaccination (Kaplan-Meier plots for time from vaccination to preterm birth; term birth censored at 37 weeks in panel C, indicated by crosses) among all infants (C) and preterm infants (D).

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine.

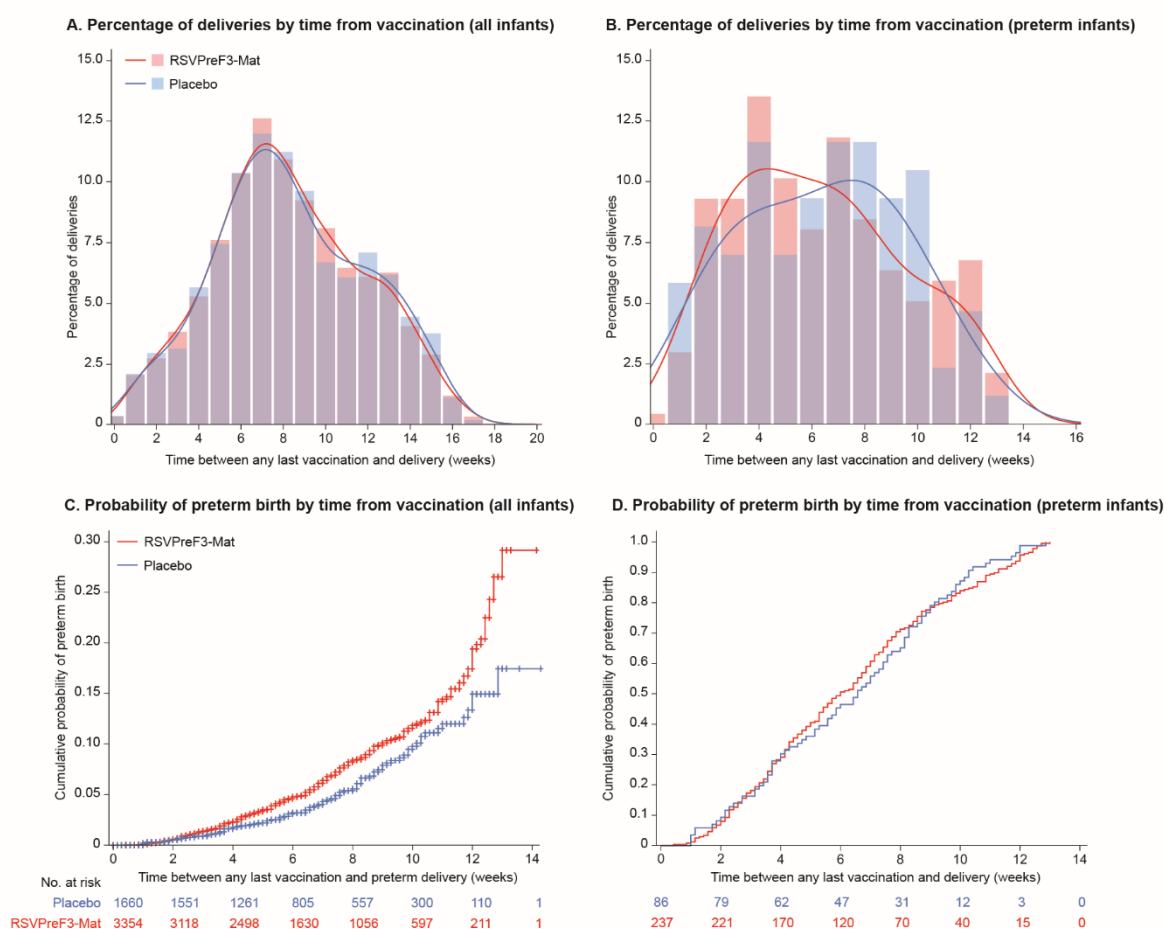
Figure S3. Monthly preterm birth rates relative to monthly reported COVID-19 cases in the trial (infant cohort)



Post-hoc analysis based on October 4, 2022 data lock point. Lines (red for RSVPreF3-Mat and blue for placebo) indicate the monthly (non-cumulative) rates of preterm births throughout the trial, for months with at least 50 deliveries in total. Bars (pink for RSVPreF3-Mat and blue for placebo) indicate the number of participants who reported a COVID-19 case during the second or third trimester of pregnancy for each indicated month during the trial (including suspected cases).

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine.

