ORIGINAL ARTICLE

Respiratory Syncytial Virus Vaccination during Pregnancy and Effects in Infants

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ABSTRACT

BACKGROUND

Respiratory syncytial virus (RSV) is the dominant cause of severe lower respiratory tract infection in infants, with the most severe cases concentrated among younger infants.

METHODS

Healthy pregnant women, at 28 weeks 0 days through 36 weeks 0 days of gestation, with an expected delivery date near the start of the RSV season, were randomly assigned in an overall ratio of approximately 2:1 to receive a single intramuscular dose of RSV fusion (F) protein nanoparticle vaccine or placebo. Infants were followed for 180 days to assess outcomes related to lower respiratory tract infection and for 364 days to assess safety. The primary end point was RSV-associated, medically significant lower respiratory tract infection up to 90 days of life, and the primary analysis of vaccine efficacy against the primary end point was performed in the per-protocol population of infants (prespecified criterion for success, lower bound of the 97.52% confidence interval [CI] of ≥30%).

RESULTS

A total of 4636 women underwent randomization, and there were 4579 live births. During the first 90 days of life, the percentage of infants with RSV-associated, medically significant lower respiratory tract infection was 1.5% in the vaccine group and 2.4% in the placebo group (vaccine efficacy, 39.4%; 97.52% CI, –1.0 to 63.7; 95% CI, 5.3 to 61.2). The corresponding percentages for RSV-associated lower respiratory tract infection with severe hypoxemia were 0.5% and 1.0% (vaccine efficacy, 48.3%; 95% CI, –8.2 to 75.3), and the percentages for hospitalization for RSV-associated lower respiratory tract infection were 2.1% and 3.7% (vaccine efficacy, 44.4%; 95% CI, 19.6 to 61.5). Local injection-site reactions among the women were more common with vaccine than with placebo (40.7% vs. 9.9%), but the percentages of participants who had other adverse events were similar in the two groups.

CONCLUSIONS

RSV F protein nanoparticle vaccination in pregnant women did not meet the prespecified success criterion for efficacy against RSV-associated, medically significant lower respiratory tract infection in infants up to 90 days of life. The suggestion of a possible benefit with respect to other end-point events involving RSV-associated respiratory disease in infants warrants further study. (Funded by Novavax and the Bill and Melinda Gates Foundation; ClinicalTrials.gov NCT02624947.)

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*A complete list of the investigators in the Prepare Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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Respiratory syncytial virus (RSV) is the dominant cause of hospitalizations in infants with lower respiratory tract infections. In 2015, an estimated 3.2 million hospitalizations for RSV-associated lower respiratory tract infection occurred in children younger than 5 years of age worldwide; 118,000 of the hospitalized children died. Approximately 44% of those hospitalizations and 46% of the in-hospital deaths occurred in infants younger than 6 months of age.[1] No licensed RSV vaccine exists, and timely, active immunization against RSV infection in the first 3 to 6 months of life may be challenging. Passive immunity through transfer of IgG antibodies from immunized pregnant women offers an alternative and is endorsed by the World Health Organization (WHO) for the prevention of tetanus, influenza, and pertussis in infants.[2-4] Passive immunity conferred by palivizumab, a monoclonal antibody to RSV fusion (F) protein, reduced the risk of hospitalization for RSV-associated lower respiratory tract infection among premature infants and among infants with chronic lung disease or congenital heart disease,[5] and motavizumab (a higher-potency monoclonal antibody) reduced the risk of hospitalization for RSV-associated lower respiratory tract infection by 87% among American Indian infants born at term.[6]

In a previous trial, recombinant RSV F protein nanoparticle vaccine (RSV F vaccine) had an acceptable safety profile when administered in pregnant women and elicited RSV A and B neutralizing antibodies, antibodies to RSV F protein site II epitope (palivizumab-competitive antibodies), and antibodies to other epitopes with broadly neutralizing activity. These antibodies were efficiently transferred to the infants.[7] Here, we describe the results of a phase 3 trial evaluating the safety and immunogenicity of RSV F vaccine in pregnant women and vaccine efficacy against RSV-associated lower respiratory tract infection in their infants through the first 90 and 180 days of life.

METHODS

TRIAL DESIGN AND OVERSIGHT

A randomized, observer-blind, placebo-controlled trial was performed at 87 sites in Argentina, Australia, Chile, Bangladesh, Mexico, New Zealand, the Philippines, South Africa, Spain, the United Kingdom, and the United States. Healthy women 18 to 40 years of age with low-risk singleton pregnancies received vaccine or placebo between 28 weeks 0 days and 36 weeks 0 days of gestation, before the seasonal circulation of RSV in their locale (see Section S1.1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Inclusion and exclusion criteria are provided in Section S1.2 and the randomization scheme in Section S1.3. The full protocol with the statistical analysis plan is also available at NEJM.org.

The trial staff conducted weekly active surveillance of parents or caregivers until 180 days after delivery (see Section S1.4) for the detection of symptoms of lower respiratory tract infection. Evaluations could also be triggered by spontaneous reports from the parent or caregiver. The evaluation of infants included physical examination, determination of respiratory rate, and pulse oximetry with the use of a RAD-5 pulse oximeter (Masimo) provided by the sponsor (Novavax). Nasal swab samples were obtained with the use of a nasal FLOQSwab (Copan Diagnostics) and were placed into a transport medium, stored at –70°C, and shipped to the Marshfield Clinic Research Institute (Marshfield, Wisconsin), where the validated eSensor RVP multiplex assay (GenMark) was used for viral diagnosis.

