ORIGINAL ARTICLE

Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants

B. Kampmann, S.A. Madhi, I. Munjal, E.A.F. Simões, B.A. Pahud, C. Llapur, J. Baker, G. Pérez Marc, D. Radley, E. Shittu, J. Glanternik, H. Snaggs, J. Baber, P. Zachariah, S.L. Barnabas, M. Fausett, T. Adam, N. Perreras, M.A. Van Houten, A. Kantele, L.-M. Huang, L.J. Bont, T. Otsuki, S.L. Vargas, J. Gullam, B. Tapiero, R.T. Stein, F.P. Polack, H.J. Zar, N.B. Staerke, M. Duron Padilla, P.C. Richmond, K. Koury, K. Schneider, E.V. Kalinina, D. Cooper, K.U. Jansen, A.S. Anderson, K.A. Swanson, W.C. Gruber, and A. Gurtman, for the MATISSE Study Group*

ABSTRACT

BACKGROUND

Whether vaccination during pregnancy could reduce the burden of respiratory syncytial virus (RSV)–associated lower respiratory tract illness in newborns and infants is uncertain.

METHODS

In this phase 3, double-blind trial conducted in 18 countries, we randomly assigned, in a 1:1 ratio, pregnant women at 24 through 36 weeks' gestation to receive a single intramuscular injection of 120 μg of a bivalent RSV prefusion F protein–based (RSVpreF) vaccine or placebo. The two primary efficacy end points were medically attended severe RSV-associated lower respiratory tract illness and medically attended RSV-associated lower respiratory tract illness in infants within 90, 120, 150, and 180 days after birth. A lower boundary of the confidence interval for vaccine efficacy (99.5% confidence interval [CI] at 90 days; 97.58% CI at later intervals) greater than 20% was considered to meet the success criterion for vaccine efficacy with respect to the primary end points.

RESULTS

At this prespecified interim analysis, the success criterion for vaccine efficacy was met with respect to one primary end point. Overall, 3682 maternal participants received vaccine and 3676 received placebo; 3570 and 3558 infants, respectively, were evaluated. Medically attended severe lower respiratory tract illness occurred within 90 days after birth in 6 infants of women in the vaccine group and 33 infants of women in the placebo group (vaccine efficacy, 81.8%; 99.5% CI, 40.6 to 96.3); 19 cases and 62 cases, respectively, occurred within 180 days after birth (vaccine efficacy, 69.4%; 97.58% CI, 44.3 to 84.1). Medically attended RSV-associated lower respiratory tract illness occurred within 90 days after birth in 24 infants of women in the vaccine group and 56 infants of women in the placebo group (vaccine efficacy, 57.1%; 99.5% CI, 14.7 to 79.8); these results did not meet the statistical success criterion. No safety signals were detected in maternal participants or in infants and toddlers up to 24 months of age. The incidences of adverse events reported within 1 month after injection or within 1 month after birth were similar in the vaccine group (13.8% of women and 37.1% of infants) and the placebo group (13.1% and 34.5%, respectively).

CONCLUSIONS

RSVpreF vaccine administered during pregnancy was effective against medically attended severe RSV-associated lower respiratory tract illness in infants, and no safety concerns were identified. (Funded by Pfizer; MATISSE ClinicalTrials.gov number, NCT04424316.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Munjal can be contacted at iona.munjal@pfizer.com or at Vaccine Research and Development, Pfizer, 401 N. Middletown Rd., Pearl River, NY 10965.

*The members of the MATISSE Study Group are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Kampmann, Madhi, and Munjal contributed equally to this article.

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Respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory tract illness and a leading cause of death in infants younger than 6 months of age, particularly in low- and middle-income countries.[1-3] Severe RSV-associated lower respiratory tract illness peaks in the first 2 to 3 months of life, despite the presence of naturally acquired maternal antibodies.[1,4-7] RSV typically spreads during winter epidemics in temperate climates and during rainy seasons in tropical regions,[1] although shifts in seasonality occurred during the coronavirus disease 2019 (Covid-19) pandemic.[8,9] In a recent European study, approximately 50% of hospitalizations for respiratory tract illness in children younger than 1 year of age were associated with RSV, and approximately 60% of these illnesses occurred in infants younger than 3 months of age.[10] In low-income countries, it is estimated that more than 80% of RSV-attributable deaths do not occur in the hospital.[3]

Maternal vaccination leads to transplacental transfer of increased levels of maternal antibodies to provide protection in infants immediately after birth and during the first months of life.[1,11-16] This strategy is used to protect infants from tetanus, pertussis, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and influenza,[11,17-19] although no vaccine has been licensed for use in pregnancy specifically to protect infants from these diseases, other than influenza in certain countries.[20] RSV prefusion F protein–based vaccine (RSVpreF) administered during the late second or third trimester of pregnancy may protect infants from severe RSV illness during the first few months of life; this would be particularly important in low- and middle-income countries, where the burden of RSV-associated lower respiratory tract illness is highest.[3]

Despite more than 50 years of development efforts,[14] no RSV vaccine has been licensed. The prefusion form of the RSV fusion (F) glycoprotein (preF) is a major target of potent virus neutralizing antibodies and a key vaccine antigen.[21,22] The investigational bivalent RSVpreF vaccine contains stabilized preF glycoproteins from the two main cocirculating antigenic subgroups (RSV A and RSV B).[23,24] In a phase 2b, proof-of-concept trial, RSVpreF vaccine administered to women in the late second or third trimester of pregnancy had an acceptable safety profile and elicited neutralizing antibody responses that were efficiently transferred to infants. That trial provided evidence of the efficacy of RSVpreF vaccine when administered to pregnant women to prevent RSV-associated lower respiratory tract illness in infants.[25] Recently, an interim analysis of another phase 3 trial (RSV Vaccine Efficacy Study in Older Adults Immunized against RSV Disease [RENOIR]) showed that active vaccination with RSVpreF in persons who were at least 60 years of age prevented RSV-associated lower respiratory tract illness.[26] Here, we report the results of a phase 3 trial (Maternal Immunization Study for Safety and Efficacy [MATISSE]) evaluating the efficacy and safety of maternal RSVpreF vaccination in preventing RSV-associated lower respiratory tract illness in infants.

METHODS

PARTICIPANTS AND TRIAL OVERSIGHT

This phase 3, double-blind, randomized, placebo-controlled trial that was conducted in 18 countries over four RSV seasons (two in the Northern Hemisphere and two in the Southern Hemisphere) evaluated the efficacy and safety of maternal RSVpreF immunization against medically attended RSV-associated lower respiratory tract illness in infants followed for 1 to 2 years. Eligible participants were healthy women, 49 years of age or younger, at 24 through 36 weeks' gestation on the day of planned injection, with an uncomplicated, singleton pregnancy and no known increased risk of pregnancy complications. Additional eligibility criteria and information regarding ethical trial conduct are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. Further details are provided in the protocol (available at NEJM.org). Eligible women were randomly assigned, in a 1:1 ratio, to receive a single intramuscular injection of 120 μg of RSVpreF vaccine (60 μg each of RSV A and RSV B antigens) or placebo.

The protocol was approved by the ethics committee at each site, and all the participants provided written informed consent. The sponsor (Pfizer) designed and conducted the trial and was responsible for data collection, analysis, and interpretation. The first draft of the manuscript was written by medical writers (paid by Pfizer) under the direction of the authors. Pfizer manufactured RSVpreF vaccine and placebo. All the

data were available to the authors. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

EFFICACY END POINTS

The two primary efficacy end points were medically attended severe RSV-associated lower respiratory tract illness and medically attended RSV-associated lower respiratory tract illness in infants within 90, 120, 150, and 180 days after birth. Secondary end points included medically attended RSV-associated lower respiratory tract illness, RSV-associated hospitalization, and medically attended lower respiratory tract illness of any cause, all occurring within 360 days after birth. Exploratory end points included medically attended RSV-associated respiratory tract illness and medically attended RSV-associated lower respiratory tract illness due to RSV A or RSV B. Table S1 in the Supplementary Appendix provides further details regarding case definitions and the role of the end-point adjudication committee, which confirmed that each case met prespecified trial definition criteria, including whether criteria were met in the subgroup of participants with medically attended severe RSV-associated lower respiratory tract illness.

