ORIGINAL ARTICLE

Prefusion F Protein–Based Respiratory Syncytial Virus Immunization in Pregnancy

Eric A.F. Simões, M.D., Kimberly J. Center, M.D., Alan T.N. Tita, M.D., Ph.D., Kena A. Swanson, Ph.D., David Radley, M.S., John Houghton, D.O., Stephanie B. McGrory, B.S.N., Emily Gomme, Ph.D., Marquita Anderson, M.D., John P. Roberts, M.D., Daniel A. Scott, M.D., Kathrin U. Jansen, Ph.D., William C. Gruber, M.D., Philip R. Dormitzer, M.D., Ph.D., and Alejandra C. Gurtman, M.D.

ABSTRACT

BACKGROUND

Respiratory syncytial virus (RSV), a major cause of illness and death in infants worldwide, could be prevented by vaccination during pregnancy. The efficacy, immunogenicity, and safety of a bivalent RSV prefusion F protein–based (RSVpreF) vaccine in pregnant women and their infants are uncertain.

METHODS

In a phase 2b trial, we randomly assigned pregnant women, at 24 through 36 weeks' gestation, to receive either 120 or 240 μg of RSVpreF vaccine (with or without aluminum hydroxide) or placebo. The trial included safety end points and immunogenicity end points that, in this interim analysis, included 50% titers of RSV A, B, and combined A/B neutralizing antibodies in maternal serum at delivery and in umbilical-cord blood, as well as maternal-to-infant transplacental transfer ratios.

RESULTS

This planned interim analysis included 406 women and 403 infants; 327 women (80.5%) received RSVpreF vaccine. Most postvaccination reactions were mild to moderate; the incidence of local reactions was higher among women who received RSVpreF vaccine containing aluminum hydroxide than among those who received RSVpreF vaccine without aluminum hydroxide. The incidences of adverse events in the women and infants were similar in the vaccine and placebo groups; the type and frequency of these events were consistent with the background incidences among pregnant women and infants. The geometric mean ratios of 50% neutralizing titers between the infants of vaccine recipients and those of placebo recipients ranged from 9.7 to 11.7 among those with RSV A neutralizing antibodies and from 13.6 to 16.8 among those with RSV B neutralizing antibodies. Transplacental neutralizing antibody transfer ratios ranged from 1.41 to 2.10 and were higher with nonaluminum formulations than with aluminum formulations. Across the range of assessed gestational ages, infants of women who were immunized had similar titers in umbilical-cord blood and similar transplacental transfer ratios.

CONCLUSIONS

RSVpreF vaccine elicited neutralizing antibody responses with efficient transplacental transfer and without evident safety concerns. (Funded by Pfizer; ClinicalTrials.gov number, NCT04032093.)

From the University of Colorado School of Medicine and Children's Hospital Colorado, Aurora (E.A.F.S.); Vaccine Research and Development, Pfizer, Pearl River, NY (K.J.C., K.A.S., D.R., S.B.M., E.G., D.A.S., K.U.J., W.C.G., P.R.D., A.C.G.); the Center for Women's Reproductive Health and the Department of Obstetrics and Gynecology, University of Alabama, Birmingham (A.T.N.T.); the Iowa Clinic, Des Moines (J.H.); and Gadolin Research, Beaumont (M.A.), and Ventavia Research Group, Plano (J.P.R.) — both in Texas. Dr. Gurtman can be contacted at alejandra.gurtman@pfizer.com or at Vaccine Research and Development, Pfizer, 401 N. Middletown Rd., Pearl River, NY 10960.

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Worldwide, respiratory syncytial virus (RSV) is associated with the deaths of approximately 118,200 children annually, with approximately half the deaths occurring in infants younger than 6 months of age and the vast majority occurring in developing countries.[1,2] In the United States, RSV is a common cause of hospitalization in infants, with an estimated annual incidence exceeding 2000 cases of RSV pneumonia per 100,000 infants.[3-5]

Currently, no specific therapy or vaccine to treat or prevent RSV infection is available. A humanized monoclonal antibody, palivizumab, is approved to prevent serious RSV disease in infants with specific risk factors[6]; clinical trials have shown that other monoclonal antibodies against the RSV fusion (F) protein — nirsevimab[7] and motavizumab[8] — have efficacy. Limitations to the use of palivizumab include the administration of multiple doses during the respiratory virus season,[8] recommendations regarding use in only a small number of infants who are at high risk for severe RSV disease,[9] an efficacy of approximately 45 to 55% among high-risk infants,[6] and expense.[10] However, trials of these prophylactic monoclonal antibodies have shown that serum antibodies can prevent RSV-associated lower respiratory tract illness in infants.[7,8,11]

In the 1960s, immunization with a formalin-inactivated, whole-virus vaccine led to enhanced (i.e., more severe) disease after subsequent natural RSV infection in infants,[12] and the subsequent development of vaccines has been hampered by an inability to balance side effects with immunogenicity.[13] Vaccine-mediated enhancement of RSV disease has been observed only in persons who have not previously had RSV infection. Adults have universally had exposure to RSV,[14] so the immunization of pregnant women could circumvent the risk of disease enhancement and passively protect infants before the peak incidence of RSV disease at approximately 6 weeks of age.[9,15,16] The effect of maternal immunization on protection against influenza, tetanus, and pertussis in infants is well established.[17-19]

Determination of the prefusion structure of the RSV F protein, the primary target of neutralizing antibodies, has revitalized the development of a vaccine against RSV.[20-22] In preparation for a pivotal phase 3 efficacy trial, we conducted a multicountry, observer-blinded, randomized, placebo-controlled, proof-of-concept, phase 2b trial of a bivalent RSV prefusion F protein–based vaccine candidate (RSVpreF vaccine) for women in the late second or third trimester of pregnancy. Here, we report on a planned interim analysis of the safety and immunogenicity of RSVpreF vaccine and of the transplacental transfer of RSV neutralizing antibodies. We also report on an exploratory analysis of the effect of maternal immunization on the prevention of RSV-associated lower respiratory tract illness in infants during the 2019–2020 RSV season in the Northern Hemisphere.

