ORIGINAL ARTICLE

Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults

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ABSTRACT

BACKGROUND

Respiratory syncytial virus (RSV) infection causes considerable illness in older adults. The efficacy and safety of an investigational bivalent RSV prefusion F protein–based (RSVpreF) vaccine in this population are unknown.

METHODS

In this ongoing, phase 3 trial, we randomly assigned, in a 1:1 ratio, adults (≥60 years of age) to receive a single intramuscular injection of RSVpreF vaccine at a dose of 120 μg (RSV subgroups A and B, 60 μg each) or placebo. The two primary end points were vaccine efficacy against seasonal RSV-associated lower respiratory tract illness with at least two or at least three signs or symptoms. The secondary end point was vaccine efficacy against RSV-associated acute respiratory illness.

RESULTS

At the interim analysis (data-cutoff date, July 14, 2022), 34,284 participants had received RSVpreF vaccine (17,215 participants) or placebo (17,069 participants). RSV-associated lower respiratory tract illness with at least two signs or symptoms occurred in 11 participants in the vaccine group (1.19 cases per 1000 person-years of observation) and 33 participants in the placebo group (3.58 cases per 1000 person-years of observation) (vaccine efficacy, 66.7%; 96.66% confidence interval [CI], 28.8 to 85.8); 2 cases (0.22 cases per 1000 person-years of observation) and 14 cases (1.52 cases per 1000 person-years of observation), respectively, occurred with at least three signs or symptoms (vaccine efficacy, 85.7%; 96.66% CI, 32.0 to 98.7). RSV-associated acute respiratory illness occurred in 22 participants in the vaccine group (2.38 cases per 1000 person-years of observation) and 58 participants in the placebo group (6.30 cases per 1000 person-years of observation) (vaccine efficacy, 62.1%; 95% CI, 37.1 to 77.9). The incidence of local reactions was higher with vaccine (12%) than with placebo (7%); the incidences of systemic events were similar (27% and 26%, respectively). Similar rates of adverse events through 1 month after injection were reported (vaccine, 9.0%; placebo, 8.5%), with 1.4% and 1.0%, respectively, considered by the investigators to be injection-related. Severe or life-threatening adverse events were reported in 0.5% of vaccine recipients and 0.4% of placebo recipients. Serious adverse events were reported in 2.3% of participants in each group through the data-cutoff date.

CONCLUSIONS

RSVpreF vaccine prevented RSV-associated lower respiratory tract illness and RSV-associated acute respiratory illness in adults (≥60 years of age), without evident safety concerns. (Funded by Pfizer; RENOIR ClinicalTrials.gov number, NCT05035212; EudraCT number, 2021-003693-31.)

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*The members of the RENOIR Clinical Trial Group are listed in the Supplementary Appendix, available at NEJM.org.

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Respiratory syncytial virus (RSV) infection is a common cause of lower respiratory tract illness worldwide, with a risk of severe illness among infants, young children, and older adults.[1] The risk of severe RSV disease increases among older adults who are frail or have coexisting conditions.[2] RSV illness develops in approximately 3 to 7% of healthy older adults in the United States and Europe each year, with an estimated 177,000 hospitalizations and 14,000 deaths each year in the United States.[3,4] The severity of illness among older adults who are hospitalized with RSV disease is substantial; 18% are admitted to an intensive care unit, 31% receive home health services at discharge, and 26% die within 1 year after admission.[5] The diagnosis of RSV infection in adults is probably underestimated because, unlike the case with influenza, the reporting of RSV infections is not required by law in most jurisdictions, and testing, which is not routinely performed, may be unreliable.[6,7] RSV shedding also occurs at higher levels and for a longer duration in older adults than in younger adults.[8] Taken together, the overall RSV disease burden in older adults is high, and a vaccine to protect this population from RSV-associated lower respiratory tract illness is an unmet medical need.