Surveillance for respiratory tract illness in infants started at 72 hours after birth and continued through 12 months of age (24 months of age in those enrolled during the first trial year). Nasal swabs for reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays were obtained at any medically attended visit for respiratory infection. We conducted surveillance for medically attended respiratory tract illnesses in infants who were 6 months of age or younger through weekly contact with the infants' parents or legal guardians.

SAFETY END POINTS

The primary safety end points were reactogenicity and adverse events in the maternal participants and adverse events and newly diagnosed chronic medical conditions in the infants. An external data monitoring committee was responsible for ongoing safety data monitoring. We observed maternal participants for at least 30 minutes after injection to detect acute reactions. Prespecified local reactions and systemic events, including fever, were recorded by means of an electronic diary for 7 days after vaccination; systemic events at baseline (≤7 days before vaccination) were also recorded. For each maternal participant, including her fetus, data on adverse events were collected from the time of informed consent to 1 month after injection, and data on serious adverse events were collected from the time of informed consent through 6 months after delivery.

Safety end points in the infant participants included adverse events from birth to 1 month of age. Additional safety end points were serious adverse events and newly diagnosed chronic medical conditions from birth through 12 months of age (birth through 24 months of age in infants enrolled during the first trial year).

Adverse events of special interest were preterm birth or delivery (birth at <37 weeks' gestation), low birth weight (≤2500 g), developmental delay (assessed according to the standard of care), or a positive RT-PCR–based or antigen-based SARS-CoV-2 test. Extremely preterm birth (<28 weeks' gestation), extremely low birth weight (≤1000 g), and congenital anomalies were reported as serious adverse events.

STATISTICAL ANALYSIS

The sample size was selected on the basis of the number of maternal participants needed in order to accrue the prespecified number of cases of lower respiratory tract illness in infants. Vaccine efficacy with respect to either of the two primary end points was sufficient to indicate trial success. The evaluable population consisted of all infant participants who were eligible, were born to the maternal participants who had received the randomly assigned vaccine or placebo at least 14 days before delivery, did not receive palivizumab or another monoclonal antibody targeting RSV, had no major protocol violations, and had not received transfusions (of any blood products) of more than 20 ml per kilogram of body weight within 180 days after birth (Table S2). The safety population consisted of all maternal participants who had undergone randomization and received vaccine or placebo and all the infant participants who were born to those maternal participants. We calculated that 124 cases of medically attended RSV-associated lower respiratory tract illness occurring within 90 days after birth in the evaluable population would give the trial at least 90% power to reject the

null hypothesis, if true vaccine efficacy against medically attended RSV-associated lower respiratory tract illness was assumed to be 60%.

As prespecified in the protocol, the data monitoring committee could conduct the first interim analysis after the occurrence of at least 43 cases of medically attended RSV-associated lower respiratory tract illness within 90 days after birth and the second interim analysis after the occurrence of at least 62 cases. Analysis of all the remaining efficacy end points could be conducted if the interim analysis showed that the success criterion for vaccine efficacy with respect to either primary end point through 90 days had been met. The type I error rate was strongly controlled across the multiple primary and secondary end points, with accounting for the two interim analyses. The Supplementary Appendix provides further details on sample-size determination, imputation of missing data, and additional statistical considerations.

Vaccine efficacy, estimated with the use of the binomial distribution of the number of cases of disease in the RSV vaccine group and given the total number of cases in both groups,[27] was defined as $(1-\mathrm{RR})\times 100$, where RR is the relative risk of the end point of interest based on the incidence in the vaccine group as compared with the placebo group. A lower boundary of the confidence interval that was greater than 20% was considered to meet the success criterion for vaccine efficacy with respect to the primary end points, and a lower boundary of 0% was considered to meet the success criterion for vaccine efficacy with respect to the secondary end points; these criteria were agreed on with regulatory agencies and are typical of requirements for some novel vaccines.

The probability of primary-end-point coverage for confidence intervals was 99.5% at 90 days (determined by means of an alpha-spending function and a Bonferroni procedure) and 97.58% at later intervals (based on a two-sided alpha level of 0.0483 and a Bonferroni procedure). Confidence intervals for the secondary end points were adjusted with the use of the Bonferroni procedure and accounted for results with respect to the primary end points. Exploratory efficacy end points had no prespecified success criterion and are presented with unadjusted 95% confidence intervals; these should not be used to draw conclusions about vaccine efficacy for these end points. All observations after trial discontinuation or protocol violation were censored. The Supplementary Appendix provides further details on considerations for determination of vaccine efficacy.

Figure 1 (facing page). Enrollment, Randomization, Administration of Vaccine or Placebo, and Follow-up.

Shown are data on maternal participants (Panel A) and infant participants (Panel B) at the data-cutoff date for safety (September 2, 2022). Among infant participants who were enrolled from the maternal vaccine group during the first year of the trial, 1971 were enrolled with a planned follow-up of 24 months and 1599 were enrolled with a planned follow-up of 12 months. Trial completion in infants refers to whether they completed 12 or 24 months of follow-up as assigned. One maternal participant and 2 infant participants did not meet eligibility criteria and were not included in the safety population. Among infant participants who were enrolled from the maternal placebo group during the first year of the trial, 1967 were enrolled with a planned follow-up of 24 months and 1591 were enrolled with a planned follow-up of 12 months. The trial is ongoing; at the data-cutoff date, some participants had not yet completed planned follow-up visits. RSVpreF denotes respiratory syncytial virus prefusion F protein–based vaccine.

For analyses of the safety end points, point estimates and exact two-sided 95% confidence intervals (calculated with the use of the Clopper–Pearson method) were based on the percentage of participants reporting each event in each trial group. Event rates were considered to be similar (i.e., no evidence of a difference) in the two groups if the unadjusted 95% confidence interval for the risk difference included zero. Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 25.0. Missing electronic diary data were not imputed.

RESULTS

PARTICIPANTS

From June 17, 2020, through October 2, 2022, a total of 7392 women underwent randomization and 7358 received either RSVpreF vaccine (3682 participants) or placebo (3676 participants). A total of 3578 women who received RSVpreF vaccine and 3570 of those who received placebo had given birth and 2840 and 2843, respectively, had completed the trial at the time of this analysis (Fig. 1). Overall, 3570 infants born to mothers who had received RSVpreF vaccine and 3558 born to those who had received placebo were