METHODS

PARTICIPANTS AND OVERSIGHT

We conducted a trial in the United States, Chile, Argentina, and South Africa to assess the safety and immunogenicity of RSVpreF vaccine in healthy pregnant women (18 to 49 years of age) at 24 through 36 weeks' gestation and their infants. The protocol, available with the full text of this article at NEJM.org, was approved by the ethics committee at each site, and all the participants provided written informed consent.

Eligible women, who were recruited from the site investigators' participant panels and with the use of a digital media campaign directed at participants, were monitored for safety through the use of an electronic diary for 1 week after vaccination and at planned visits 2 and 4 weeks later, at delivery, and at 1, 6, and 12 months after birth. Infants were enrolled at birth and were evaluated 1, 2, 4, 6, and 12 months later. Blood from the maternal participants was drawn before vaccination, 2 and 4 weeks later, at delivery, and at 1 and 6 months after birth. Umbilical-cord blood was obtained, and infants were randomly assigned into two phlebotomy cohorts for blood draws at 1 and 4 months of age or at 2 and 6 months of age. The Supplementary Appendix (available at NEJM.org) and the protocol list all the entry criteria and additional details regarding the trial design, methods, and safety monitoring.

The interim analysis for this ongoing trial involved only participants from the United States and was conducted in accordance with prespeci-

fied guidance of the Center for Biologics Evaluation and Research supporting the initiation of phase 3 trials. Vaccination before the onset of the usual RSV season in each hemisphere was planned, because then the infants were likely to be 6 months of age or younger when they were exposed to RSV. In the United States, maternal vaccination from August 14 through November 6, 2019, and infant follow-up through the 2019–2020 RSV season in the Northern Hemisphere preceded the major effects of the coronavirus disease 2019 (Covid-19) pandemic on RSV transmission. In the Southern Hemisphere, the pandemic decreased RSV circulation and impeded trial execution; the results in the Southern Hemisphere are limited and remain incomplete.

The sponsor designed the trial, performed the serologic and RT-PCR assays, and analyzed the data. The trial investigators collected the data and conducted the trial under confidentiality agreements with the sponsor. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

TRIAL OBJECTIVES

The primary safety end points included the following: solicited local and systemic reactions recorded with the use of an electronic diary kept by the participants for 7 days after vaccination; unsolicited adverse events that occurred during the month after vaccination (in maternal participants) or during the first month of life (in infant participants); and serious adverse events, medically attended adverse events, and adverse events of special interest that occurred throughout the observation period, from the first participant's vaccination through January 31, 2020. In the infants, adverse events of special interest included congenital anomalies and developmental delay. In accordance with the protocol, congenital anomalies are reported as serious adverse events.

In this interim analysis, the immunogenicity end points were 50% titers of RSV A, B, and combined A/B neutralizingantibodies in maternal serum at delivery and in umbilical-cord blood, as well as transplacental transfer ratios. Descriptions of the assays and of conversion of the neutralizing titers to the World Health Organization International Standard[23,24] are provided in the Supplementary Appendix.

RSV-associated lower respiratory tract illness in infants was an exploratory end point. We conducted active surveillance for acute respiratory illness through weekly contact with the infants' parents or guardians. The evaluation of illness in infants included physical examination and reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays of nasal swabs. Cases of RSV-associated lower respiratory tract illness were identified by means of RT-PCR assays that were positive for RSV. Samples for these assays were obtained from infants with acute respiratory illnesses that met prespecified clinical criteria in the protocol, as determined by an internal adjudication panel whose members were unaware of the trial-group assignments. Vaccine efficacy was analyzed post hoc. Details regarding methods of surveillance for respiratory illness are provided in the Supplementary Appendix.

RANDOMIZATION AND BLINDING

Randomization was performed centrally, and eligible participants were randomly assigned, in a 1:1:1:1:1 ratio, to receive a single intramuscular injection of 120 μg or 240 μg of RSVpreF vaccine (equal parts RSV A and B antigens), formulated with or without aluminum hydroxide, or placebo. Additional information regarding trial blinding is provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The trial sample size was selected according to the likelihood of detecting adverse events. This interim analysis was planned in order to review available safety and immunogenicity data in participants in the United States before the initiation of the phase 3 trial. No formal statistical hypothesis testing was used; all analyses are descriptive.

All the safety end points were evaluated with numbers, percentages, and two-sided exact 95% confidence intervals. For the immunogenicity analyses, geometric mean titers at each time point were calculated, and the geometric mean titer ratios for neutralizing antibody titers in the RSVpreF vaccine groups relative to the placebo group were calculated. For each mother–infant pair, the transplacental transfer ratio was calculated as the ratio of the RSV-neutralizing titers in infants and mothers. We calculated the con-

fidence intervals by exponentiating the limits of the confidence intervals for the mean of the logarithmically transformed assay results computed with the use of Student's t distribution. Vaccine efficacy was estimated post hoc as the relative risk reduction in the combined RSVpreF vaccine groups as compared with the placebo group. Confidence intervals were calculated with the use of an exact conditional method based on binomial distribution.[25] Missing safety, immunogenicity, and efficacy data were not imputed. Additional details regarding the statistical analysis are provided in the Supplementary Appendix.