Figure S4. Time between any vaccination during pregnancy and delivery among all infants (infant cohort) and preterm infants (infant cohort, preterm subgroup)



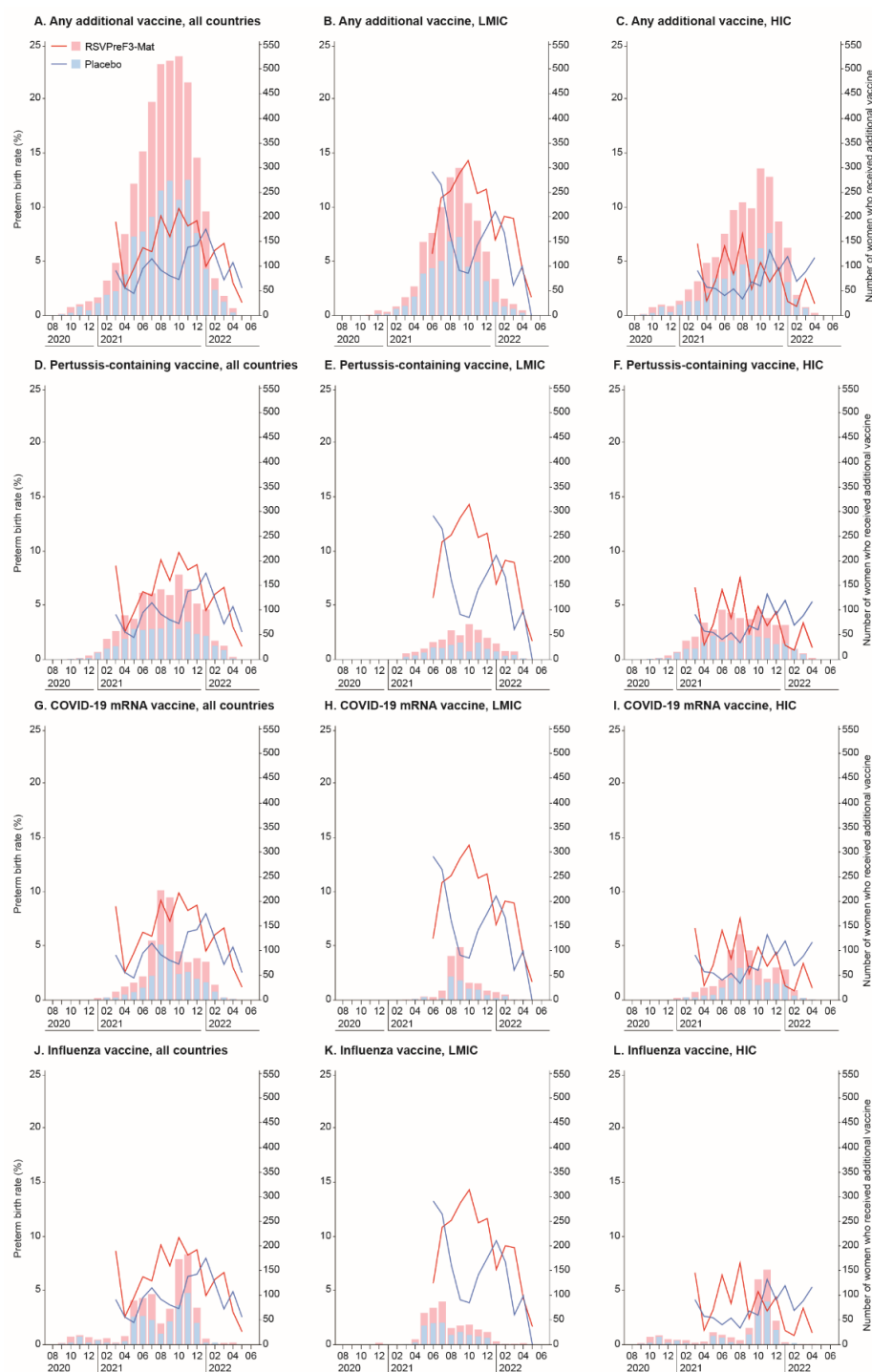
Post-hoc analysis based on October 4, 2022 data lock point. In panels A and B, bars (pink for RSVPreF3-Mat and blue for placebo) show the percentages of infants born by time interval (in weeks) between any last vaccination (RSVPreF3-Mat, placebo, or any other vaccine received during the second or third trimester of pregnancy) and delivery among all infants (A) and preterm infants (B); lines (red for RSVPreF3-Mat and blue for placebo) are corresponding smoothed density curves.

Panels C and D show the cumulative probability of preterm birth by time from any last vaccination (Kaplan-Meier plots for time from vaccination to preterm birth; term birth censored at 37 weeks in panel C, indicated by crosses) among all infants (C) and preterm infants (D). For panel C, 219 participants who received their last vaccine after 37 weeks' gestation and before delivery were excluded from this analysis.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine.

Note, when only considering vaccines other than RSVPreF3-Mat or placebo, time from last vaccination to delivery was also similar in the RSVPreF3-Mat group and the placebo group (data not shown).