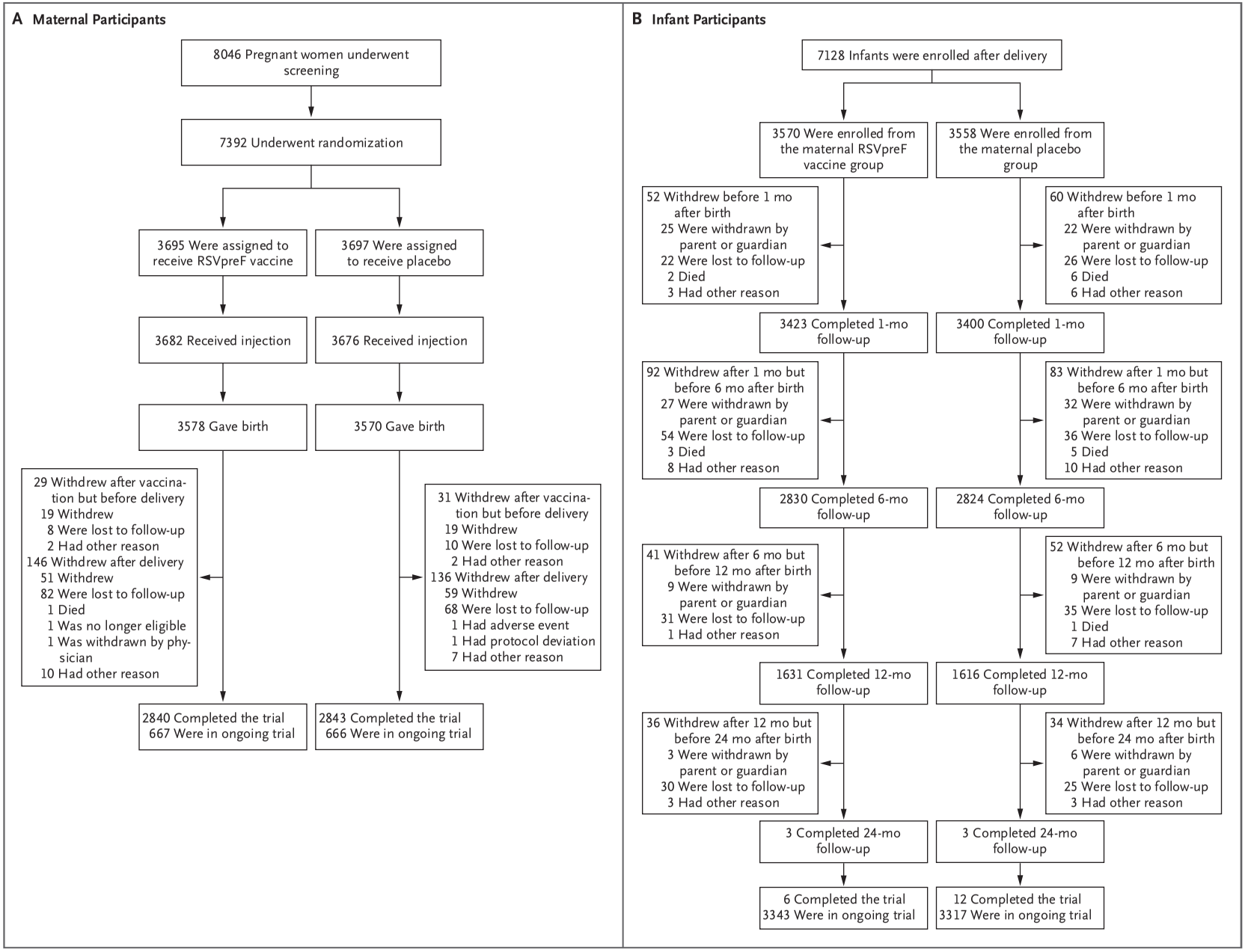

A Maternal Participants
8046 Pregnant women underwent screening
7392 Underwent randomization
3695 Were assigned to receive RSVpreF vaccine
3697 Were assigned to receive placebo
3682 Received injection
3676 Received injection
3578 Gave birth
3570 Gave birth
29 Withdrew after vaccination but before delivery
19 Withdrew
8 Were lost to follow-up
2 Had other reason
146 Withdrew after delivery
51 Withdrew
82 Were lost to follow-up
1 Died
1 Was no longer eligible
1 Was withdrawn by physician
10 Had other reason
31 Withdrew after vaccination but before delivery
19 Withdrew
10 Were lost to follow-up
2 Had other reason
136 Withdrew after delivery
59 Withdrew
68 Were lost to follow-up
1 Had adverse event
1 Had protocol deviation
7 Had other reason
2840 Completed the trial
667 Were in ongoing trial
2843 Completed the trial
666 Were in ongoing trial
B Infant Participants
7128 Infants were enrolled after delivery
3570 Were enrolled from the maternal RSVpreF vaccine group
3558 Were enrolled from the maternal placebo group
52 Withdrew before 1 mo after birth
25 Were withdrawn by parent or guardian
22 Were lost to follow-up
2 Died
3 Had other reason
60 Withdrew before 1 mo after birth
22 Were withdrawn by parent or guardian
26 Were lost to follow-up
6 Died
6 Had other reason
3423 Completed 1-mo follow-up
3400 Completed 1-mo follow-up
92 Withdrew after 1 mo but before 6 mo after birth
27 Were withdrawn by parent or guardian
54 Were lost to follow-up
3 Died
8 Had other reason
83 Withdrew after 1 mo but before 6 mo after birth
32 Were withdrawn by parent or guardian
36 Were lost to follow-up
5 Died
10 Had other reason
2830 Completed 6-mo follow-up
2824 Completed 6-mo follow-up
41 Withdrew after 6 mo but before 12 mo after birth
9 Were withdrawn by parent or guardian
31 Were lost to follow-up
1 Had other reason
52 Withdrew after 6 mo but before 12 mo after birth
9 Were withdrawn by parent or guardian
35 Were lost to follow-up
1 Died
7 Had other reason
1631 Completed 12-mo follow-up
1616 Completed 12-mo follow-up
36 Withdrew after 12 mo but before 24 mo after birth
3 Were withdrawn by parent or guardian
30 Were lost to follow-up
3 Had other reason
34 Withdrew after 12 mo but before 24 mo after birth
6 Were withdrawn by parent or guardian
25 Were lost to follow-up
3 Had other reason
3 Completed 24-mo follow-up
3 Completed 24-mo follow-up
6 Completed the trial
3343 Were in ongoing trial
12 Completed the trial
3317 Were in ongoing trial

Table 1. Demographic and Clinical Characteristics of the Maternal and Infant Participants in the Safety Population.*