Despite more than 50 years of development, no RSV vaccine has been licensed.[9] Challenges in development have included the lack of a precise protection correlate and poor immunogenicity of previous vaccine candidates.[9,10] Development of protein-subunit vaccines has focused on the RSV fusion (F) glycoprotein, and the metastable prefusion form (preF) is a major target of the most potent virus neutralizing antibodies.[11,12] Thus, stabilized preF is a key vaccine antigen.

The investigational bivalent RSV prefusion F protein–based (RSVpreF) vaccine contains stabilized prefusion F glycoproteins from the two major cocirculating antigenic subgroups (RSV A and RSV B).[13,14] In phase 1–2 clinical studies, vaccination of adults with RSVpreF formulations at a 120-μg dose level substantially increased RSV neutralizing titers and had an acceptable safety and side-effect profile.[15-17] In an RSV challenge study involving healthy persons who were 18 to 50 years of age, the vaccine efficacy was 87% (95% confidence interval [CI], 54 to 96) against symptomatic RSV infection confirmed by any detectable viral RNA on at least 2 consecutive days.[13] These safety, immunogenicity, and efficacy data provided support for the advancement of RSVpreF vaccine to a pivotal phase 3 trial, RSV Vaccine Efficacy Study in Older Adults Immunized against RSV Disease (RENOIR), involving adults who were at least 60 years of age as well as to a phase 3 trial, Maternal Immunization Study for Safety and Efficacy (MATISSE),[18] evaluating the efficacy and safety of maternal RSVpreF vaccination in preventing RSV-associated lower respiratory tract illness in infants. Here, we describe the results of an interim analysis of the RENOIR trial regarding the efficacy and safety of RSVpreF vaccine in the first RSV season after injection.

METHODS

PARTICIPANTS AND TRIAL OVERSIGHT

In this prespecified interim analysis of an ongoing, phase 3, multicenter, double-blind, randomized, placebo-controlled trial, we evaluated the efficacy and safety of RSVpreF vaccine in preventing RSV-associated lower respiratory tract illness during the first RSV season after injection (August 31, 2021, through July 14, 2022). Eligible participants were at least 60 years of age. Healthy participants or those with stable chronic conditions, including chronic cardiopulmonary disease (e.g., chronic obstructive pulmonary disease and asthma), from 240 sites across Argentina, Canada, Finland, Japan, the Netherlands, South Africa, and the United States were included. Apart from persons with stable human immunodeficiency virus, hepatitis B virus, or hepatitis C virus infection, immunocompromised persons were excluded. Influenza and coronavirus disease 2019 (Covid-19) vaccines could be administered 14 days or more before administration of the trial vaccine or placebo. Additional eligibility criteria and information regarding ethical trial conduct are summarized 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).

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 the collection, analysis, and interpretation of the data. 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, who vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PROCEDURES

Participants were randomly assigned in a 1:1 ratio to receive one intramuscular injection of unadjuvanted RSVpreF vaccine at a dose of 120 μg (containing 60 μg each of RSV A and RSV B antigens) or placebo. Placebo was lyophilized to match the appearance of RSVpreF vaccine but did not contain the active ingredients (i.e., RSV A and RSV B preF antigens, which are based on the currently predominant Ontario and Buenos Aires genotypes, respectively).

EFFICACY END POINTS

The first primary end point was the efficacy of RSVpreF vaccine in preventing RSV-associated lower respiratory tract illness (i.e., acute respiratory illness) with at least two signs or symptoms (i.e., cough, wheezing, sputum production, shortness of breath, or tachypnea) lasting more than 1 day and RSV infection that was confirmed by means of reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay (or by means of nucleic acid amplification test if RT-PCR testing was unavailable) within 7 days after the onset of signs or symptoms. The second primary end point was the efficacy of RSVpreF vaccine in preventing RSV-associated lower respiratory tract illness with at least three signs or symptoms (indicating a worse clinical disease presentation) lasting more than 1 day and RSV infection that was confirmed by means of RT-PCR assay (or by means of nucleic acid amplification test if RT-PCR testing was unavailable) within 7 days after the onset of signs or symptoms.