RESULTS

TRIAL PARTICIPANTS

This prespecified interim analysis involved a cohort of 406 pregnant women and 403 infants for whom relevant data were available as of January 31, 2020 (Fig. 1). A total of 327 of the 406 women (80.5%) received RSVpreF vaccine. Race and ethnic group were reported by the participants. Most maternal participants (80%) were White, 16% were Black, 3% were Asian, and 1% were multiracial or had unreported race; 28% were Hispanic or Latina. The median age at vaccination was 27 years (range, 18 to 42), and the median gestation was 31 weeks 3 days (range, 24 weeks 0 days to 36 weeks 6 days). The complete demographic characteristics of the trial participants are provided in Table S1 in the Supplementary Appendix.

SAFETY

All 406 pregnant participants were included in the safety analyses. The reporting period for serious adverse events was up to approximately 5.5 months from trial entry to the interim analysis.

With respect to reactogenicity (local reactions and systemic reactions) within 7 days after vaccination, the most common injection-site reaction was mild-to-moderate pain, which was reported more frequently by participants who received RSVpreF vaccine containing aluminum hydroxide than by those who received RSVpreF vaccine without aluminum hydroxide (Fig. 2A and Table S2). Redness and swelling, which were mostly mild, were reported only by recipients of RSVpreF vaccine.

Figure 2B and 2C and Table S3 show fever and systemic reactions. A total of 5.1% or fewer recipients of RSVpreF vaccine (at any dose level) had a temperature of 38.0°C or higher; none of the participants had a temperature higher than 38.9°C. Most systemic reactions were mild or moderate and were similar in the RSVpreF vaccine and placebo groups, with the exception of muscle pain, which was reported more frequently in the RSVpreF vaccine groups.

There were no appreciable between-group differences in reported unsolicited adverse events within 1 month after vaccination (Table 1). The most reported categories of adverse events were infections, gastrointestinal disorders, and pregnancy-related conditions, including preterm delivery; the frequency of these events was similar in all the groups (Table S4). Serious adverse events were reported by less than 5% of the participants during the month after vaccination. No adverse events were considered by the investigators to be related to vaccination.

Serious adverse events that occurred during the observation period were reported with similar frequency in all the groups (Tables S5 and S6). A total of 55 serious adverse events were reported in 43 of the 406 maternal participants (10.6% of the total cohort); most serious adverse events (46 of 55 events [84%]) were directly related to complications of pregnancy, labor, delivery, and the immediate postpartum period. One stillbirth occurred in a woman who had received placebo at 31 weeks 5 days' gestation. The remainder of the serious adverse events in the maternal participants (e.g., 1 case each of appendicitis, gastroenteritis, pyelonephritis, and influenza) were considered by the investigators to be unrelated to pregnancy. None of the serious adverse events were considered by the investigators to be related to vaccination.

The safety analyses included data on 403 infants; 50.4% were female. The reporting period for serious adverse events was up to approximately 5 months, from birth to the interim analysis.

Overall, 170 of 403 infants (42.2%) had an adverse event in the first month of life, and the frequency of these events was similar among the trial groups (Table 1). None of the adverse events were considered by the investigators to be related to maternal vaccination (Table S7). The most commonly reported adverse events in the first month of life included neonatal jaundice or