Characteristic	RSVpreF Vaccine	Placebo	Total
Maternal participants			
Age at injection — yr			
Mean	29.1±5.6	29.0±5.7	29.0±5.7
Median (range)	29 (16–45)	29 (14–47)	29 (14–47)
Gestation at injection — wk			
Mean	30.8±3.5	30.8±3.6	30.8±3.5
Median (range)	31.3 (24.0–36.6)	31.3 (24.0–36.9)	31.3 (24.0–36.9)
Race or ethnic group — no./total no. (%)†			
White	2383/3682 (64.7)	2365/3675 (64.4)	4748/7357 (64.5)
Black	720/3682 (19.6)	723/3675 (19.7)	1443/7357 (19.6)
Asian	454/3682 (12.3)	464/3675 (12.6)	918/7357 (12.5)
Multiracial	30/3682 (0.8)	21/3675 (0.6)	51/7357 (0.7)
Race not reported	41/3682 (1.1)	45/3675 (1.2)	86/7357 (1.2)
Race unknown	7/3682 (0.2)	8/3675 (0.2)	15/7357 (0.2)
Hispanic or Latinx	1049/3682 (28.5)	1075/3675 (29.3)	2124/7357 (28.9)
Not Hispanic or Latinx	2603/3682 (70.7)	2567/3675 (69.8)	5170/7357 (70.3)
American Indian or Alaska Native	38/3682 (1.0)	37/3675 (1.0)	75/7357 (1.0)
Native Hawaiian or other Pacific Islander	9/3682 (0.2)	12/3675 (0.3)	21/7357 (0.3)
Ethnic group not reported or unknown	30/3682 (0.8)	33/3675 (0.9)	63/7357 (0.9)
Infant participants			
Sex — no./total no. (%)			
Male	1816/3568 (50.9)	1793/3558 (50.4)	3609/7126 (50.6)
Female	1752/3568 (49.1)	1765/3558 (49.6)	3517/7126 (49.4)
Gestational age at birth — no./total no. (%)			
24 to <28 wk	1/3568 (<0.1)	1/3558 (<0.1)	2/7126 (<0.1)
28 to <34 wk	20/3568 (0.6)	11/3558 (0.3)	31/7126 (0.4)
34 to <37 wk	180/3568 (5.0)	157/3558 (4.4)	337/7126 (4.7)
37 to <42 wk	3343/3568 (93.7)	3356/3558 (94.3)	6699/7126 (94.0)
≥42 wk	21/3568 (0.6)	30/3558 (0.8)	51/7126 (0.7)
Apgar score, 5 min			
<4 — no./total no. (%)	8/3528 (0.2)	5/3517 (0.1)	13/7045 (0.2)
4 to <7 — no./total no. (%)	29/3528 (0.8)	27/3517 (0.8)	56/7045 (0.8)
7 to 10 — no./total no. (%)	3491/3528 (99.0)	3485/3517 (99.1)	6976/7045 (99.0)
Median (range)	9 (1–10)	9 (2–10)	9 (1–10)
Outcome — no./total no. (%)			
Normal	3172/3568 (89.9)	3149/3558 (88.5)	6321/7126 (88.7)
Congenital malformation or anomaly	174/3568 (4.9)	203/3558 (5.7)	377/7126 (5.3)
Other neonatal problems	219/3568 (6.1)	200/3558 (5.6)	419/7126 (5.9)
Extremely low birth weight, ≤1000 g — no./total no. (%)	1/3568 (<0.1)	2/3558 (<0.1)	3/7126 (<0.1)
Very low birth weight, >1000 to 1500 g — no./total no. (%)‡	3/3568 (<0.1)	6/3558 (0.2)	9/7126 (0.1)
Low birth weight, >1500 to 2500 g — no./total no. (%)‡	177/3568 (5.0)	147/3558 (4.1)	324/7126 (4.5)
Developmental delay — no./total no. (%)‡	12/3568 (0.3)	10/3558 (0.3)	22/7126 (0.3)

* Plus–minus values are means ±SD. The safety population consisted of all the maternal participants who underwent randomization and received vaccine or placebo and all their infants (except one maternal infant and two infant participants, who did not meet eligibility criteria). Percentages may not total 100 because of rounding. RSVpreF denotes respiratory syncytial virus prefusion F protein–based vaccine.
† Race or ethnic group was reported by the maternal participants.
‡ This outcome was an adverse event of special interest reported at any time after birth during the trial period.

evaluated. At the time of this analysis, data from 85% of the scheduled follow-up through 180 days were available, with 1-month, 6-month, and 12-month follow-up completed by 6823 infants (96%), 5654 infants (79%), and 3247 infants (46%), respectively.

Demographic characteristics were broadly similar across the trial groups (Table 1), and the trial participants were representative of the population at risk for RSV-related illness (Table S3). Maternal participants were enrolled in 18 countries; the countries with the highest enrollment were the United States (45%), South Africa (13%), Argentina (12%), and Japan (6%) (Table S4). Among the maternal participants, 64% were White, 20% Black, and 12% Asian; 29% were Hispanic or Latinx. At the time of injection, the median age of the women was 29 years (range, 14 to 47) and the median gestation was 31.3 weeks (range, 24.0 to 36.9). Among the infant participants, 51% were male and 94% were born at term (37 to <42 weeks). At the time of the analysis, adherence to the collection of nasal swabs at visits to assess for medically attended respiratory tract illness was greater than 95%, and in 927 of the 971 visits (including 794 cases of medically attended lower respiratory tract illnesses of any cause within 180 days after birth), infants met the criteria for medically attended lower respiratory tract illness of any cause.

EFFICACY

This prespecified interim analysis of efficacy was conducted in October 2022. The data-cutoff date for efficacy was September 30, and the data-cutoff date for safety was September 2. At this analysis, 80 evaluable cases of medically attended RSV-associated lower respiratory tract illness within 90 days after birth had accrued (174 cases within 180 days), including 39 evaluable cases of medically attended severe RSV-associated lower respiratory tract illness within 90 days after birth (81 cases within 180 days). The data monitoring committee recommended stopping the trial for efficacy because the success criterion for vaccine efficacy was met for one of the two primary efficacy end points. An earlier interim analysis is described in the Supplementary Appendix.

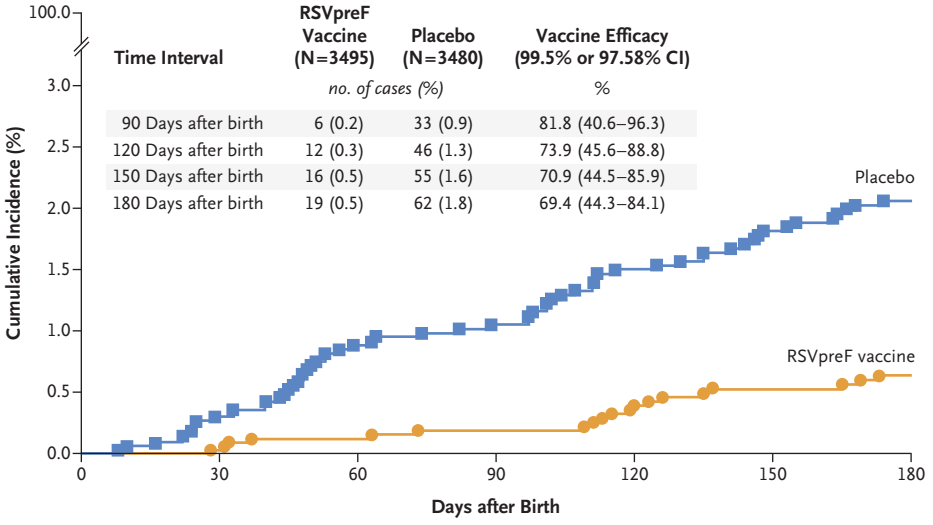
On the basis of case accrual through the data-cutoff date, the efficacy of RSVpreF vaccine met the statistical success criterion (lower boundary of the confidence interval >20%) for a decrease in the incidence of medically attended severe RSV-associated lower respiratory tract illness among infants through 180 days after birth (Fig. 2A). Within 90 days after birth, 6 infants of mothers in the vaccine group and 33 infants of those in the placebo group had medically attended severe RSV-associated lower respiratory tract illness (vaccine efficacy, 81.8%; 99.5% confidence interval [CI], 40.6 to 96.3); within 180 days after birth, there were 19 cases and 62 cases, respectively (vaccine efficacy, 69.4%; 97.58% CI, 44.3 to 84.1). In a sensitivity analysis (Table S5), we used multiple imputation to examine the effect of missing laboratory (nasal swab) results under various assumptions, some of which were unfavorable to the vaccine. In each group, data were missing for 3 additional infants who would have qualified as having cases of medically attended severe RSV-associated lower respiratory tract illness within 90 days after birth. Imputation showed that missing results had no effect on the conclusions.

Within 90 days after birth, 24 infants of mothers in the vaccine group and 56 infants of those in the placebo group had medically attended RSV-associated lower respiratory tract illness (vaccine efficacy, 57.1%; 99.5% CI, 14.7 to 79.8). The statistical success criterion for this end point (lower boundary of the confidence interval >20%) was not met. Within 180 days after birth, 57 infants of mothers in the vaccine group and 117 infants of those in the placebo group had medically attended RSV-associated lower respiratory tract illness (vaccine efficacy, 51.3%; 97.58% CI, 29.4 to 66.8) (Fig. 2B).