For the primary end points, we calculated the relative risk of a first episode of RSV-associated lower respiratory tract illness (using definitions of ≥2 or ≥3 signs or symptoms, as described in Table S1 in the Supplementary Appendix) in the RSVpreF vaccine group as compared with the placebo group in the first RSV season and starting on day 15 after injection. The RSV season is defined in the Supplementary Appendix.

The secondary end point was the first episode of RSV-associated acute respiratory illness, defined as at least one symptom of an acute respiratory illness (sore throat, cough, nasal congestion or discharge, wheezing, sputum production, or shortness of breath — any of which were new or had increased in intensity) with RT-PCR–confirmed RSV infection within 7 days after symptom onset. Starting on day 15 until the end of the RSV season, all the participants completed screening questionnaires in an electronic diary approximately weekly or when signs or symptoms developed. Participants performed nasal swabbing on days 2 and 3 after the onset of at least one symptom of acute respiratory illness (day 1 was the day of onset), returned swabs as instructed, and arranged an in-person or virtual visit for respiratory illness. Additional nasal swabs were obtained at in-person visits. Participants who were unable to perform nasal swabbing on days 2 and 3 did so as close as possible to those days (on two different days) up to day 7. Follow-up for surveillance of acute respiratory illness in the participants is ongoing for two RSV seasons after injection of RSVpreF vaccine or placebo.

SAFETY END POINTS

The data monitoring committee is responsible for ongoing monitoring of safety. In this interim analysis, safety evaluations included assessment of reactogenicity events, including fever, as recorded by participants in an electronic diary for 7 days after injection in a subgroup from the United States and Japan. Data on unsolicited adverse events in all the participants were collected from enrollment through 1 month after injection. Collection of data on serious adverse events and newly diagnosed chronic medical conditions is ongoing throughout the duration of the trial (i.e., through the end of the second RSV season after injection).

STATISTICAL ANALYSIS

The trial sample size was selected on the basis of the final primary efficacy end points as defined in the protocol. We calculated that 59 participants with RSV-associated lower respiratory tract illness with at least two signs or symptoms would give the trial 90% power to reject the null hypothesis that vaccine efficacy against RSV-associated lower respiratory tract illness would be 20% or less, assuming that the true efficacy of the vaccine is 70%, with a 1:1 randomization ratio and a 5% overall type I error rate.

As prespecified in the protocol, the data monitoring committee could conduct an interim analysis when at least 29 evaluable participants had had a first episode of RSV-associated lower respiratory tract illness with at least two signs or symptoms. The interim analysis reported here was conducted when 44 participants had had at least two signs or symptoms. After the data monitoring committee declared that the success criterion for vaccine efficacy with respect to RSV-associated lower respiratory tract illness with at least two signs or symptoms had been met, planned analyses of cases of RSV-associated lower respiratory tract illness with at least three signs or symptoms were performed because the prespecified minimum number of 15 cases had been met. Severe RSV-associated lower respiratory tract illness was not included in the analysis because the number of cases of severe disease that had accrued at the data-cutoff date did not meet the prespecified minimum number of cases for the interim analysis. The Supplementary Appendix provides further details regarding sample-size determination and additional statistical considerations.

The primary efficacy end points were assessed in the evaluable efficacy population, which consisted of eligible participants who had received vaccine or placebo as randomly assigned, had no major protocol violations, and had a minimum follow-up through day 15 after injection (Table S2). Missing data were not imputed. Vaccine efficacy was defined as (1−risk ratio) × 100%, where the risk ratio is the ratio of the number of confirmed cases of a first episode of RSV-associated lower respiratory tract illness in the RSVpreF vaccine group to the corresponding number in the placebo group. Confidence intervals were calculated with the use of the conditional exact test based on the binomial distribution of P (the number of cases in the RSVpreF vaccine group, given the total number of cases in both groups), adjusted by means of Pocock error spending[19] for the interim analysis (associated type I error, 3.34%; 96.66% confidence interval). The secondary end point of RSV-associated acute respiratory illness is descriptive without type I error spending, so a nominal 95% confidence interval was applied. The widths of the confidence intervals were not adjusted for multiplicity and should not be used in place of hypothesis testing.