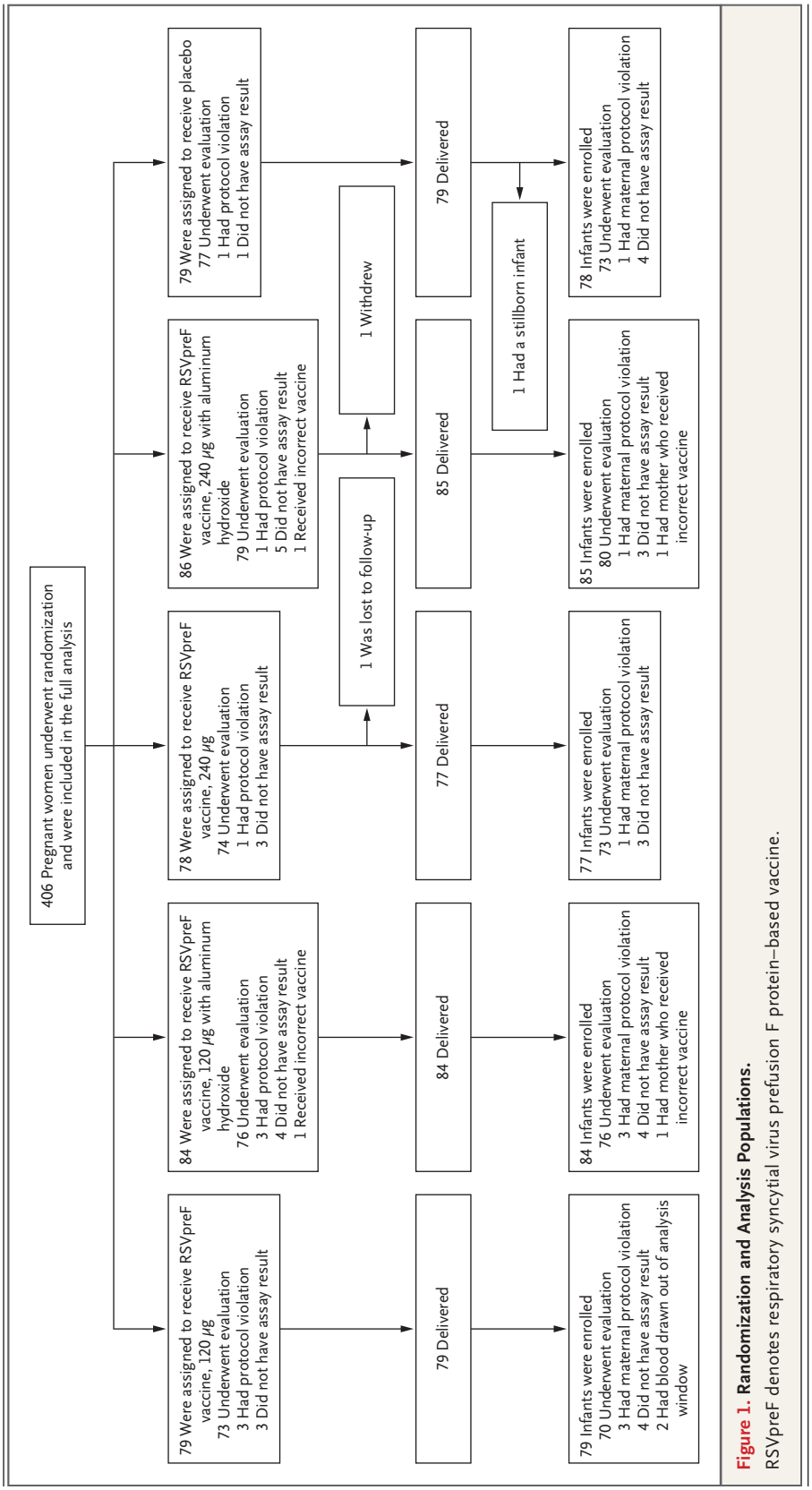

Figure 1. Randomization and Analysis Populations.
RSVpreF denotes respiratory syncytial virus prefusion F protein–based vaccine.

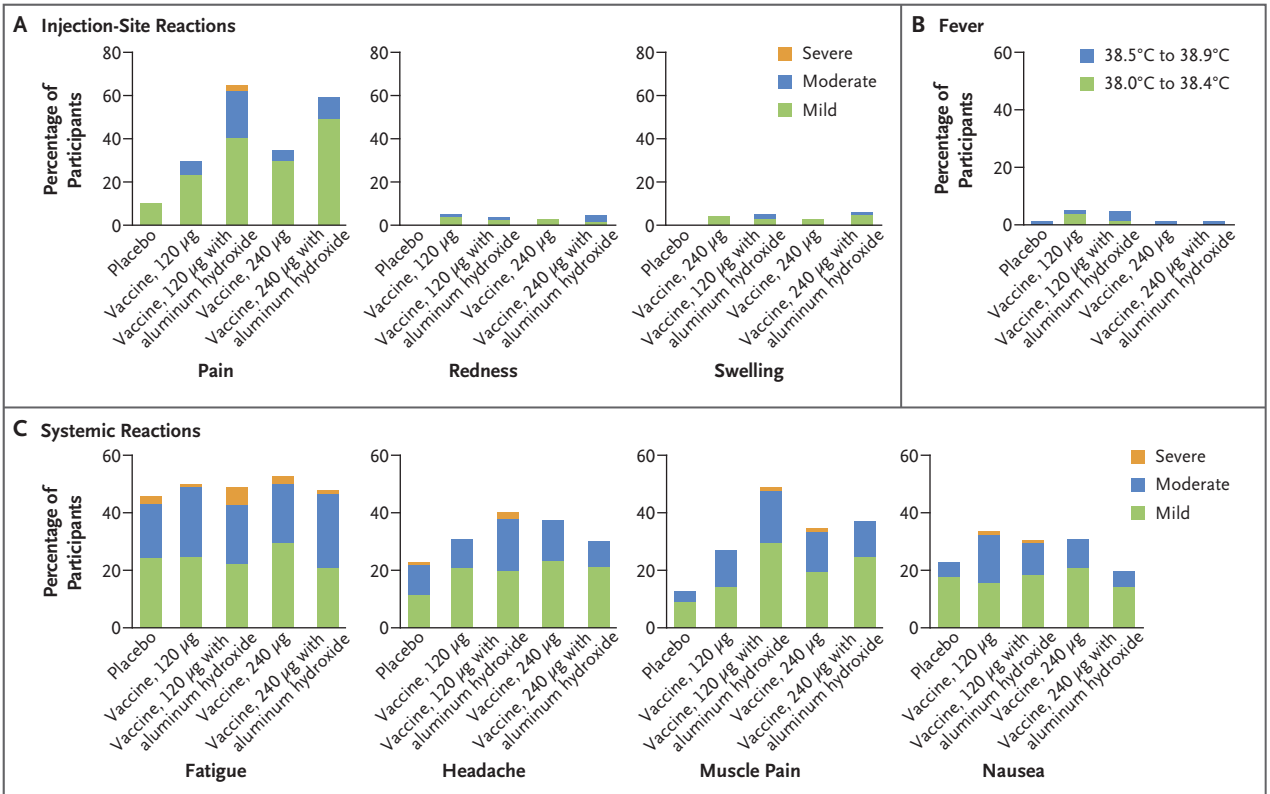

Figure 2. Injection-Site Reactions, Fever, and Systemic Reactions Reported within 7 Days after Vaccination, According to Vaccine Group and Severity.