When medically attended RSV-associated lower respiratory tract illness within cumulative intervals beyond 180 days after birth was evaluated as a secondary end point with a lower boundary of the confidence interval of 0%, the incidence of this illness was lower in the vaccine group than in the placebo group at all time points from 0 to 210 days and from 0 to 360 days after birth (Table S6). There were fewer cases of RSV-associated hospitalization through 180 days of age among infants of mothers in the vaccine group than among those of mothers in the placebo group (lower boundary of the confidence interval >0%). Vaccine efficacy was 67.7% (99.17% CI, 15.9 to 89.5) with respect to RSV-associated hospitalization within 90 days after birth, and it

A Medically Attended Severe RSV-Associated Lower Respiratory Tract Illness

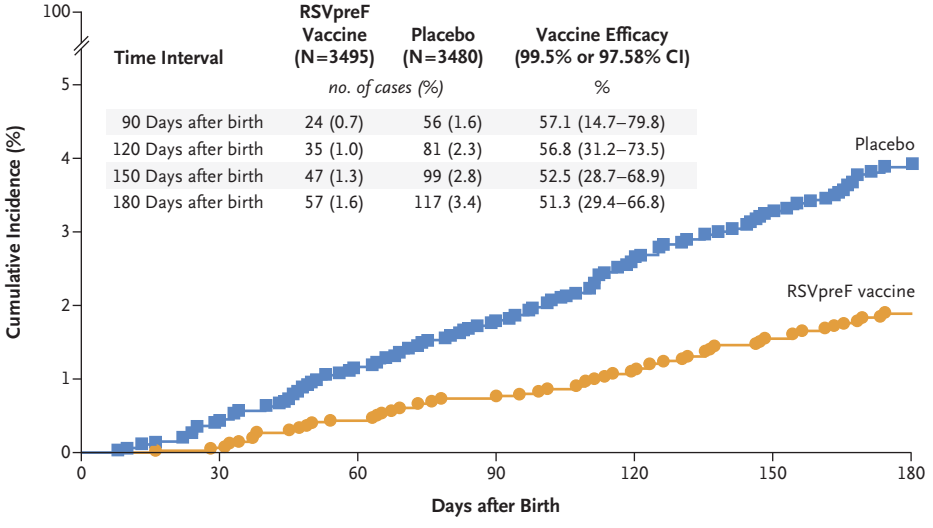
Time Interval	RSVpreF Vaccine (N=3495)	Placebo (N=3480)	Vaccine Efficacy (99.5% or 97.58% CI)
	no. of cases (%)		%
90 Days after birth	6 (0.2)	33 (0.9)	81.8 (40.6–96.3)
120 Days after birth	12 (0.3)	46 (1.3)	73.9 (45.6–88.8)
150 Days after birth	16 (0.5)	55 (1.6)	70.9 (44.5–85.9)
180 Days after birth	19 (0.5)	62 (1.8)	69.4 (44.3–84.1)



No. at Risk							
Placebo	3480	3292	2973	2899	2833	2776	2749
RSVpreF vaccine	3495	3349	3042	2981	2916	2867	2820

B Medically Attended RSV-Associated Lower Respiratory Tract Illness

Time Interval	RSVpreF Vaccine (N=3495)	Placebo (N=3480)	Vaccine Efficacy (99.5% or 97.58% CI)
	no. of cases (%)		%
90 Days after birth	24 (0.7)	56 (1.6)	57.1 (14.7–79.8)
120 Days after birth	35 (1.0)	81 (2.3)	56.8 (31.2–73.5)
150 Days after birth	47 (1.3)	99 (2.8)	52.5 (28.7–68.9)
180 Days after birth	57 (1.6)	117 (3.4)	51.3 (29.4–66.8)



No. at Risk							
Placebo	3480	3288	2964	2879	2804	2738	2700
RSVpreF vaccine	3495	3348	3035	2968	2898	2845	2792

was 56.8% (99.17% CI, 10.1 to 80.7) with respect to RSV-associated hospitalization within 180 days after birth (Table S7). RSVpreF vaccination did not prevent medically attended lower respiratory tract illness from any cause within 90 days after birth (vaccine efficacy, 7.0%; 99.17% CI, −22.3 to 29.3) (Table S8). In an exploratory analysis, vaccine efficacy against medically attended RSV-associated respiratory tract illness was 39.1% (95% CI, 16.7 to 55.7) within 90 days after birth and 37.9% (95% CI, 24.0 to 49.5) within 180 days after birth (Table S9). Additional exploratory and sensitivity analyses are provided in Table S10.

SAFETY

Most reactogenicity events in maternal participants were mild to moderate in severity (Fig. 3). Local reactions were more commonly reported

Figure 2 (facing page). Vaccine Efficacy.

Panel A shows vaccine efficacy with respect to medically attended severe RSV-associated lower respiratory tract illness and Panel B shows vaccine efficacy with respect to medically attended RSV-associated lower respiratory tract illness occurring within 180 days after birth in infant participants. Data are for the evaluable efficacy population. Cases of RSV-associated illness of any severity were confirmed by the end-point adjudication committee. Vaccine efficacy was calculated as 1 − (P/[1 − P]), where P is the number of cases of illness in the RSVpreF group divided by the total number of cases of illness. At 90 days, we used 99.5% confidence intervals (CIs) (determined by the alpha-spending function and adjusted with the use of the Bonferroni procedure), and at later intervals, we used 97.58% CIs (based on a two-sided alpha level of 0.0483 adjusted with the use of the Bonferroni procedure). The criterion for vaccine efficacy with respect to the primary end points was a lower boundary of the confidence interval greater than 20%. Infants were considered to have medically attended RSV-associated lower respiratory tract illness if they had a medically attended visit for a respiratory tract illness and a reverse-transcriptase–polymerase-chain-reaction assay or nucleic acid amplification test that was positive for RSV, as well as fast breathing (respiratory rate ≥60 breaths per minute in infants <2 months of age [<60 days of age], ≥50 breaths per minute in infants 2 to <12 months of age, or ≥40 breaths per minute in infants 12 to 24 months of age), oxygen saturation as measured by pulse oximetry (Spo_2) of less than 95%, or chest wall indrawing. Infants were considered to have medically attended severe RSV-associated lower respiratory tract illness if they had a medically attended visit for a respiratory tract illness and an RSV-positive test, as well as very fast breathing (respiratory rate ≥70 breaths per minute in infants <2 months of age [<60 days of age], ≥60 breaths per minute in infants 2 to <12 months of age, or ≥50 breaths per minute in infants 12 to 24 months of age), Spo_2 of less than 93%, use of a high-flow nasal cannula or mechanical ventilation, admission to an intensive care unit for more than 4 hours, or lack of response or unconsciousness. Each square or circle represents one case of illness.

in recipients of the RSVpreF vaccine than in recipients of placebo; the most common was injection-site pain (in 41% of participants in the vaccine group and 10% of those in the placebo group) (Fig. 3A). The percentages of maternal participants who reported systemic events within 7 days after injection were similar in the two groups, apart from muscle pain and headache, which were reported more frequently by recipients of the vaccine (muscle pain in 27% of the vaccine recipients vs. 17% of the placebo recipients, and headache in 31% vs. 28%, respectively) (Fig. 3B).