Details of the immunogenicity and safety evaluations are provided in Sections S1.5 and S1.6. RSV serologic tests included measurements of serum anti-F IgG concentrations and levels of antibodies competitive with palivizumab (i.e., antibodies that block binding of the neutralizing and protective monoclonal antibody palivizumab to RSV F protein and thus are likely to bind at or near the same site on the F protein). RSV A and B microneutralization assays have been completed in a subgroup comprising participants in the first two seasons of the trial to date; further testing is under way to examine the hypothesis that these assays may provide correlates of risk.[7]

The sponsor designed the trial and analyzed the data with input from the investigators; the investigators collected the data and conducted the trial. The first and last authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The investigators worked under confidentiality agreements with the sponsor.

The protocol was reviewed and approved by regulatory authorities in all countries and by ethical review committees at all trial sites. All the

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maternal participants provided written informed consent, and parental consent for the participation of infants was obtained according to the standards at each trial site. An independent data and safety monitoring board monitored safety in an unblinded manner throughout active enrollment.

TRIAL OBJECTIVES

The primary objective was to show the efficacy of maternal immunization with RSV F protein vaccine for the protection of infants against RSV-associated, medically significant lower respiratory tract infection up to 90 days of life (the primary end point). RSV-associated, medically significant lower respiratory tract infection was defined as at least one manifestation of lower respiratory tract infection (cough, nasal flaring, indrawing of the lower chest wall, subcostal retractions, stridor, rales, rhonchi, wheezing, crackles or crepitations, or observed apnea) plus hypoxemia (peripheral oxygen saturation of <95% at sea level or of <92% at an altitude of >1800 m) or tachypnea (≥70 breaths per minute from 0 to 59 days of age and ≥60 breaths per minute at 60 days of age or older); the presence of RSV in nasal swab samples was confirmed by the central laboratory.

There were two secondary objectives. The first was to show vaccine efficacy against RSV-associated lower respiratory tract infection with severe hypoxemia through 90 days of life, and the second was to show vaccine efficacy against RSV-associated lower respiratory tract infection with documented hospitalization through 90 days of life. RSV-associated lower respiratory tract infection was defined as at least one manifestation of lower respiratory tract infection (cough, nasal flaring, indrawing of the lower chest wall, subcostal retractions, stridor, rales, rhonchi, wheezing, crackles or crepitations, or observed apnea). Severe hypoxemia was defined as the presence of one of the following criteria: a peripheral oxygen saturation lower than 92% at sea level or lower than 87% at an altitude greater than 1800 m or the use of high-flow nasal cannula, continuous positive airway pressure, bilevel positive airway pressure, bubble continuous positive airway pressure, bag-mask ventilation, intubation with subsequent mechanical (or manual) ventilation, or extracorporeal membrane oxygenation. Further details of the secondary objectives are provided in Section S1.7.

Figure 1 (facing page). Screening, Enrollment, and Randomization.

Data regarding the disposition and demographic characteristics of the participants, safety, and immunogenicity were obtained from the complete and locked database (date of data extraction, September 27, 2019). Efficacy data were obtained from the locked database after all the participants had completed the 180-day follow-up (date of data extraction, January 30, 2019); these data represented the official efficacy analysis set. The safety population comprised all maternal participants who had undergone randomization and received the respiratory syncytial virus fusion protein nanoparticle vaccine (RSV F vaccine) or placebo and their live-born infants. Data on exclusions are derived from incomplete informed consent documentation, lost or incomplete source documentation, or both. The intention-to-treat efficacy analysis population included all maternal participants and their infants in the safety analysis population for whom at least one respective post-treatment or postpartum efficacy measurement was available for both the mother and the infant, as evidenced by collection of surveillance observations. The maternal participants in the per-protocol efficacy analysis population were those who received the assigned RSV F vaccine or placebo, had at least one post-treatment encounter with trial personnel during which active or passive surveillance (or both) for RSV illness could have been performed, and had no major protocol deviations affecting the primary efficacy end point, as determined and documented by the sponsor before database lock and unblinding. The infant participants in the per-protocol efficacy population were those who were born at 37 weeks or more of gestation, who were born to maternal participants who had undergone randomization and received the assigned vaccine or placebo at least 2 weeks before delivery, and who did not receive prophylactic treatment with palivizumab between the day of birth and day 180 after delivery, had at least one postpartum encounter with trial personnel during which active or passive surveillance (or both) for RSV illness could have been performed, and had no major protocol deviations affecting the primary efficacy end point, as determined and documented by the sponsor before database lock and unblinding. Participants who were excluded from one or more analysis populations may have had more than one of the listed major protocol deviations or exclusionary characteristics. Per-protocol status in an infant required elements of per-protocol performance in the mother.

If vaccine efficacy was shown through 90 days for the primary and secondary objectives, a hierarchical sequence of hypothesis testing was to be carried out to examine vaccine efficacy up to 120, 150, and 180 days of life. Details of other secondary analyses (e.g., safety and immunogenicity), exploratory analyses (e.g., between-group differences in the percentages of infants with lower respiratory tract infection from any cause),