The total number of participants in each vaccine or placebo group ranged from 78 to 86. Injection-site (local) reactions, temperature, and systemic reactions were recorded in electronic diaries for 7 days after vaccination (the day of vaccination was day 1). Grade 4 reactions warranted confirmation by the investigators; no grade 4 reactions were reported. In Panel A, pain at the injection site was graded as mild (does not interfere with activity), moderate (interferes with activity), severe (prevents daily activity), or grade 4 (led to an emergency department visit or hospitalization). A total of 29.5% to 64.6% of the participants in the RSVpreF vaccine groups reported mild-to-moderate pain, which was reported more frequently by those who received RSVpreF vaccine formulations containing aluminum hydroxide than by those who received formulations without aluminum hydroxide; mild-to-moderate pain was reported by 10.1% of the placebo recipients. Both redness and swelling were graded as mild (>2.0 to 5.0 cm in diameter), moderate (>5.0 to 10.0 cm in diameter), severe (>10.0 cm in diameter), or grade 4 (necrosis or exfoliative dermatitis in participants with redness and necrosis in those with swelling). In Panel B, fever was graded as mild (38.0°C to 38.4°C) or moderate (38.5°C to 38.9°C). In Panel C, systemic reactions were graded as mild (does not interfere with activity), moderate (interferes somewhat with activity), severe (prevents daily activity), or grade 4 (led to an emergency department visit or hospitalization). Complete data regarding common systemic events are shown in Table S3.

hyperbilirubinemia, delivery complications, and minor gastrointestinal and infectious conditions that are common in neonates. Preterm birth was reported as an adverse event, regardless of outcome. Fifteen of 403 infants (3.7%) across all the groups were born prematurely, most in the 36th week of gestation (31 weeks 3 days to 36 weeks 6 days) (Table S8).

Serious adverse events of similar frequency and type were reported among all groups throughout the observation period; none were considered by the investigators to be related to maternal vaccination. A total of 94 infants had a serious adverse event during the observation period, and 81 of these 94 infants had these events in the first month of life (Table 1 and Tables S9 and S10). Congenital anomalies were reported in 69 of 403 infants (17.1%). In 54 of these 69 infants (78%), these anomalies, including congenital nevi and umbilical hernias, were considered by the investigators to be mild or clinically nonsignificant findings and were consistent with expected background incidences (Tables S11 and S12). Three infants were hospi-

Table 1. Adverse Events in the Maternal and Infant Participants.*

Variable	RSVpreF Vaccine, 120 μg		RSVpreF Vaccine, 120 μg with Aluminum Hydroxide		RSVpreF Vaccine, 240 μg		RSVpreF Vaccine, 240 μg with Aluminum Hydroxide		Placebo	
	no.	*% (95% CI)†*	*no.*	*% (95% CI)†*	*no.*	*% (95% CI)†*	*no.*	*% (95% CI)†*	*no.*	*% (95% CI)†*
Maternal participants										
Participants in the group	79		84		78		86		79	
Participants with ≥1 occurrence of any adverse event through 1 mo after vaccination	19	24 (15 to 35)	22	26 (17 to 37)	24	31 (21 to 42)	23	27 (18 to 37)	15	19 (11 to 29)
Serious adverse event through 1 mo after vaccination	1	1 (0 to 7)	3	4 (1 to 10)	2	3 (<1 to 9)	4	5 (1 to 12)	2	3 (<1 to 9)
Immediate adverse event through 1 mo after vaccination‡	0	0 (0 to 5)	0	0 (0 to 4)	0	0 (0 to 5)	0	0 (0 to 4)	0	0 (0 to 5)
Severe adverse event through 1 mo after vaccination§	1	1 (0 to 7)	3	4 (1 to 10)	0	0 (0 to 5)	2	2 (<1 to 8)	2	3 (<1 to 9)
Life-threatening adverse event through 1 mo after vaccination§	1	1 (0 to 7)	0	0 (0 to 4)	1	1 (0 to 7)	0	0 (0 to 4)	0	0 (0 to 5)
Adverse event related to vaccination through 1 mo after vaccination	0	0 (0 to 5)	0	0 (0 to 4)	0	0 (0 to 5)	0	0 (0 to 4)	0	0 (0 to 5)
Medically attended adverse event during the trial period¶	5	6 (2 to 14)	6	7 (3 to 15)	3	4 (1 to 11)	9	10 (5 to 19)	2	3 (<1 to 9)
Adverse event leading to withdrawal from the trial through 1 mo after vaccination	0	0 (0 to 5)	0	0 (0 to 4)	0	0 (0 to 5)	0	0 (0 to 4)	0	0 (0 to 5)
Infant participants										
Participants in the group	79		84		77		85		78	
Participants with ≥1 occurrence of any adverse event in the first mo of life	35	44 (33 to 56)	37	44 (33 to 55)	31	40 (29 to 52)	37	44 (33 to 55)	30	38 (28 to 50)
Serious adverse event in the first mo of life	18	23 (14 to 34)	17	20 (12 to 30)	17	22 (13 to 33)	17	20 (12 to 30)	12	15 (8 to 25)
Severe adverse event in the first mo of life§	3	4 (1 to 11)	5	6 (2 to 13)	2	3 (<1 to 9)	3	4 (1 to 10)	3	4 (1 to 11)
Life-threatening adverse event in the first mo of life§	0	0 (0 to 5)	4	5 (1 to 12)	2	3 (<1 to 9)	0	0 (0 to 4)	0	0 (0 to 5)
Adverse event related to vaccination in the first mo of life	0	0 (0 to 7)	0	0 (0 to 4)		0 (0 to 5)	0	0 (0 to 4)	0	0 (0 to 5)
Medically attended adverse event during the trial period¶	3	4 (1 to 11)	5	6 (2 to 13)	4	5 (1 to 13)	5	6 (2 to 13)	2	3 (<1 to 9)
Adverse event leading to withdrawal in the first mo of life	0	0 (0 to 5)	0	0 (0 to 4)	0	0 (0 to 5)	0	0 (0 to 4)	0	0 (0 to 5)
Protocol-specified adverse event of special interest: congenital anomaly during the trial period	17	22 (13 to 32)	13	16 (8 to 25)	15	20 (11 to 30)	15	18 (10 to 27)	9	12 (5 to 21)

* CI denotes confidence interval, and RSVpreF respiratory syncytial virus prefusion F protein–based vaccine.
† Exact two-sided confidence intervals were calculated with the use of the Clopper–Pearson method.
‡ In maternal participants, immediate adverse events were those that occurred within the first 30 minutes after administration of the RSVpreF vaccine.
§ The severity of events was determined by the investigators. All adverse events were assessed for severity, which is distinct from seriousness.
¶ Medically attended adverse events were nonserious adverse events that resulted in an evaluation at a medical facility.