Statistical methods used in sensitivity analyses to estimate vaccine efficacy, such as adjustments for follow-up time and time to first episode (based on hazard ratios), are described in the Supplementary Appendix. Subgroup analyses for the primary end points are descriptively summarized according to age stratum and risk status. Cumulative case accrual in the RSVpreF vaccine group and the placebo group is presented according to the trial day after injection.

For the safety end points, descriptive statistics for binary variables were used, with Clopper–Pearson 95% confidence intervals presented as percentages. Reactogenicity events were assessed in a subgroup of the safety population (participants who received RSVpreF vaccine or placebo) that consisted of participants at selected U.S. and Japanese sites who recorded these events in an electronic diary. Descriptive statistics were used for continuous variables; confidence intervals for the means of continuous variables were calculated with the use of Student's t-test distribution.

RESULTS

PARTICIPANTS

From August 31, 2021, through July 14, 2022, a total of 35,971 participants were enrolled. At the time of the interim analysis (data-cutoff date, July 14, 2022), a total of 34,284 participants had received RSVpreF vaccine (17,215 participants) or placebo (17,069 participants) (Fig. 1). The median age of the participants was 67 years (range, 59 to 97), 51% were male, 78% White, 13% Black, and 37% Hispanic or Latinx. The demographic characteristics were broadly similar across the trial groups (Table 1), and the trial participants were representative of the older population at risk for RSV-related illness (Table S3).

EFFICACY

At the cutoff date for surveillance of acute respiratory illness (July 8, 2022, which was selected to allow collection of nasal swabs up to 7 days after symptom onset, without extending beyond the July 14, 2022, data-cutoff date for the interim analysis), the mean duration of surveillance was 7 months, and 45 participants had reported at least two signs or symptoms after injection. One episode was reported before day 15; 44 episodes