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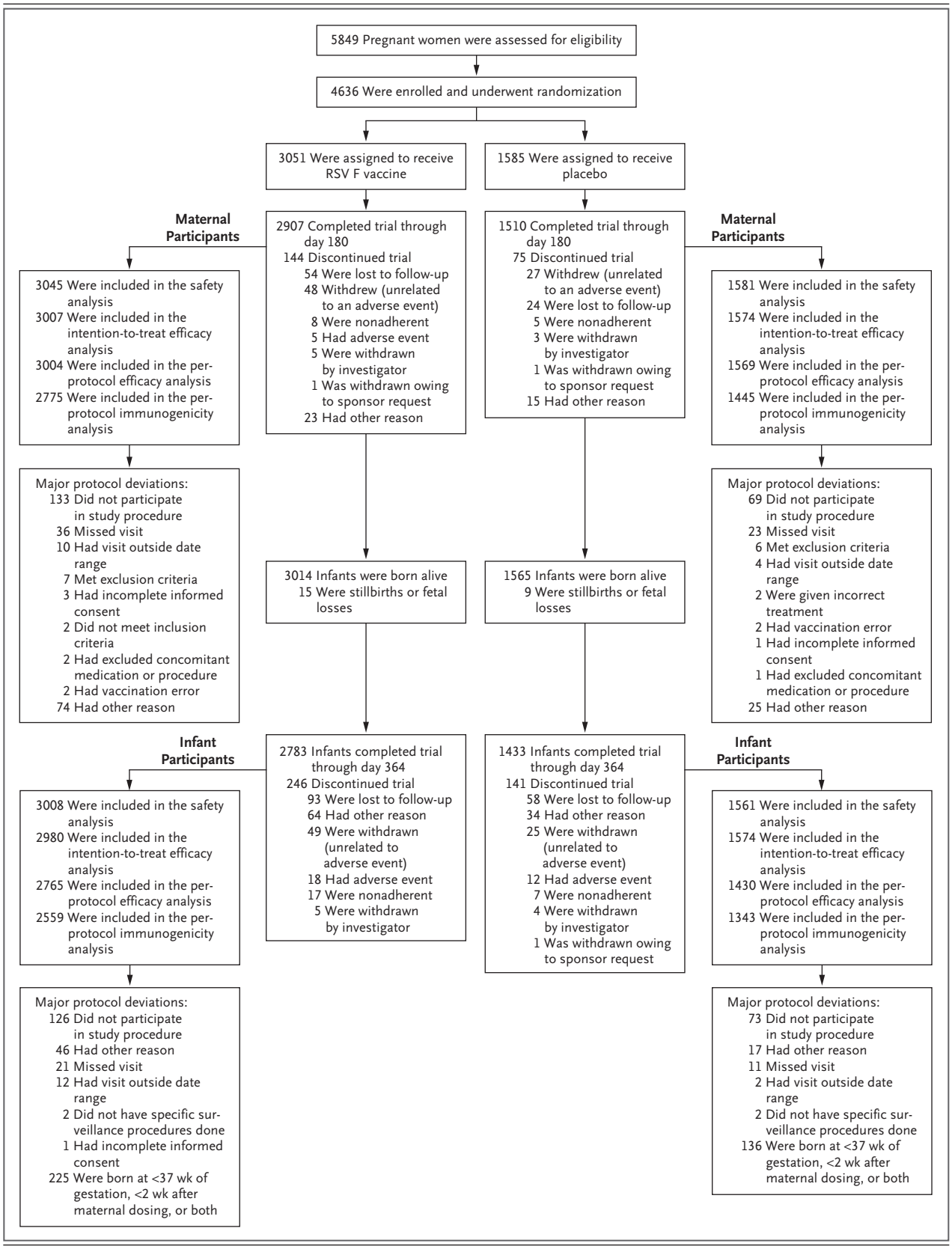

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Table 1. Baseline Demographic Characteristics and Other Characteristics of the Maternal Participants and Birth and Household Characteristics of their Infants.*

Characteristic	RSV F Vaccine	Placebo
Maternal participants		
Maternal participants — no.†	3045	1581
Demographic characteristics at baseline		
Maternal age — yr	26±5.3	26±5.2
Race — no. (%)‡		
Black	1335 (43.8)	682 (43.1)
White	903 (29.7)	489 (30.9)
Asian	320 (10.5)	168 (10.6)
Other	487 (16.0)	242 (15.3)
Hispanic or Latino ethnic group — no.(%)§	409 (13.4)	212 (13.4)
Body-mass index¶	28.6±5.0	28.5±5.1
Primigravida — no. (%)	1060 (34.8)	525 (33.2)
≤3 Prior pregnancies — no. (%)	2916 (95.8)	1515 (95.8)
Other characteristics		
Gestational age at the time vaccine or placebo was administered — wk	32±2.6	32±2.6
Method of delivery		
Vaginal — no./total no. (%)‖	2201/3007 (73.2)	1132/1555 (72.8)
Cesarean — no./total no. (%)**	806/3007 (26.8)	423/1555 (27.2)
Data not available — no./total no. (%)	38/3045 (1.2)	26/1581 (1.6)
Infant participants		
Infant participants — no.	3008	1561
Birth characteristics		
Male sex — no. (%)	1556 (51.7)	799 (51.2)
Interval from vaccine or placebo administration to delivery		
Mean — days	51.9±20.4	51.3±20.7
<14 days — no. (%)	50 (1.7)	36 (2.3)
14 to <30 days — no. (%)	437 (14.5)	216 (13.8)
≥30 days — no. (%)	2521 (83.8)	1309 (83.9)
Gestational age at delivery††		
Mean — wk	39.3±1.5	39.3±1.6
≥37 wk — no./total no. (%)	2811/2986 (94.1)	1458/1554 (93.8)
<37 wk — no./total no. (%)	175/2986 (5.9)	96/1554 (6.2)
Data not available — no./total no. (%)	22/3008 (0.7)	7/1561 (0.4)
Weight — kg	3.2±0.5	3.2±0.5
Length — cm	50.0±2.9	50.2±3.1
Frontal-occipital circumference — cm	34.2±2.1	34.2±1.8
Median Apgar score (interquartile range)		
At 1 min	9 (8–9)	9 (8–9)
At 5 min	10 (9–10)	9.5 (9–10)

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Table 1. (Continued.)