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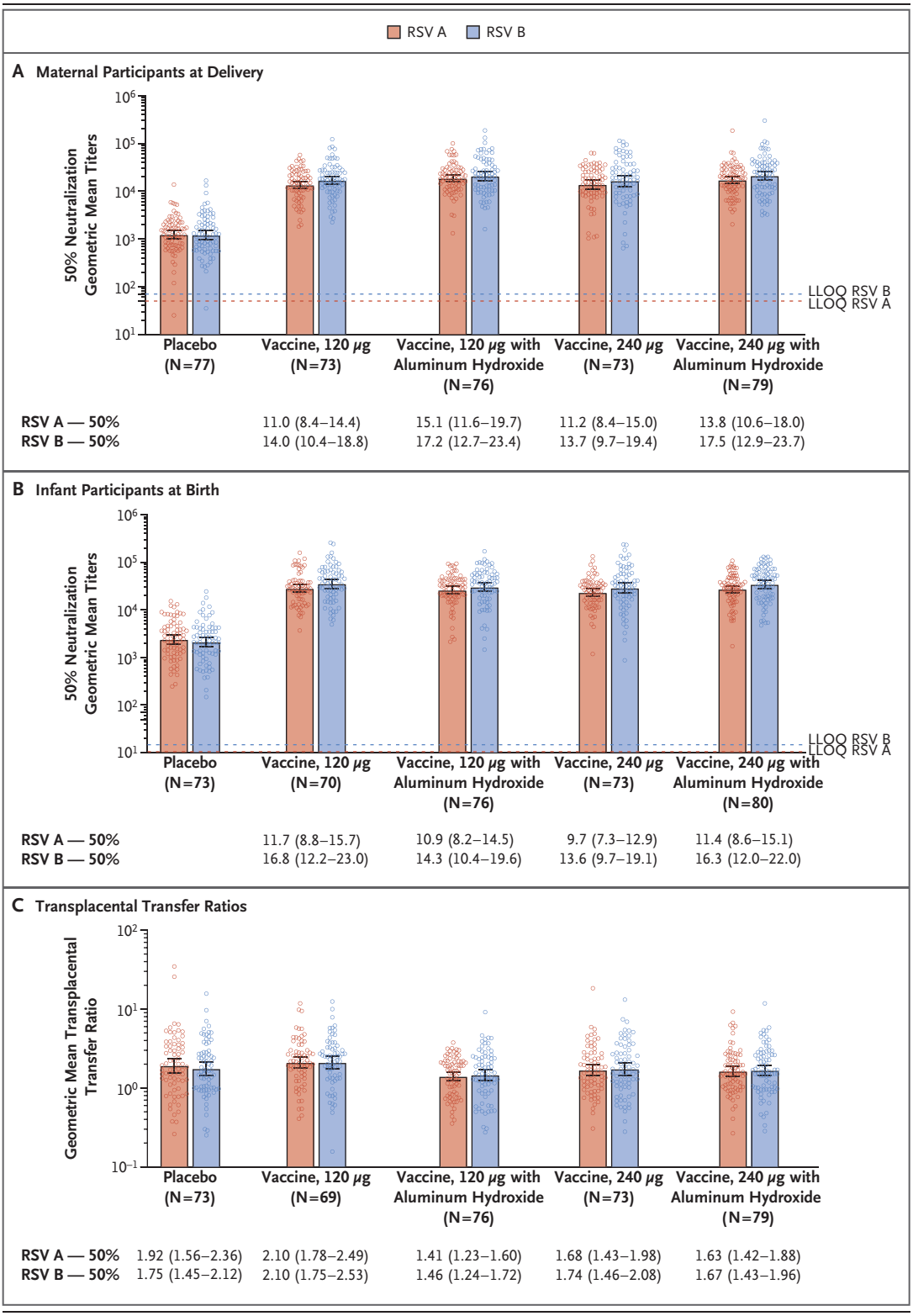

Figure 3 (facing page). Geometric Mean 50% Neutralizing Titers in RSV A and RSV B Assays at Delivery or Birth and Geometric Mean Transplacental Transfer Ratios.

Geometric mean 50% neutralizing titers in vaccine recipients (or their infants) relative to placebo recipients (or their infants) are shown. I bars indicate 95% confidence intervals, and individual data points are represented by circles. The total number of women in each of the vaccine and placebo groups ranged from 73 to 79, and the total number of infants ranged from 70 to 80. Panel A shows these data for maternal participants at delivery (from serum samples), and Panel B shows these data for infants at birth (from umbilical-cord blood samples). Below each graph are the corresponding geometric mean titer ratios for each vaccine group as compared with the placebo group. Dashed lines denote the lower limits of quantitation (LLOQ) for both the RSV A and RSV B assays. The geometric mean titer ratio was calculated as the group mean difference between the RSV group and the placebo group in logarithmically transformed neutralizing titers, back transformed to the original units, with confidence intervals calculated as stated above. Panel C shows the geometric mean transplacental transfer ratios of RSV A and RSV B for all mother–infant pairs. For each mother–infant pair, the transfer ratio was calculated as the ratio of the infant's RSV-neutralizing titers to the mother's RSV-neutralizing titers.

talized for acute respiratory illness. RSV infection was identified in 2 infants, both of whom were in the second month of life.