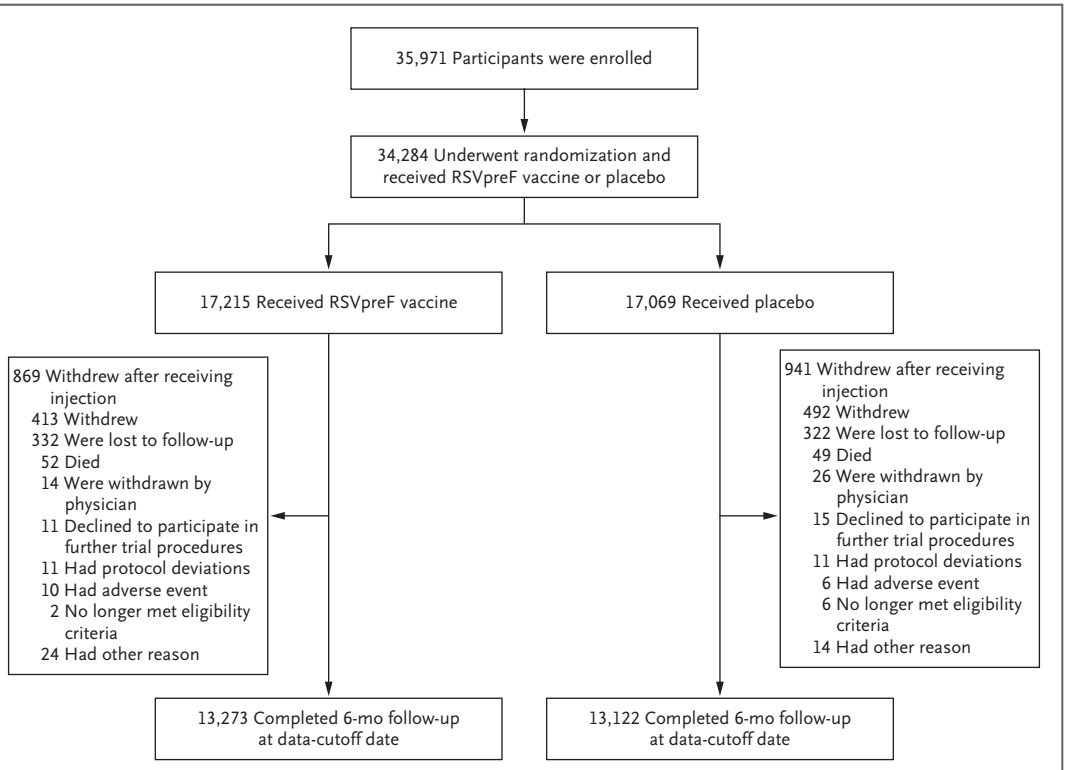


Figure 1. Enrollment, Randomization, Administration of Vaccine or Placebo, and Follow-up.

The data-cutoff date was July 14, 2022. The 34,284 participants who underwent randomization received either respiratory syncytial virus prefusion F protein–based (RSVpreF) vaccine or placebo and were included in the safety population. At the data-cutoff date, follow-up of 16,286 participants in the RSVpreF vaccine group and 16,188 participants in the placebo group was ongoing.

were reported as the first episode on or after day 15 and were included in the analyses of vaccine efficacy.

Figure 2 and Table S4 show the efficacy of RSVpreF vaccine against a first episode of RSV-associated lower respiratory tract illness on or after day 15 (14 days after injection). A total of 44 cases of RSV-associated lower respiratory tract illness with at least two signs or symptoms had occurred (11 cases in the vaccine group [1.19 cases per 1000 person-years of observation] and 33 cases in the placebo group [3.58 cases per 1000 person-years of observation]), corresponding to a vaccine efficacy of 66.7% (96.66% confidence interval [CI], 28.8 to 85.8). At the interim analysis, the efficacy of RSVpreF vaccine met the statistical success criterion (lower boundary of the confidence interval >20%) for a decrease in the incidence of RSV-associated lower respiratory tract illness with at least two signs or symptoms. Given these positive results, this primary end point was also met for the primary analysis as described in the protocol. A total of 16 cases of RSV-associated lower respiratory tract illness with at least three signs or symptoms had occurred (2 in the vaccine group [0.22 cases per 1000 person-years of observation] and 14 in the placebo group [1.52 cases per 1000 person-years of observation]), corresponding to a vaccine efficacy of 85.7% (96.66% CI, 32.0 to 98.7). Vaccine efficacy values that were calculated in sensitivity analyses and according to RSV A and RSV B subgroups were generally similar to those of the primary end points, although the latter had wide confidence intervals reflecting small subgroup sizes. Vaccine efficacy was maintained through the end of the first RSV season (Fig. S1 and Table S5).