Characteristic	RSV F Vaccine	Placebo
Household characteristics at day 0 — no. (%)		
Infants with a smoker living in the household	755 (25.1)	414 (26.5)
Infants with other children <5 yr of age living in the household	1161 (38.6)	618 (39.6)
Infants with other children <5 yr of age who attend group care ≥3 days/wk living in the household	590 (19.6)	326 (20.9)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. RSV F vaccine denotes respiratory syncytial virus fusion protein nanoparticle vaccine.
† Of the 4636 maternal participants enrolled, 10 (0.2%) had incomplete consent or other source documentation that could not be recovered (4 in the vaccine group and 6 in the placebo group). These participants and their infants were excluded from all analyses.
‡ Race was reported by the maternal participant of each mother–infant pair for herself and for her infant.
§ Ethnic group was reported by the maternal participant of each mother–infant pair for herself and for her infant.
¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.
‖ Vaginal deliveries included spontaneous vaginal deliveries and forceps- or vacuum-assisted deliveries.
** Cesarean deliveries included planned repeat and primary procedures, cesarean section after failed attempts at vaginal delivery, and emergency procedures. Emergency cesarean deliveries accounted for 6.5% of all deliveries in high-income countries and for 14.5% of all deliveries in low- or middle-income countries; no effect of vaccine administration was observed in either economic stratum.
†† Gestational age at delivery was calculated only for participants for whom the protocol-mandated dating ultrasonography result was available.

and post hoc analyses (e.g., comparisons between high-income countries and low- or middle-income countries, as classified according to the World Bank ranking,[8] with respect to primary, secondary, and exploratory end points of lower respiratory tract infection) are provided in Section S1.8 and in the protocol and statistical analysis plan.

RANDOMIZATION AND CONDUCT OF THE TRIAL

Randomization was performed centrally, with a separate blocking strategy for each trial site and with stratification according to maternal age (see Section S1.3). We randomly assigned women, in 1:1 ratio in the first global RSV season and in a 2:1 ratio thereafter, to receive vaccine (120 μg of RSV F vaccine adsorbed to 0.4 mg of aluminum)[9] or placebo (formulation buffer without aluminum). The trial was planned as a group-sequential design with up to two interim analyses. However, enrollment was slower than planned, and after 2 years, the sponsor elected to conduct an informational analysis (performed by the independent statistician who conducted analyses for the data and safety monitoring board). This analysis indicated that vaccine efficacy was present at a prespecified minimum level (approximately 40%) that was deemed to be sufficient to warrant further investment, with no other information provided. Enrollment was continued for a further season in the Northern and Southern Hemispheres and then terminated after enrollment in the vaccine group exceeded the minimum safety database target of 3000, at which point it was believed that a sufficient number of cases had been captured to test the primary hypothesis. End-point data that were accrued after the data lock for the informational analysis were included in the final analysis.

STATISTICAL ANALYSIS

We planned to enroll up to 8618 pregnant women on the basis of a group sequential design with two planned interim analyses with approximately 4600 and 6600 enrolled participants, a projected percentage of infants with a primary end-point event of 4% and a vaccine efficacy of approximately 60%. The primary and secondary efficacy analyses were performed in the per-protocol population, which included infants who were born at 37 weeks or more of gestation, who were born to maternal participants who had undergone randomization and received the assigned vaccine or placebo at least 2 weeks before delivery, and who did not receive prophylactic treatment with palivizumab between the day of birth and day 180 after delivery, had at least one post-

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partum encounter with trial personnel during which active or passive surveillance (or both) for RSV illness could have been performed, and had no major protocol deviations affecting the primary efficacy end point, as determined and documented by the sponsor before database lock and unblinding (see Section S1.9). These efficacy analyses were performed with clinical data generated by trained staff at the trial sites, including pulse oximetry measurements obtained with the sponsor-provided device; RSV diagnoses were made at the trial central laboratory with the use of the molecular assay validated for the trial. Prespecified analyses of the primary and secondary end points, based on the same data, were also performed in the intention-to-treat population, which included participants who had any visit during which efficacy data might have been gathered, regardless of treatment errors or protocol deviations.

In order to maximize illness ascertainment, particularly in seriously ill infants hospitalized at institutions unaffiliated with trial sites and thus not readily accessible to site staff and protocol pulse oximetry, we also performed exploratory "expanded-data" intention-to-treat analyses that included physical findings, pulse oximetry data, and RSV diagnoses extracted from the medical records of infants hospitalized for respiratory or infectious illness. Further exploratory analyses of lower respiratory illnesses from any cause, irrespective of the detection of a specific pathogen, in both the per-protocol and intention-to-treat populations also used these expanded data. All primary and secondary end points, as well as exploratory end points of RSV illnesses that met the primary and secondary end-point definitions but that were evaluated with the use of expanded data, were validated by an independent adjudication committee of three pediatricians before the data were unblinded. Estimates of vaccine efficacy were calculated as percentages [(1–relative risk) × 100] and were based on the relative risk and confidence intervals obtained with the use of Poisson regression models with robust error variance.[10] The reported confidence intervals for secondary, exploratory, and post hoc analyses were not adjusted for multiplicity and should be viewed as descriptive and not used to infer definitive treatment effects for these end points. Vaccine efficacy against the primary end point (RSV-associated, medically significant lower respiratory tract infection) through the first 90 days of life was analyzed with the use of a one-sided type I error rate of 0.0124 based on a Pocock spending function (i.e., lower bound of a two-sided 97.52% confidence interval). This type I error rate arose from the original group-sequential design but was retained to guard against type I error inflation after the informational analysis. The Food and Drug Administration criterion for success with respect to the primary objective (i.e., to show vaccine efficacy against the primary end point) was a lower bound of the 97.52% confidence interval of 30% or greater; the criterion of other authorities was a lower bound greater than 0%. All other efficacy analyses used a 95% confidence interval, with a lower bound greater than 0% as the criterion of success (without adjustment for multiplicity).

RESULTS

PATIENTS

Between December 3, 2015, and May 2, 2018, a total of 4636 women were enrolled, of whom 3051 (65.8%) were randomly assigned to receive the RSV F vaccine (Fig. 1). Among the 4636 women enrolled, 52.3% were enrolled in South Africa and 23.3% were enrolled in the United States (Table S1). There were 4579 live births. Of the 4636 women, 10 (0.2%) had incomplete consent or other source documentation that could not be recovered (4 in the vaccine group and 6 in the placebo group). These participants and their infants were excluded from all analyses. A total of 4195 infants (91.6%) were included in the per-protocol population, and 4527 infants (98.9%) were included in the intention-to-treat population (Fig. 1). The characteristics of the women at baseline and of the infants, as well as gestational age at the time that vaccine or placebo was administered, were similar in the two trial groups (Table 1), including when stratified according country income level (high-income country or low- or middle-income country) (Tables S2 and S3).