IMMUNOGENICITY

The evaluable immunogenicity populations included 379 maternal participants and 372 infants; the reasons for the exclusion of participants from the analysis populations are shown in Figure 1 and Tables S13 and S14. The 50% geometric mean titers of RSV A and B neutralizing antibodies at delivery or birth and the geometric mean titer ratios for neutralizing antibodies in the vaccine recipients (or their infants) relative to the placebo recipients (or their infants) are shown in Figure 3, with transplacental transfer ratios for all groups. The geometric mean titer ratios for neutralizing antibodies in the maternal participants (RSVpreF vaccine groups relative to the placebo group) ranged from 11.0 to 15.1 for RSV A neutralizing antibodies and from 13.7 to 17.5 for RSV B neutralizing antibodies (Fig. 3A and Table S15). The geometric mean titer ratios for neutralizing titers in umbilical-cord blood ranged from 9.7 to 11.7 for RSV A neutralizing antibodies and from 13.6 to 16.8 for RSV B neutralizing antibodies (Fig. 3B); the complete geometric mean titers of neutralizing antibodies in infant umbilical-cord blood are shown in Table S16.

The geometric mean transplacental transfer ratios for RSV A or B neutralizing antibodies in the groups receiving RSVpreF vaccine without aluminum hydroxide ranged from 1.68 to 2.10; those in groups receiving RSVpreF vaccine with aluminum hydroxide ranged from 1.41 to 1.67 (Fig. 3C and Table S17). The geometric mean titer ratios for neutralizing antibodies and transplacental transfer ratios were similar in infants born to mothers immunized between 24 to less than 27 weeks' gestation, between 27 to less than 30 weeks' gestation, between 30 to less than 33 weeks' gestation, and between 33 to less than 36 weeks' gestation (Fig. S1).

EFFICACY

The trial was ongoing at the time of the interim analysis described here, so we were able to continue active surveillance for acute respiratory illness among participants in the United States and perform a post hoc analysis of the preliminary efficacy of RSVpreF vaccine. RSV-associated lower respiratory tract illness was monitored in infants throughout the 2019–2020 RSV illness season in the United States (from September 2019 through May 2020) in order to establish the baseline incidence in preparation for the phase 3 trial. The post hoc analysis included all the infants. A total of 508 infants were enrolled in the United States; of these infants, 405 had mothers who had received RSVpreF vaccine and 103 had mothers who had received placebo.

In the U.S. cohort of 508 infants, 172 (33.9%) had at least one acute respiratory illness; of these 172 infants, 26 (15.1%) were positive for RSV on an RT-PCR assay. RSV-associated acute respiratory illness was first identified in November 2019, peaked in January and February 2020, and was last identified in early March 2020, consistent with national surveillance data[26] and historical trends.[27]

In the post hoc analysis, 8 infants had illness that met the case definition of medically attended

Table 2. Efficacy of Maternal Vaccination against RSV-Associated Lower Respiratory Tract Illness in the U.S. Cohort of 508 Infants.

Efficacy End Point	RSVpreF Vaccine (N=405)	Placebo (N=103)	Estimated Vaccine Efficacy (95% CI)
	number of infants with event		*percent*
Any medically attended RSV-associated lower respiratory tract illness*	3	5	84.7 (21.6 to 97.6)
Medically attended severe RSV-associated lower respiratory tract illness†	1	3‡	91.5 (–5.6 to 99.8)

* Any medically attended RSV-associated lower respiratory tract illness was defined as a medically attended visit (i.e, the infant participant was taken to or seen by a health care provider in an outpatient or inpatient visit, emergency department, or urgent care clinic, or in a home visit) and the presence of one of the following signs of RSV-associated lower respiratory tract illness: tachypnea (respiratory rate ≥60 breaths per minute in infants younger than 2 months [60 days] of age or ≥50 breaths per minute in those 2 to 12 months of age); a peripheral capillary oxygen saturation as measured by pulse oximetry (Spo_2) below 95% while the infant was breathing ambient air; and indrawing of the chest wall.

† A medically attended severe RSV-associated lower respiratory tract illness was defined as a medically attended visit and the presence of one of the following signs of severe RSV-associated lower respiratory tract illness: tachypnea (respiratory rate ≥70 breaths per minute in infants younger than 2 months [60 days] of age or ≥60 breaths per minute in those between 2 months and 12 months of age); Spo_2 <93% while the infant was breathing ambient air; use of oxygen delivered through a high-flow nasal cannula or mechanical ventilation; admission to an intensive care unit for more than 4 hours; and unresponsiveness or unconsciousness.

‡ Two of these three infants (boys who were 38 and 48 days of age) were hospitalized in order to maintain hydration and receive supplemental oxygen by nasal cannula.

RSV-associated lower respiratory tract illness and 4 of these infants had illness that met the case definition of severe RSV-associated lower respiratory tract illness (data and definitions are provided in Table 2). In the placebo group, 5 of 103 infants had medically attended RSV-associated lower respiratory tract illness; 3 of these cases were severe, and 2 infants were hospitalized and received oxygen through a nasal cannula. In the four RSVpreF vaccine groups combined, 3 of 405 infants had medically attended RSV-associated lower respiratory tract illness; 1 of these infants had a severe case but was not hospitalized. This case distribution corresponds with observed efficacies of 84.7% (95% confidence interval [CI], 21.6 to 97.6) against medically attended RSV-associated lower respiratory tract illness and 91.5% (95% CI, –5.6 to 99.8) against severe RSV-associated lower respiratory tract illness.