The percentages of maternal participants with any adverse events reported within 1 month after injection were similar in the vaccine group (13.8%) and the placebo group (13.1%) (Fig. 4A and Table S11). The percentages of infant participants with any adverse events reported within 1 month after birth were 37.1% in the vaccine group and 34.5% in the placebo group (Fig. 4A and Table S12). Among the infant participants, the incidences of adverse events of special interest (Fig. 4B) and newly diagnosed chronic medical conditions (Fig. S1) were similar in the two groups. Among maternal participants, the incidences of serious adverse events through 6 months after injection were similar in the two groups; the most frequent were preeclampsia (in 1.8% of participants in the vaccine group and 1.4% of those in the placebo group) and fetal distress syndrome (in 1.8% and 1.6%, respectively) (Fig. 4C and Table S13). The incidences of premature delivery were similar in the two groups (28 cases [0.8%] in the vaccine group and 23 cases [0.6%] in the placebo group). Serious adverse events in four RSVpreF vaccine recipients (pain in an arm followed by bilateral lower-extremity pain, premature labor, systemic lupus erythematosus, and eclampsia — in one recipient each) and in one placebo recipient (premature placental separation) were assessed by the investigator as being related to the injection. The incidence of reported serious adverse events in infants from birth through 24 months was similar in the two groups (Fig. 4C and Table S14). No serious adverse events in infants were considered by the investigators to be related to the vaccine.

One recipient of RSVpreF vaccine died from postpartum hemorrhage and hypovolemic shock. During the trial, stillbirth occurred in 10 participants in the vaccine group and 8 participants in the placebo group, and spontaneous abortion during a subsequent pregnancy occurred in 1 participant in the vaccine group and 2 participants in the placebo group. A total of 17 deaths in infants and toddlers from birth through 24 months of age were reported (5 in the vaccine group [0.1%] and 12 in the placebo group [0.3%]) (Table S15). One death that was considered by the end-point adjudication committee to be associated with RSV infection occurred 120 days after birth in an infant whose mother had received placebo.

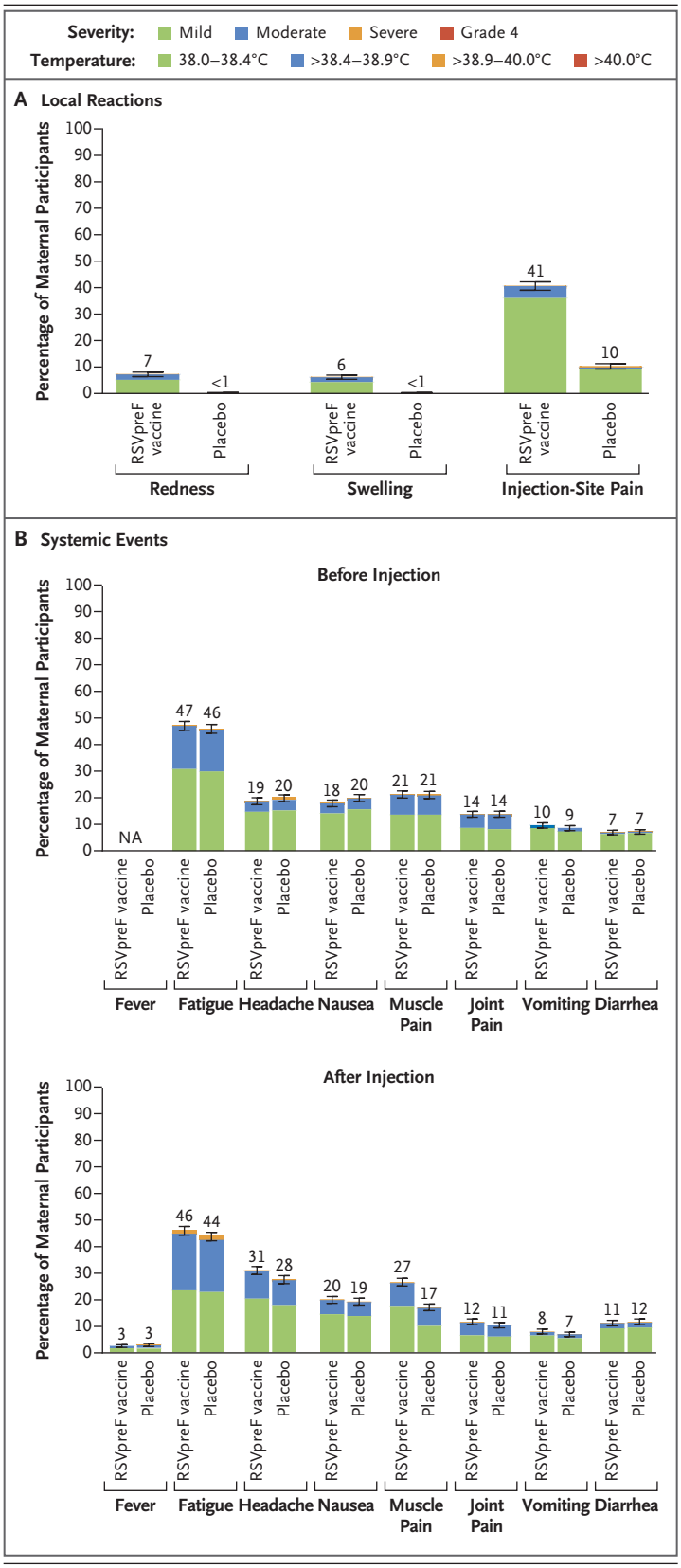
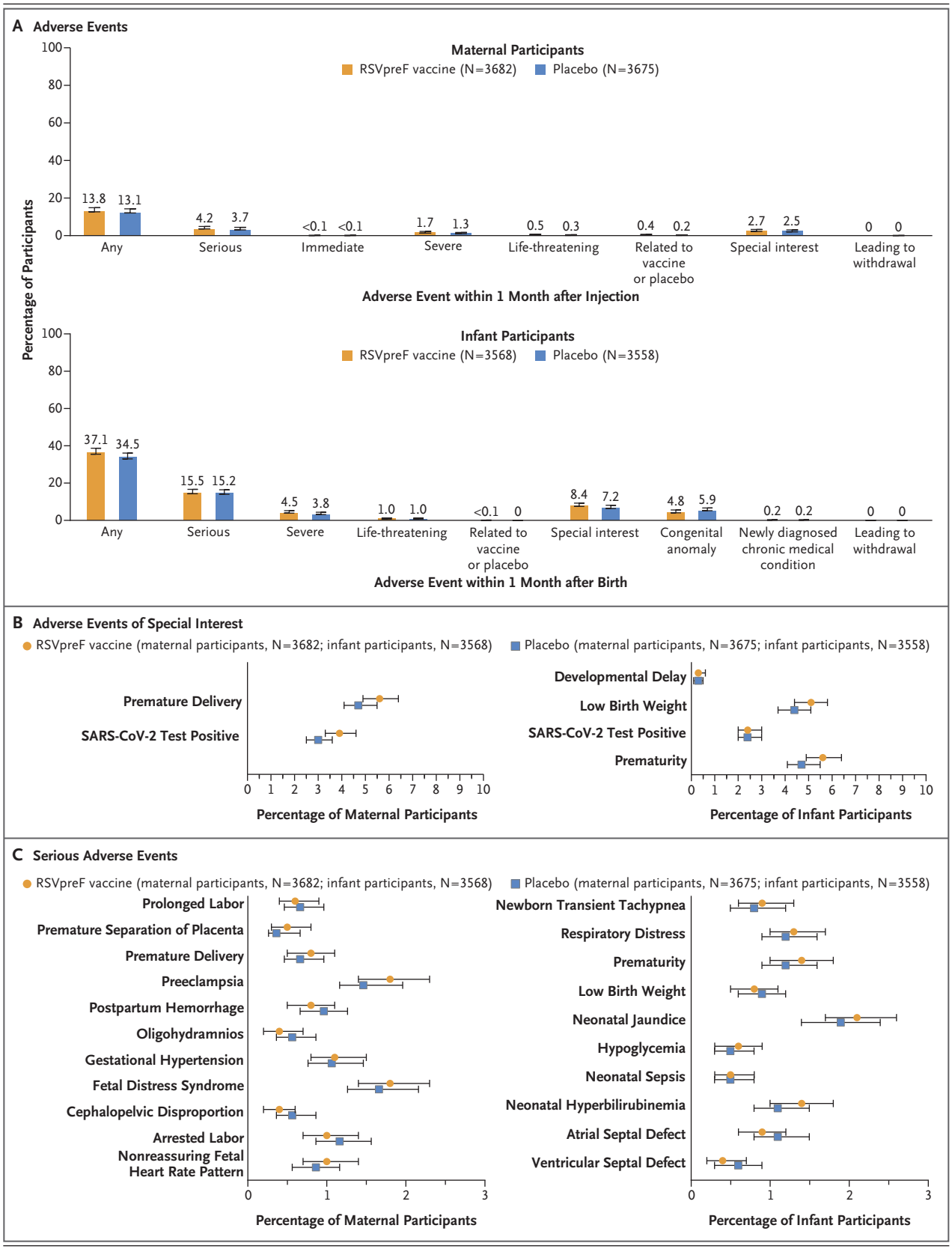


Figure 3. Local Reactions and Systemic Events in the Maternal Participants.