PRIMARY AND SECONDARY END POINTS

The percentage of infants who had RSV-associated, medically significant lower respiratory tract infection through 90 days was 1.5% in the vaccine group and 2.4% in the placebo group (estimated vaccine efficacy in the per-protocol analy-

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Table 2. Efficacy of Maternal Vaccination against Lower Respiratory Tract Infection in Infants.*

Efficacy End Point	Per-Protocol Analyses†			Exploratory Expanded-Data Intention-to-Treat Analyses‡		
	RSV F Vaccine	Placebo	Vaccine Efficacy (95% CI)	RSV F Vaccine	Placebo	Vaccine Efficacy (95% CI)
	% of infants (no./total no.)		%	*% of infants (no./total no.)*		%
Primary end point						
RSV-associated medically significant lower respiratory tract infection up to 90 days of life	1.5 (41/2765)	2.4 (35/1430)	39.4 (5.3 to 61.2)§	2.3 (70/2980)	4.0 (62/1547)	41.4 (18.0 to 58.1)¶
Secondary end points						
RSV-associated lower respiratory tract infection with severe hypoxemia up to 90 days of life	0.5 (14/2765)	1.0 (14/1430)	48.3 (–8.2 to 75.3)	0.9 (27/2980)	2.2 (34/1547)	58.8 (31.9 to 75.0)
Hospitalization for RSV-associated lower respiratory tract infection up to 90 days of life	2.1 (57/2765)	3.7 (53/1430)	44.4 (19.6 to 61.5)	2.2 (65/2980)	4.1 (63/1547)	46.4 (24.7 to 61.9)
	no. of events per 100 infants (no. of events/ total no. of infants)			*no. of events per 100 infants (no. of events/ total no. of infants)*		
Exploratory all-cause end points						
Medically significant lower respiratory tract infection from any cause up to 90 days of life	5.5 (153/2765)	7.2 (103/1430)	23.2 (1.4 to 40.2)	5.9 (175/2980)	7.5 (116/1547)	21.7 (1.0 to 38.1)
Lower respiratory tract infection from any cause with severe hypoxemia up to 90 days of life	1.7 (47/2765)	3.1 (45/1430)	46.0 (18.7 to 64.1)	1.7 (51/2980)	3.2 (50/1547)	47.0 (21.8 to 64.2)
Hospitalization for lower respiratory tract infection from any cause up to 90 days of life	4.3 (120/2765)	6.0 (86/1430)	27.8 (4.8 to 45.3)	4.2 (125/2980)	6.6 (102/1547)	36.4 (17.4 to 51.0)

* End-point definitions are provided in the Methods section of the article and in Sections S1.4 and S1.7 in the Supplementary Appendix. The definitions for the exploratory all-cause end points followed the definitions of primary and secondary end points but with no requirement for confirmation of RSV infection or confirmation by the clinical end-point adjudication committee. Primary and secondary end-point events and exploratory end-point events involving RSV-associated lower respiratory tract infection were reviewed and confirmed by an independent clinical end-point adjudication committee comprising not less than three pediatricians before unblinding of the data. The reported confidence intervals for vaccine efficacy were not adjusted for multiplicity and hence cannot be used to infer effects.

† The infant participants in the per-protocol efficacy population were those who were born at 37 weeks or more of gestation, who were born to maternal participants who had undergone randomization and received the assigned vaccine or placebo at least 2 weeks before delivery, and who did not receive prophylactic treatment with palivizumab between the day of birth and day 180 after delivery, had at least one postpartum encounter with trial personnel during which active or passive surveillance (or both) for RSV illness could have been performed, and had no major protocol deviations affecting the primary efficacy end point, as determined and documented by the sponsor before database lock and unblinding. Primary and secondary end-point analyses in the per-protocol population were performed with the use of data based on observations from physical examination by trained clinical site personnel; pulse oximetry data that were generated with the use of the protocol-mandated Masimo Rad-5 pulse oximeter; and RSV molecular diagnostic data based on the validated GenMark eSensor assay in place at the central laboratory (Marshfield Clinic Research Institute, Marshfield, Wisconsin). All exploratory end-point analyses allowed the use of data abstracted from hospital records, as for the intention-to-treat analyses (see below).

‡ The intention-to-treat population comprised all living infants with any efficacy data, regardless of gestational age, proximity of delivery to the time of maternal vaccination, or the presence of treatment errors or protocol deviations or violations. The expanded data used in the exploratory intention-to-treat analyses included the information used for primary and secondary end points as described above, supplemented by data abstracted from the hospital records of admitted participants. The intention-to-treat analysis of the primary and secondary end points that used data that were restricted to the end points evaluated according to protocol-dictated standards is reported in Table S15 in the Supplementary Appendix.

§ The 97.52% confidence interval was –1.0 to 63.7.

¶ The 97.52% confidence interval was 13.9 to 60.1.