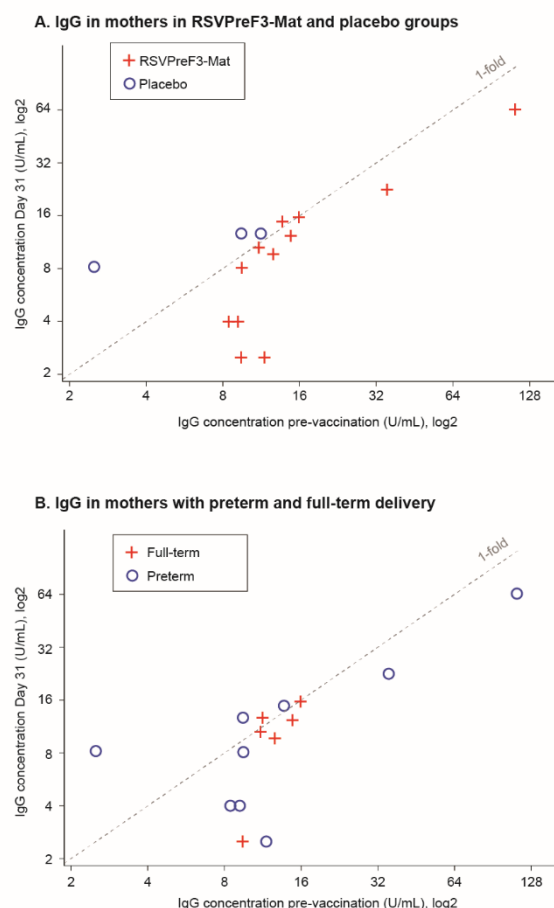
Figure S5. Monthly preterm birth rates relative to monthly numbers of participants receiving additional vaccines during the second or third trimester of pregnancy (infant cohort)



Post-hoc analysis based on October 4, 2022 data lock point. Lines (red for RSVPreF3-Mat and blue for placebo) indicate the monthly (non-cumulative) rates of preterm births throughout the trial, for months with at least 50

deliveries in total. Bars (pink for RSVPreF3-Mat and blue for placebo) indicate the number of maternal participants who received vaccines other than the study vaccine during the second or third trimester of pregnancy, with panels A–C plotting participants receiving any additional vaccine and panels D–L plotting participants receiving pertussis-containing (D–F), COVID-19 mRNA (G–I), or influenza vaccines (J–L). RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine; LMIC, low- and middle-income country; HIC, high-income country.

Figure S6. Annexin A5-binding IgG concentrations at Day 31 post-vaccination versus pre-vaccination (investigation cohort)



Post-hoc analysis based on September 5, 2022 data lock point. Graphs show individual results of annexin A5-binding immunoglobulin G (IgG) concentrations at Day 31 post-vaccination versus pre-vaccination in maternal participants in the RSVPreF3-Mat (red crosses) and placebo (blue circles) groups (panel A) and in maternal participants with a full-term delivery (≥ 37 weeks, red crosses) or preterm delivery (< 37 weeks, blue circles) (panel B). In total, 616 samples (444 in RSVPreF3-Mat and 172 in placebo) were tested pre-vaccination and 527 (378 in RSVPreF3-Mat and 149 in placebo) at Day 31 post-vaccination. Of these, 17 (15 in RSVPreF3-Mat, 2 in placebo; pre-vaccination) and 11 (8 in RSVPreF3-Mat, 3 in placebo; Day 31) were positive for annexin A5-binding IgG. In the RSVPreF3-Mat group, no participant had an increase in annexin A5-binding IgG (panel A, markers above the 1-fold line). Therefore, the low levels of annexin A5 in the vaccine are not associated with preterm birth.

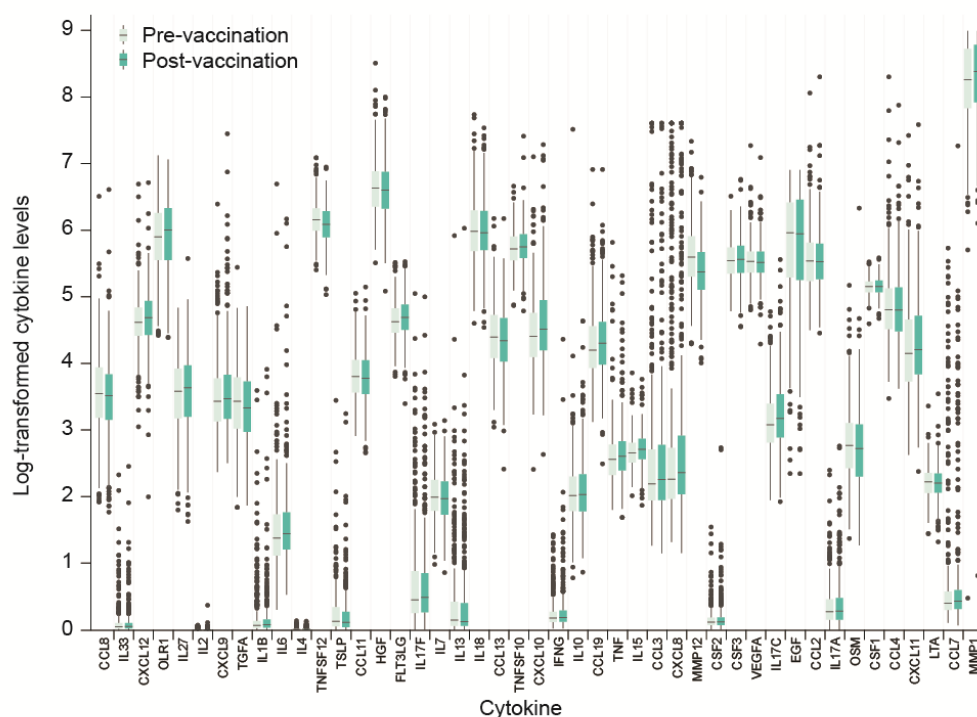
Seronegative values were included when at least one visit was positive. Seronegative values of <5 U/mL were converted to 2.5 U/mL, seronegative values of <8 U/mL were converted to 4 U/mL.