Panel A shows local reactions within 7 days after injection, and Panel B shows systemic events, including fever, before and within 7 days after injection (in 3637 to 3663 participants in the vaccine group and in 3621 to 3639 participants in the placebo group). Data are from the safety population. Severity and fever scales are summarized in Table S16. I bars denote 95% confidence intervals.

Figure 4 (facing page). Adverse Events in the Maternal and Infant Participants.

Panel A shows the percentages of participants who reported at least one adverse event, according to category, within 1 month after injection (maternal participants) or at least 1 month after birth (infant participants). Any event was defined as at least one occurrence in any category. An immediate adverse event was defined as any adverse event that occurred within 30 minutes after injection. Severe and life-threatening adverse events according to system organ class and preferred term are summarized in Table S17 (events in maternal participants) and Table S18 (events in infant participants). Related adverse events were assessed by the investigator as being related to the vaccine or placebo. Exact two-sided 95% confidence intervals were calculated with the use of the Clopper–Pearson method. I bars denote 95% confidence intervals. Panel B shows adverse events of special interest (occurring in >0.1% of participants in either group) from injection through 6 months after delivery in maternal participants and from birth through 24 months of age in infant participants. All congenital anomalies were reported as serious adverse events by definition. Low birth weight was defined as greater than 1500 g to 2500 g. Prematurity in infants was defined as birth before 37 weeks' gestation. SARS-CoV-2 denotes severe acute respiratory syndrome coronavirus 2. In Panels B and C, error bars denote 95% confidence intervals. Panel C shows the most commonly reported serious adverse events (occurring in >0.4% of participants in either group) from injection through 6 months after delivery in maternal participants and from birth through 24 months of age in infant participants. The duration from injection to delivery among preterm deliveries is shown in Table S19. Data are from the maternal and infant safety populations. The data-cutoff date was September 2, 2022. The only adverse events that were considered by the investigator to be related to the RSVpreF vaccine and that were reported in more than one maternal recipient in either group were lymphadenopathy and injection-site bruising (each reported in two RSVpreF recipients [<0.1%]). One adverse event (<0.1%) (prematurity) in an infant was considered by the investigator to be related to maternal RSVpreF vaccination. This event occurred 86 days after maternal vaccination at a gestational age at birth of 36 weeks and 4 days.


A Adverse Events
Maternal Participants
RSVpreF vaccine (N=3682)
Placebo (N=3675)
Percentage of Participants
100
80
60
40
20
0
13.8
13.1
4.2
3.7
<0.1
<0.1
1.7
1.3
0.5
0.3
0.4
0.2
2.7
2.5
0
0
Any
Serious
Immediate
Severe
Life-threatening
Related to vaccine or placebo
Special interest
Leading to withdrawal
Adverse Event within 1 Month after Injection
Infant Participants
RSVpreF vaccine (N=3568)
Placebo (N=3558)
37.1
34.5
15.5
15.2
4.5
3.8
1.0
1.0
<0.1
0
8.4
7.2
4.8
5.9
0.2
0.2
0
0
Any
Serious
Severe
Life-threatening
Related to vaccine or placebo
Special interest
Congenital anomaly
Newly diagnosed chronic medical condition
Leading to withdrawal
Adverse Event within 1 Month after Birth
B Adverse Events of Special Interest
RSVpreF vaccine (maternal participants, N=3682; infant participants, N=3568)
Placebo (maternal participants, N=3675; infant participants, N=3558)
Premature Delivery
SARS-CoV-2 Test Positive
0 1 2 3 4 5 6 7 8 9 10
Percentage of Maternal Participants
Developmental Delay
Low Birth Weight
SARS-CoV-2 Test Positive
Prematurity
0 1 2 3 4 5 6 7 8 9 10
Percentage of Infant Participants
C Serious Adverse Events
RSVpreF vaccine (maternal participants, N=3682; infant participants, N=3568)
Placebo (maternal participants, N=3675; infant participants, N=3558)
Prolonged Labor
Premature Separation of Placenta
Premature Delivery
Preeclampsia
Postpartum Hemorrhage
Oligohydramnios
Gestational Hypertension
Fetal Distress Syndrome
Cephalopelvic Disproportion
Arrested Labor
Nonreassuring Fetal Heart Rate Pattern
0 1 2 3
Percentage of Maternal Participants
Newborn Transient Tachypnea
Respiratory Distress
Prematurity
Low Birth Weight
Neonatal Jaundice
Hypoglycemia
Neonatal Sepsis
Neonatal Hyperbilirubinemia
Atrial Septal Defect
Ventricular Septal Defect
0 1 2 3
Percentage of Infant Participants

DISCUSSION

In this worldwide, phase 3 trial, maternal vaccination with RSVpreF was efficacious in preventing medically attended severe RSV-associated lower respiratory tract illness in infants, with vaccine efficacy of 81.8% (99.5% CI, 40.6 to 96.3) within 90 days after birth and 69.4% (97.58% CI, 44.3 to 84.1) within 180 days after birth. The success criterion for vaccine efficacy was met for this primary end point.

RSV-associated lower respiratory tract illness in young infants is associated with a high burden of illness and death across countries and health systems, especially in low- and middle-income countries.[3,28] In a phase 3 trial, injection with nirsevimab, a monoclonal antibody, protected infants from medically attended RSV-associated lower respiratory tract infection through 150 days after the injection (the primary end point), with efficacy of 74.5% (95% CI, 49.6 to 87.1).[29] Nirsevimab was recently authorized in Europe for use in infants from the time of birth during the RSV season,[30] although its affordability in low- and middle-income countries is uncertain.[31] In other regions, the use of monoclonal antibodies is limited to high-risk populations, and no therapeutic options other than supportive care exist.[32,33]

In addition, vaccination offers the possibility of an immune response to multiple neutralizing epitopes, thus reducing the risk of immune escape observed with some monoclonal antibodies.[34] Passive transfer of maternal antibodies can protect the youngest and most vulnerable infants immediately after birth, before effective immune responses can be elicited from active vaccination in infants.[35] In our trial, the youngest infant with medically attended severe RSV-associated lower respiratory tract illness was 8 days of age, a finding that highlights that RSV prevention is needed to protect young infants from birth through the period of greatest vulnerability.[1,4,7,12,17]

For the second primary end point of medically attended RSV-associated lower respiratory tract illness within 90 days after birth, the criterion for vaccine efficacy was not met (the lower boundary of the 99.5% CI was 14.7%, so it was not >20%). For the secondary end point of medically attended RSV-associated lower respiratory tract illness through 360 days, RSVpreF vaccine met the efficacy criterion (the lower boundary of the confidence interval was >0% rather than >20%). RSVpreF vaccine also met the efficacy criterion for hospitalization through 180 days after birth (the lower boundary of the confidence interval was >0%). Alongside reduction in medically attended RSV-associated respiratory tract illness through 180 days after birth, these results indicate protection of RSVpreF vaccine across the spectrum of RSV illness severity. This finding is consistent with the preliminary efficacy reported in a phase 2b trial of RSVpreF vaccination in pregnant women.[25]

RSVpreF is a maternal vaccine with efficacy against RSV-associated lower respiratory tract illness in infants; a previous phase 3 trial of maternal vaccination with an investigational recombinant RSV F vaccine that was not stabilized in the prefusion conformation did not meet the prespecified success criterion with respect to the primary end point of RSV-associated, medically significant lower respiratory tract illness within 90 days after birth (vaccine efficacy, 39.4%; 97.52% CI, −1.0 to 63.7).[36] However, the incidence of hospitalization for RSV-associated lower respiratory tract illness (a secondary end point) was lower in the vaccine group than in the placebo group (vaccine efficacy, 44.4%; 95% CI, 19.6 to 61.5).