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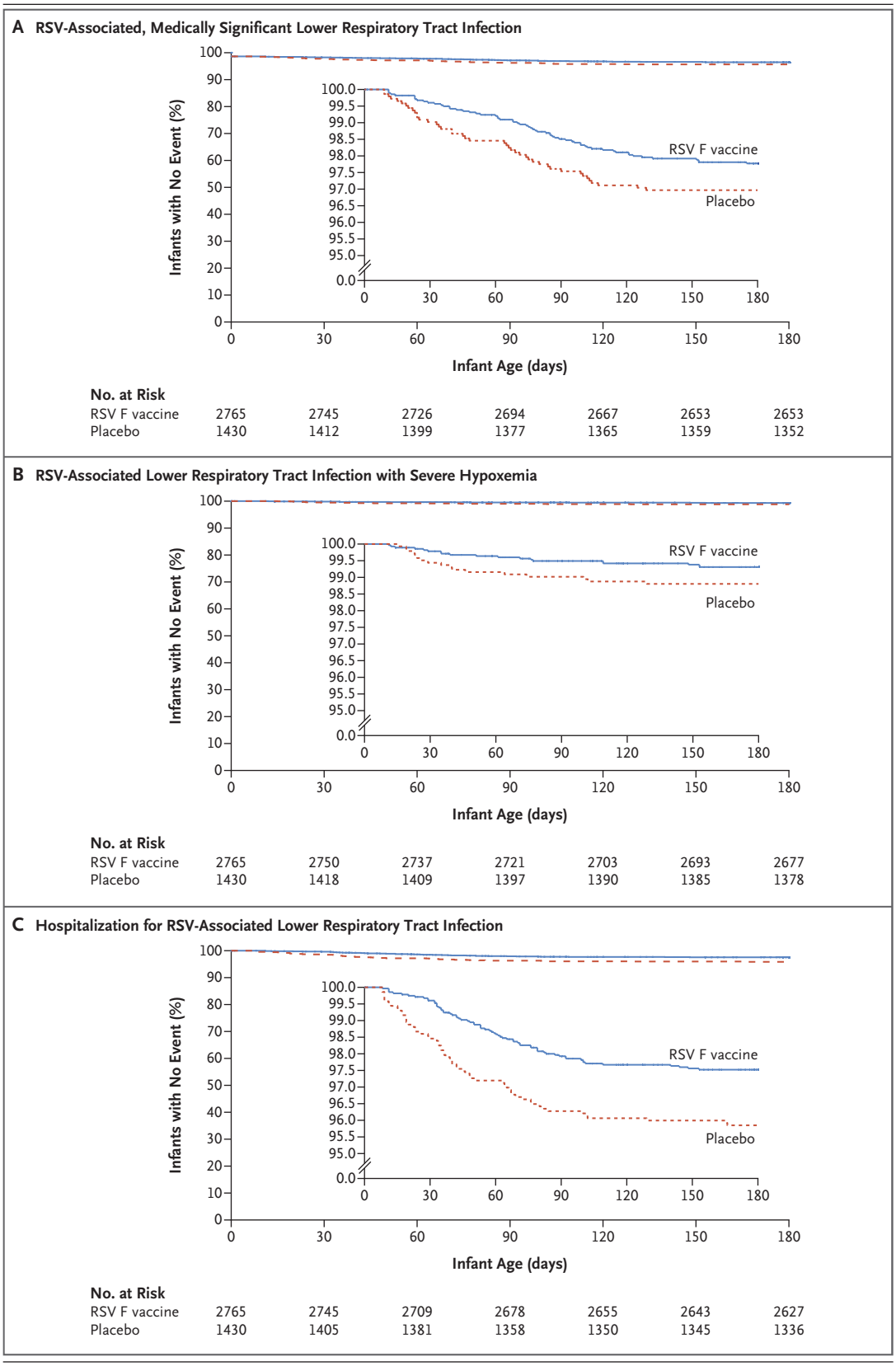

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Figure 2 (facing page). Kaplan–Meier Survival Plots for the Primary and Secondary Efficacy End Points in the Per-Protocol Population.

Shown are the Kaplan–Meier survival plots for the primary efficacy end point of RSV-associated, medically significant lower respiratory tract infection (Panel A) and the secondary efficacy end points of RSV-associated lower respiratory tract infection with severe hypoxemia (Panel B) and hospitalization for RSV-associated lower respiratory tract infection (Panel C). For each panel, the main figure depicts the percentage of infants in the per-protocol population who survived without the occurrence of the specified end-point event as a function of time from delivery. Because the events under study occurred in 5% of the infant population or less over the first 180 days of life, insets are provided to show the same data on an enlarged y axis.

sis, 39.4%; 97.52% confidence interval [CI], –1.0 to 63.7; 95% CI, 5.3 to 61.2) (Table 2). An analysis that was based on the same definition and data but that was performed in the intention-to-treat population yielded an efficacy estimate of 32.2% (95% CI, –4.2 to 55.9) (Table S15). The results of analyses that used expanded data sources in the intention-to-treat population are provided in Table 2. The results for various efficacy end points in infants at 120, 150, and 180 days of life are provided in Table S14. Kaplan–Meier survival curves based on analyses in the per-protocol population are provided in Figure 2.

The percentage of infants in the per-protocol population with RSV-associated lower respiratory tract infection with severe hypoxemia through 90 days was 0.5% in the vaccine group and 1.0% in the placebo group (vaccine efficacy, 48.3%; 95% CI, –8.2 to 75.3; vaccine efficacy in the intention-to-treat population was 44.4% (95% CI, –14.9 to 73.1), as determined with the use of clinical site data only, and 58.8% (95% CI, 31.9 to 75.0), as determined with the use of expanded data (Table 2 and Table S15). The percentage of infants in the per-protocol population who were hospitalized for RSV-associated lower respiratory tract infection through 90 days was 2.1% in the vaccine group and 3.7% in the placebo group (vaccine efficacy, 44.4%; 95% CI, 19.6 to 61.5); the results in the intention-to-treat population were closely similar to those of the per-protocol analysis: 48.1% (95% CI, 26.1 to 63.5), as determined with the use of clinical site data only, and 46.4% (95% CI, 24.7 to 61.9), as determined with the use of expanded data (Table 2 and Table S15). Point estimates of vaccine efficacy through 120, 150, and 180 days of life declined relative to the first 90 days of life with respect to the end point of RSV-associated, medically significant lower respiratory tract infection, but the estimates remained similar throughout with respect to the end points of hospitalization for RSV-associated lower respiratory tract infection and RSV-associated lower respiratory tract infection with severe hypoxemia in both the per-protocol and expanded-data intention-to-treat analyses.