DISCUSSION

Our findings in this interim analysis indicate that RSVpreF vaccine elicited neutralizing titers in maternal serum obtained at deliveries that occurred, on average, approximately 7 weeks after immunization. The neutralizing titers were transferred across the placenta efficiently, and a post hoc analysis suggested that the transferred antibodies prevented medically attended RSV-associated lower respiratory tract illnesses in infants. The concept of protection of infants from disease by transplacental transfer of antibodies elicited by colonization[28,29] or by immunization during pregnancy is well established.[17,18]

In a previous study, immunization of healthy 18- to 49-year-old adults (men and nonpregnant women) with a single dose of 120 or 240 μg RSVpreF vaccine with or without aluminum hydroxide elicited geometric mean factor increases from baseline ranging from 7.9 to 9.6 (RSV A) and from 7.7 to 11.1 (RSV B) at 2 months after immunization.[30] In the current trial, the 50% RSV geometric mean titer ratios for neutralizing antibodies in pregnant vaccine recipients relative to pregnant placebo recipients ranged from 11.0 to 15.1 for RSV A and from 13.7 to 17.5 for RSV B at deliveries that occurred, on average, approximately 7 weeks after immunization; these responses were at least as high as those to RSVpreF vaccine in nonpregnant adults. As in nonpregnant adults,[30] neutralizing titers elicited by 120 μg or 240 μg of RSVpreF vaccine were similar. However, although maternal titers were somewhat higher after vaccination with a formulation containing aluminum hydroxide, there was no ad-

vantage in infants, in whom neutralizing titers were higher in the non–aluminum hydroxide groups.

In our analysis, the transplacental transfer ratios of 1.41 to 2.10 raised the neutralizing titers in infants higher than those in the maternal participants. The resulting geometric mean titer ratios for neutralizing antibodies in umbilical-cord blood that ranged from 9.7 to 16.8 exceeded the geometric mean titer ratios for neutralizing antibodies that ranged from 2.1 to 2.3 in a trial of maternal immunization with RSV F protein nanoparticle vaccine that was not stabilized in the prefusion conformation.[31] In that trial, RSV-associated, medically significant lower respiratory tract infection through 90 days was reduced by 39.4%.

In our analysis, the levels of RSV neutralizing titers in umbilical-cord blood did not vary substantially according to gestational age (24 to 36 weeks) at the time of immunization, findings that support an immunization window over approximately 3 months of pregnancy. This wide range of gestational ages for immunization may facilitate prenatal immunization, abrogating the need to administer tetanus–diphtheria–acellular pertussis or influenza vaccine concomitantly with RSV vaccine during the recommended prenatal visit schedule.

This trial was not designed to provide formal assessment of vaccine efficacy. Nevertheless, the post hoc exploratory efficacy analysis showed efficacy of 84.7% and 91.5% for medically attended and severe medically attended RSV-associated lower respiratory tract illness, respectively. Given the low case count, the confidence intervals associated with these point estimates are wide. However, the encouraging point estimates of efficacy are consistent with the neutralizing titers in infant umbilical-cord blood, which were higher than those associated with palivizumab (at a dose of 100 μg per milliliter) by a factor of 31 for RSV A and a factor of 17 for RSV B.[24] Palivizumab at a dose of 100 μg per milliliter has been associated with protection of infants from hospitalization in the intensive care unit for RSV-associated illnesses.[32] These serologic and initial efficacy data suggest that maternal vaccination with RSVpreF vaccine during pregnancy has the potential to protect infants from RSV infection well into their first 6 months of life.

A limitation of this interim analysis is the inclusion of only participants from the United States. The findings may have been different in the other countries where the trial is ongoing. For example, transplacental transfer ratios are lower in low-income and middle-income countries than in high-income countries.[31] Although vaccination began at 24 weeks' gestation in this trial, women who were vaccinated between 24 and 27 weeks' gestation were underrepresented in this cohort, because many had not delivered as of the data-cutoff date. The sample size in this interim analysis was too small to precisely assess the effect of prematurity on blood titers after maternal immunization. Assessments of immunogenicity in this analysis were limited to assessments at delivery and birth. The kinetics of responses to RSVpreF vaccine in the women and the data on the decay of passively transferred antibodies were not yet available, although we are following mothers and infants in this trial to determine immunogenicity through 6 months after delivery.

Finally, the observed efficacy was based on exploratory, post hoc analyses. This trial is ongoing in the Southern Hemisphere, although the Covid-19 pandemic is likely to have a considerable effect on data collection and outcomes. Given the findings of increased reactogenicity associated with aluminum hydroxide and the lack of an immunologic advantage to its inclusion in the vaccine, a phase 3 clinical efficacy trial involving infants born to women who received 120 μg of RSVpreF vaccine without aluminum hydroxide during pregnancy is under way (Maternal Immunization Study for Safety and Efficacy; ClinicalTrials.gov number, NCT04424316).

We found evidence of an acceptable safety profile for the RSVpreF vaccine in maternal recipients and their infants, elicitation of neutralizing antibody responses to RSVpreF vaccine in pregnancy, and efficient transfer of neutralizing antibodies to infants. Our trial also showed preliminary evidence of the efficacy of maternal vaccination with RSVpreF vaccine during pregnancy in preventing RSV-associated lower respiratory tract illness in infants.

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