On the basis of our efficacy criteria, there was no evidence that RSVpreF vaccination prevented medically attended lower respiratory tract illness from any cause within 90 days after birth (vaccine efficacy, 7.0%; 99.17% CI, −22.3 to 29.3). In our trial, which was conducted during the Covid-19 pandemic, medically attended RSV-associated lower respiratory tract illness within 180 days after birth constituted only 22% of medically attended lower respiratory tract illness due to any cause in the same period (174 of 794 cases). In contrast, in prepandemic studies of lower respiratory tract illness, RSV was the most common individual pathogen in areas where pneumococcal conjugate vaccines were used, and it was responsible for 50 to 80% of hospitalizations for bronchiolitis and 40% of cases of pneumonia among children younger than 1 year of age.[37,38]

The safety and side-effect profiles of RSVpreF vaccine in maternal participants were consistent with those in previous phase 1–2 clinical studies

involving adults,[23,26,39,40] with mostly mild-to-moderate reactogenicity and adverse-event and serious-adverse-event profiles that were similar to those of placebo. It is reassuring that no safety concerns were detected in the infants or mothers in this trial, although the number of participants was small. An analysis of the final trial data, including the totality of safety data and analyses according to country, is under way.

One limitation of our trial was the exclusion of women with high-risk pregnancies such as those with a current risk of preterm birth, multiple pregnancy, or a previous infant with a clinically significant congenital anomaly. Offspring of these women could be at higher risk for severe RSV-associated illness.[41] Further limitations of our trial include limited data from low-income countries where the vaccine is likely to have the greatest effect. In addition, the trial was insufficiently powered to assess differences in vaccine efficacy according to RSV antigen subgroup.

RSVpreF vaccine had a favorable safety profile and efficacy against medically attended severe RSV-associated lower respiratory tract illness and RSV-associated hospitalization in infants through 6 months of age.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

The authors' full names and academic degrees are as follows: Beate Kampmann, M.D., Ph.D., Shabir A. Madhi, M.B., B.Ch., Ph.D., Iona Munjal, M.D., Eric A.F. Simões, M.D., Barbara A. Pahud, M.D., M.P.H., Conrado Llapur, M.D., Jeffrey Baker, M.D., Gonzalo Pérez Marc, M.D., David Radley, M.S., Emma Shittu, Ph.D., Julia Glanternik, M.D., Hasra Snaggs, M.D., James Baber, M.B., Ch.B., M.P.H., Philip Zachariah, M.D., Shaun L. Barnabas, M.B., Ch.B., Ph.D., Merlin Fausett, M.D., Tyler Adam, M.D., Nicole Perreras, M.D., Marlies A. Van Houten, M.D., Ph.D., Anu Kantele, M.D., Ph.D., Li-Min Huang, M.D., Ph.D., Louis J. Bont, M.D., Ph.D., Takeo Otsuki, M.D., Ph.D., Sergio L. Vargas, M.D., Joanna Gullam, M.B., Ch.B., M.D., Bruce Tapiero, M.D., Renato T. Stein, M.D., Fernando P. Polack, M.D., Heather J. Zar, M.B., B.Ch., Ph.D., Nina B. Staerke, M.D., Ph.D., María Duron Padilla, M.D., Peter C. Richmond, M.B., B.S., Kenneth Koury, Ph.D., Katherine Schneider, Ph.D., Elena V. Kalinina, Ph.D., David Cooper, Ph.D., Kathrin U. Jansen, Ph.D., Annaliesa S. Anderson, Ph.D., Kena A. Swanson, Ph.D., William C. Gruber, M.D., and Alejandra Gurtman, M.D.

The authors' affiliations are as follows: the Medical Research Council Unit the Gambia, London School of Hygiene and Tropical Medicine, Fajara, Gambia (B.K.); the Institute for International Health Charité, Universitätsmedizin, Berlin (B.K.); the South African Medical Research Council (MRC) Vaccines and Infectious Diseases Analytics Research Unit, Infectious Diseases and Oncology Research Institute, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg (S.A.M.), and Family Centre for Research with Ubuntu, Department of Paediatrics and Child Health, University of Stellenbosch (S.L.B.), and the Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital, South African MRC Unit on Child and Adolescent Health, University of Cape Town (H.J.Z.), Cape Town — all in South Africa; Vaccine Research and Development, Pfizer, Pearl River, NY (I.M., B.A.P., D.R., J. Glanternik, H.S., P.Z., K.K., K.S., E.V.K., D.C., K.U.J., A.S.A., K.A.S., W.C.G., A.G.); Children's Hospital Colorado, Aurora (E.A.F.S.); Instituto de Maternidad y Ginecología Nuestra Señora de Las Mercedes, San Miguel de Tucumán (C.L.), and iTrials–Hospital Militar Central (G.P.M., F.P.P.) and iTrials (S.L.V.), Buenos Aires — all in Argentina; Clinical Research Prime, Idaho Falls, ID (J. Baker); Vaccine Research and Development, Pfizer, Hurley, United Kingdom (E.S.); Vaccine Clinical Research, Pfizer, Sydney, NSW (J. Baber), and the University of Western Australia School of Medicine, Vaccine Trials Group, Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, and Perth Children's Hospital, Nedlands, WA (P.C.R.) — all in Australia; Boeson Research, Missoula, MT (M.F.); Meridian Clinical Research, Hastings, NE (T.A.); Asian Hospital and Medical Center, Manila, Philippines (N.P.); the Department of Pediatrics, Spaarne Gasthuis, Haarlem and Hoofddorp (M.A.V.H.), and the Departments of Pediatrics and Immunology, University Medical Center Utrecht, Utrecht University, Utrecht, and Respiratory Syncytial Virus Network Foundation, Zeist (L.J.B.) — all in the Netherlands; Meilahti Vaccine Research Center, Inflammation Center, University of Helsinki and Helsinki University Hospital, Helsinki (A.K.); National Taiwan University Hospital, Taipei (L.-M.H.); the Department of Obstetrics and Gynecology, Sendai City Hospital, Sendai, Japan (T.O.); the Institute of Biomedical Sciences, University of Chile School of Medicine, Santiago, Chile (S.L.V.); University of Otago and New Zealand Clinical Research — both in Christchurch, New Zealand (J. Gullam); Centre Hospitalier Universitaire Sainte-Justine, Montreal (B.T.); Hospital Moinhos de Vento and Pontifícia Universidade Católica do Rio Grande do Sul — both in Porto Alegre, Brazil (R.T.S.); the Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark (N.B.S.); and Arké Study Management Organization, Mexico City (M.D.P.).

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