EXPLORATORY END POINTS

The rate of medically significant lower respiratory tract infections from any cause through the first 90 days of life was 5.5 events per 100 infants in the vaccine group and 7.2 events per 100 in the placebo group (vaccine efficacy in the per-protocol analysis, 23.2%; 95% CI, 1.4 to 40.2) (Table 2). The corresponding rates for lower respiratory tract infection from any cause with severe hypoxemia through 90 days of life were 1.7 and 3.1 events per 100 infants (vaccine efficacy, 46.0%; 95% CI, 18.7 to 64.1), and the rates for lower respiratory tract infection from any cause with hospitalization through 90 days of life were 4.3 and 6.0 events per 100 infants (vaccine efficacy, 27.8%; 95% CI, 4.8 to 45.3). The results of the expanded-data intention-to-treat analysis were similar to those of the per-protocol analysis (Table 2). The effects of vaccine on lower respiratory tract infection from any cause appeared to be durable through 180 days of life.

Estimates of vaccine efficacy against the various end points in both per-protocol and expanded-data intention-to-treat analyses, stratified according to country income level, are provided in Table S16. Efficacy estimates were greater in low- or middle-income countries than in high-income countries in general, whereas the percentages of infants with end-point events were lower in high-income countries and the confidence bounds for vaccine efficacy estimates were therefore wider. Estimates of vaccine efficacy against lower respiratory tract infection according to RSV subtype (A or B) are provided in Table S17.

Estimates of vaccine efficacy against RSV-associated lower respiratory tract infection of any severity and against RSV-associated, medically significant lower respiratory tract infection according to the definition of tachypnea used by the WHO (10 breaths per minute less than in the protocol definition) were 15 to 19% over the

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first 90 days of life, declining to 12 to 13% over the first 180 days of life (Table S18). There was no clear efficacy against lower respiratory tract infection from any cause when events of any severity were included in the analysis. The incidence of RSV-associated symptomatic respiratory tract infection was similar among the women who received RSV F vaccine (4.9% [148 of 3004]) and among those who received placebo (4.8% [76 of 1569]) through 180 days post partum.

SAFETY

Local injection-site reactions were predominantly mild and were more common among the women who received the vaccine than among those who received placebo (40.7% vs. 9.9%; P<0.001) (Table 3 and Table S4). Fever within 7 days after vaccination occurred in 1.2% of the women who received the active vaccine and in 1.6% of the women who received placebo; the frequency of systemic reactions overall was similar in the two groups of women. No clear between-group differences were observed with regard to the percentages of women who had unsolicited adverse events, including the prespecified adverse events of special interest or adverse delivery outcomes (Table 3 and Section S2.2.4 and Tables S5, S7, and S9).

The overall percentages of infants who had common or serious adverse events or protocol-defined adverse events of special interest were also similar in each trial group (Table 3, and Tables S6, S8, and S10). However, serious adverse events coded as "pneumonia" were less common among the infants in the vaccine group (2.2%) than among those in the placebo group (4.5%) through 364 days (Table 3).

IMMUNOGENICITY

Fourteen days after injection of the RSV F vaccine (the timing of peak levels in phase 2), the geometric mean concentration of palivizumab-competitive antibodies was 12.39 times (95% CI, 11.98 to 12.81) as high as it was before injection, and the geometric mean concentration of anti-F IgG was 18.59 times (95% CI, 17.84 to 19.36) as high.[7,9] Additional results for these antibodies as well as RSV A and B microneutralization titers are provided in Table S11. Transient decreases in RSV antibody levels in women were observed at the time of delivery; the levels rebounded at day 35 post partum and then declined at day 180 post partum.

The geometric mean concentrations of anti-F IgG and palivizumab-competitive antibodies in cord blood were 9501 ELISA (enzyme-linked immunosorbent assay) units (EU) per milliliter (95% CI, 9224 to 9787) and 136 μg per milliliter (95% CI, 132 to 139), respectively, among the infants in the vaccine group and 752 EU per milliliter (95% CI, 719 to 786) and 15 μg per milliliter (95% CI, 14 to 15), respectively, among the infants in the placebo group. In the vaccine group, the ratio of antibody concentration in cord blood to antibody concentration in the mother at the time of delivery was 1.04 (95% CI, 1.02 to 1.06) for palivizumab-competitive antibodies and 1.17 (95% CI, 1.14 to 1.19) for anti-F IgG. The estimated antibody half-life in the infants in the vaccine group was 49.1 for palivizumab-competitive antibodies and 38.3 for anti-F IgG. The results of analyses of transplacental antibody transfer overall and as stratified according to country income level are provided in Tables S11 and S12.

DISCUSSION

We report the results of a large-scale efficacy trial of an investigational RSV F vaccine administered during pregnancy. Vaccine efficacy against RSV-associated, medically significant lower respiratory tract infection in the first 90 days of life, during which about three quarters of cases occurred, was 39% (97.52% CI, –1.0 to 63.7) in the per-protocol analysis; these results did not meet the prespecified criterion for success (lower bound of the 97.52% CI of ≥30%). Vaccine efficacy in secondary analyses was 48.3% (95% CI, –8.2 to 75.3) against RSV-associated lower respiratory tract infection with severe hypoxemia and 44.4% (95% CI, 19.6 to 61.5) against hospitalization for RSV-associated lower respiratory tract infection.