These analyses were done on the investigation cohort, set up using a matched (1:1) case-cohort design, in which cases were preterm births and controls were term births (see this Appendix, “Statistical analyses” section).

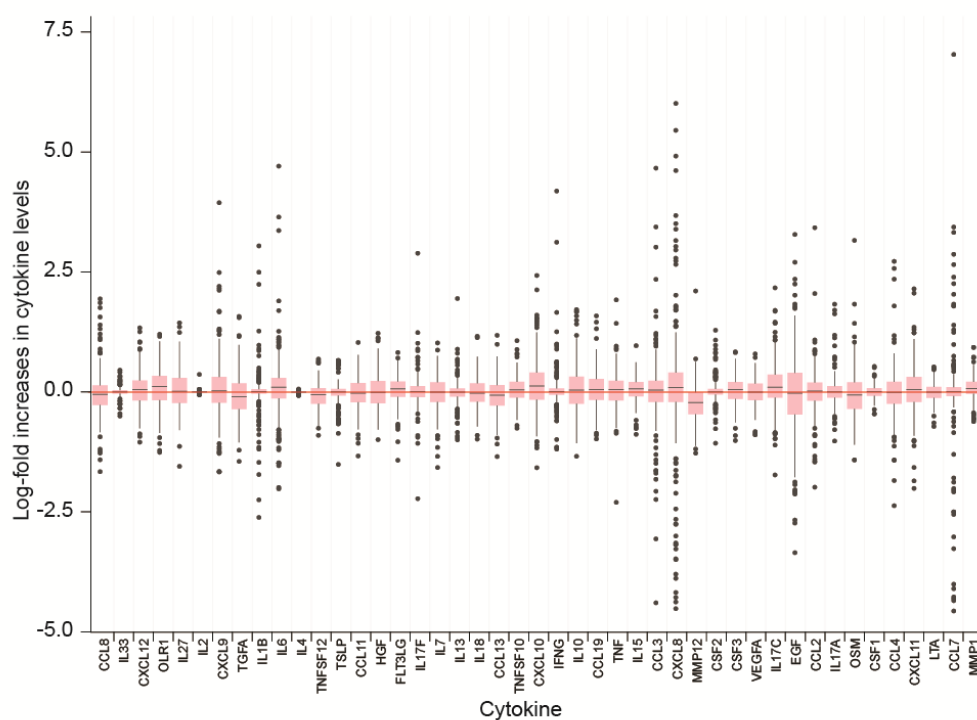
RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine.

Figure S7. Cytokine levels before and 1 month after RSVPreF3-Mat or placebo administration (investigation cohort)

A. Log-transformed cytokine levels (pooled placebo and RSVPreF3-Mat groups)



B. Log-fold increases in cytokine levels (RSVPreF3-Mat group)



Post-hoc analysis based on September 5, 2022 data lock point. Inflammatory markers (48 cytokines) were measured in serum samples taken pre-vaccination and on Day 31 post-vaccination from maternal participants in the investigation cohort, set up using a matched (1:1) case-cohort design, in which cases were women with preterm births and controls were women with term births (see this Appendix, “Statistical analyses” section). Panel A shows the log transformation of the pre-vaccination (lighter boxes) and Day 31 post-vaccination (darker boxes) cytokine levels (in pg/mL) for each cytokine for the pooled RSVPreF3-Mat and placebo groups. Panel B shows the log-fold-increase (Day 31 post-vaccination value/pre-vaccination value) in RSVPreF3-Mat-vaccinated women.

RSVPreF3-Mat, investigational maternal respiratory syncytial virus prefusion F protein-based vaccine.

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