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline (Safety Population).*

Characteristic	RSVpreF Vaccine (N = 17,215)	Placebo (N = 17,069)	Total (N = 34,284)
Age			
Mean — yr	68.3±6.14	68.3±6.18	68.3±6.16
Median (range) — yr	67 (59–95)	67 (60–97)	67 (59–97)
Age group — no. (%)			
60–69 yr†	10,757 (62.5)	10,680 (62.6)	21,437 (62.5)
70–79 yr	5,488 (31.9)	5,431 (31.8)	10,919 (31.8)
≥80 yr	970 (5.6)	958 (5.6)	1,928 (5.6)
Male sex — no. (%)	8,800 (51.1)	8,601 (50.4)	17,401 (50.8)
Race or ethnic group — no. (%)‡			
White	13,475 (78.3)	13,360 (78.3)	26,835 (78.3)
Black	2,206 (12.8)	2,207 (12.9)	4,413 (12.9)
Asian	1,352 (7.9)	1,333 (7.8)	2,685 (7.8)
Multiracial	44 (0.3)	36 (0.2)	80 (0.2)
Race not reported	56 (0.3)	50 (0.3)	106 (0.3)
Unknown	28 (0.2)	32 (0.2)	60 (0.2)
Not Hispanic or Latinx	10,740 (62.4)	10,715 (62.8)	21,455 (62.6)
Hispanic or Latinx	6,384 (37.1)	6,260 (36.7)	12,644 (36.9)
American Indian or Alaska Native	44 (0.3)	36 (0.2)	80 (0.2)
Native Hawaiian or other Pacific Islander	10 (<0.1)	15 (<0.1)	25 (0.1)
Ethnic group not reported	91 (0.5)	94 (0.6)	185 (0.5)
Country — no. (%)			
United States	10,319 (59.9)	10,182 (59.7)	20,501 (59.8)
Argentina	3,660 (21.3)	3,657 (21.4)	7,317 (21.3)
Japan	1,159 (6.7)	1,156 (6.8)	2,315 (6.8)
The Netherlands	687 (4.0)	681 (4.0)	1,368 (4.0)
Canada	509 (3.0)	506 (3.0)	1,015 (3.0)
South Africa	495 (2.9)	497 (2.9)	992 (2.9)
Finland	386 (2.2)	390 (2.3)	776 (2.3)
Prespecified high-risk condition — no. (%)			
≥1 Prespecified high-risk condition	8,867 (51.5)	8,831 (51.7)	17,698 (51.6)
Current tobacco use	2,642 (15.3)	2,571 (15.1)	5,213 (15.2)
Diabetes	3,224 (18.7)	3,284 (19.2)	6,508 (19.0)
Lung disease§	1,956 (11.4)	2,040 (12.0)	3,996 (11.7)
Heart disease¶	2,221 (12.9)	2,233 (13.1)	4,454 (13.0)
Liver disease	335 (1.9)	329 (1.9)	664 (1.9)
Renal disease	502 (2.9)	459 (2.7)	961 (2.8)
≥1 Chronic cardiopulmonary condition	2,595 (15.1)	2,640 (15.5)	5,235 (15.3)
Asthma	1,541 (9.0)	1,508 (8.8)	3,049 (8.9)
COPD	1,012 (5.9)	1,080 (6.3)	2,092 (6.1)
Congestive heart failure	293 (1.7)	307 (1.8)	600 (1.8)
No prespecified high-risk condition — no. (%)	8,348 (48.5)	8,238 (48.3)	16,586 (48.4)

* Plus–minus values are means ±SD. The safety population consisted of all enrolled participants who received respiratory syncytial virus prefusion F protein (RSVpreF) vaccine or placebo. Percentages may not total 100 because of rounding. COPD denotes chronic obstructive pulmonary disease.
† This age group includes one 59-year-old participant.
‡ Race or ethnic group was reported by the participants.
§ This category includes COPD and other lung diseases.
¶ This category includes congestive heart failure and other heart diseases.

Subgroup analyses of the primary end points according to participant age group (60 to 69 years, 70 to 79 years, or ≥80 years) and risk status (no prespecified high-risk conditions or ≥1 prespecified high-risk condition) indicated similar vaccine efficacy across subgroups, with wide confidence intervals reflecting small subgroup sizes (Table S6). Figure 2A and 2B shows the cumulative number of cases according to trial day.

The incidences of the five individual signs and symptoms of lower respiratory tract illness among all participants with RSV-associated lower respiratory tract illness are shown in Figure 3. Wheezing and shortness of breath were more common among participants with at least three signs or symptoms (in 93.8% and 68.8% of the participants, respectively) than among those with at least two signs or symptoms (in 37.8% and 28.9%, respectively).