Although there were, as expected, more local injection-site reactions with vaccine than with placebo, the overall percentages of participants having adverse events or serious adverse events were similar in the two groups. The post hoc observation that infants born to women who received the RSV F vaccine were approximately 50% less likely to have all-cause pneumonia re-

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Table 3. Safety Profile in Maternal and Infant Participants.*

Adverse Event	RSV F Vaccine	Placebo
Maternal participants reporting adverse events through the 180-day postdelivery trial visit		
Maternal participants — no.	3045	1581
Any adverse event that occurred subsequent to the administration of RSV F vaccine or placebo — no. (%)	2501 (82.1)	1204 (76.2)
Solicited adverse events — no. (%)†		
Reactogenicity within 7 days after dosing	1737 (57.0)	653 (41.3)
Local injection-site reaction	1240 (40.7)	157 (9.9)
Systemic reaction	1255 (41.2)	611 (38.6)
Fever of any severity within 7 days after dosing	37 (1.2)	25 (1.6)
Unsolicited adverse events — no. (%)	2005 (65.8)	1022 (64.6)
Severe and related adverse event‡	2 (<0.1)	4 (0.3)
Medically attended adverse event	1534 (50.4)	802 (50.7)
Serious adverse event — no. (%)§	906 (29.8)	455 (28.8)
Protocol-specified pregnancy and puerperium adverse event of special interest — no. (%)§	377 (12.4)	190 (12.0)
Infant participants with adverse events from birth through the 364th-day-of-life trial visit		
Infant participants — no.	3008	1561
Any adverse event — no. (%)	2477 (82.3)	1295 (83.0)
Severe and related adverse event‡	0	0
Medically attended adverse event	2058 (68.4)	1091 (69.9)
Serious adverse event§	1332 (44.3)	724 (46.4)
Serious adverse event with outcome of death	17 (0.6)	12 (0.8)
Protocol-specified adverse event of special interest — no. (%)¶	274 (9.1)	151 (9.7)
Serious adverse event coded to the MedDRA preferred term "pneumonia" — no. (%)‖	66 (2.2)	70 (4.5)

* Data in this table represent analyses through 180 day of postpartum follow-up for maternal participants and through 364 days of life for infant participants; there was a 14-day trial-visit window for both maternal and infant participants. Analyses were generated from the data obtained from the locked database as of September 27, 2019, and were performed in the safety analysis population (all maternal participants who had undergone randomization and received the RSV F vaccine or placebo and their live-born infants). MedDRA denotes *Medical Dictionary for Regulatory Activities*.

† Solicited adverse events were common postvaccinal adverse events that were solicited by diary from day 0 through day 6 after injection.

‡ Severe and related adverse events were those that substantially prevented the performance of normal daily activities and were assessed by the clinical investigators to be at least possibly related to the RSV F vaccine or placebo.

§ Serious adverse events were those that were fatal or life-threatening, caused or prolonged hospitalization, led to persistent disability, or were congenital anomalies or birth defects. In this trial, all congenital anomalies, regardless of how minor, were treated as serious adverse events.

¶ Protocol-defined adverse events of special interest were adverse events that occurred during pregnancy and the puerperium that reflected the recommendations of the Brighton Collaboration task forces regarding safety data collection for maternal immunization.[11].

‖ Serious adverse events coded to the MedDRA preferred term "pneumonia" showed an imbalance between the trial groups that suggested a relative risk of 0.49 in infants of immunized maternal participants, which was associated with an unadjusted P value lower than 0.001. This P value is smaller than any other in the analyses of serious adverse events by more than 2 orders of magnitude (Table S10). Further details on solicited adverse events are provided in Table S4; on unsolicited adverse events that were reported in at least 1% of maternal or infant participants in Tables S5 and S6, respectively; on all serious adverse events in maternal and infant participants in Tables S9 and S10, respectively; and all protocol-specified adverse events of special interest in maternal and infant participants in Tables S7 and S8, respectively.

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ported as a serious adverse event through 180 or 364 days of life is consistent with a potential benefit of the vaccine. Also suggestive of a possible benefit are the results with respect to the secondary end point of vaccine efficacy against RSV-associated lower respiratory tract infection with severe hypoxemia and the results of exploratory analyses of vaccine efficacy against hospitalization for lower respiratory tract infection from any cause and lower respiratory tract infection from any cause with severe hypoxemia in the first 90 days of life. Given their exploratory nature and the lack of adjustment for multiplicity, these analyses, as well as the expanded-data intention-to-treat analyses, should be viewed as hypothesis-generating.

Although the trial was not powered to evaluate vaccine efficacy according to country (or according to country income level), vaccine efficacy against RSV-associated, medically significant lower respiratory tract infection, RSV-associated lower respiratory tract infection with severe hypoxemia, and hospitalization for RSV-associated lower respiratory tract infection appeared to be greater in low- or middle-income countries than in high-income countries. However, there were substantially fewer cases and wide confidence intervals in the latter group. Further reasons for the apparent lower efficacy in high-income countries might include hospitalization for less severe cases, lower prevalence of breast-feeding, and lower background rates of severe RSV-associated lower respiratory tract infection because of factors such as less exposure to indoor smoke or to crowding and later introduction to social contact.

Our trial has several limitations. The study was underpowered because of overestimation of the percentage of infants who would have a primary end-point event, for which no applicable antecedent data existed, and because of the early termination of the trial. In addition, testing of cord blood for RSV A and B neutralizing antibodies has not yet been completed; the results of such testing are required to fully elucidate the association of RSV neutralizing antibody, anti-F IgG, and palivizumab-competitive antibody levels with the risk of RSV-associated lower respiratory tract infection in infants. Further analyses will attempt to establish correlates of protection against RSV-associated lower respiratory tract infection, which could inform immunogenicity-bridging studies. Additional studies are required to determine whether variation in vaccine efficacy between high-income countries and low- or middle-income countries is a consistent finding, as well as to evaluate the effectiveness of maternal RSV vaccination for the prevention of RSV-associated lower respiratory tract infection in infants born preterm.

In conclusion, in this randomized, placebo-controlled trial, maternal RSV F vaccine administered during pregnancy had an overall adverse event profile similar to placebo. The results with respect to the primary end point did not meet prespecified criteria for vaccine efficacy. However, the results with respect to the other end points of RSV-associated and all-cause respiratory disease in infants suggested potential benefits of maternal RSV vaccination that warrant further study of this strategy.

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APPENDIX

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