A total of 22 cases of RSV-associated acute respiratory illness (2.38 cases per 1000 person-years of observation) occurred in the vaccine group and 58 cases occurred in the placebo group (6.30 cases per 1000 person-years of observation), corresponding to vaccine efficacy of 62.1% (95% CI, 37.1 to 77.9) (Fig. 2C). Most cases of RSV-associated acute respiratory illness were caused by RSV B.

SAFETY

Among 7169 participants in the electronic diary subgroup of the safety population, more local reactions were reported by RSVpreF vaccine recipients than by placebo recipients (12% vs. 7%); the incidence of systemic events was similar in the two groups (27% and 26%, respectively) (Fig. 4). These events were generally self-limiting and mild to moderate in severity; severe events occurred in 0.7% or less of the participants in each group. After injection in both the vaccine group and the placebo group, the median onset of reactogenicity events was 2 to 4 days and the median duration of reactogenicity events was 1 to 2 days. Injection-site pain was the most common local reaction. Fatigue and headache were the most frequently reported systemic events. Fever occurred in 1% of the participants in both groups.

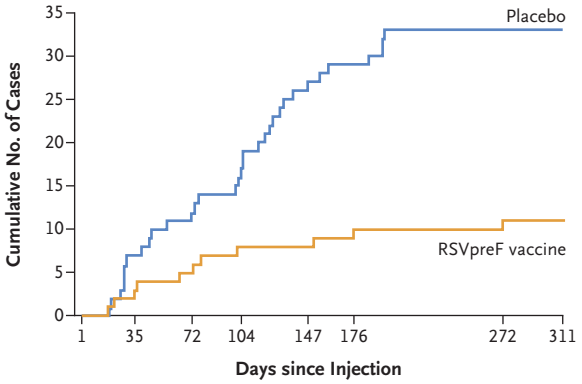
Adverse events that occurred up to 1 month after injection were reported by 9.0% of the vaccine recipients and 8.5% of the placebo recipients (Table S7). Adverse events were generally similar in the two groups; the most commonly reported adverse events were in the categories of infections and infestations (2.3% in the vaccine group and 2.2% in the placebo group) and respiratory, thoracic, and mediastinal disorders (2.2% and 2.4%, respectively) (Table S8). The most commonly reported adverse event was cough (0.6% in both groups); all other adverse events were reported in 0.5% or less of the participants in either group. Adverse events assessed by the investigator as being related to the trial intervention were reported by 1.4% of vaccine recipients and 1.0% of placebo recipients. Severe or life-threatening adverse events were reported in 0.5% of the vaccine recipients and 0.4% of the placebo recipients.

At the data-cutoff date, 2.3% of the vaccine recipients and 2.3% of the placebo recipients had reported serious adverse events, and three of these events were considered by the investigators to be related to the trial intervention. The first serious adverse event was a delayed allergic reaction 7 hours after injection of RSVpreF vaccine, with recovery on the same day. The second serious adverse event was a combination of diplopia, paresthesia of palms and soles, and oculomotor and abducens nerve paralysis 8 days after injection in a participant in the vaccine group who had a medical history of diabetes mellitus; this event was retrospectively diagnosed as being consistent with the Miller–Fisher syndrome (a subset of the Guillain–Barré syndrome characterized by ophthalmoplegia, ataxia, and areflexia). A spinal tap and nerve-conduction studies were not performed, and the participant recovered. The last serious adverse event, also in a participant in the vaccine group, was myocardial infarction that developed 6 days after injection. This participant then underwent angioplasty and later received a diagnosis of acute inflammatory demyelinating polyradiculoneuropathy, consistent with Guillain–Barré syndrome, that began 7 days after injection. The participant continued to recover and regained most motor function. No trial intervention–related deaths or adverse events leading to withdrawal from the trial were reported.

DISCUSSION

The availability of an efficacious and safe RSV vaccine for older adults would address an impor-

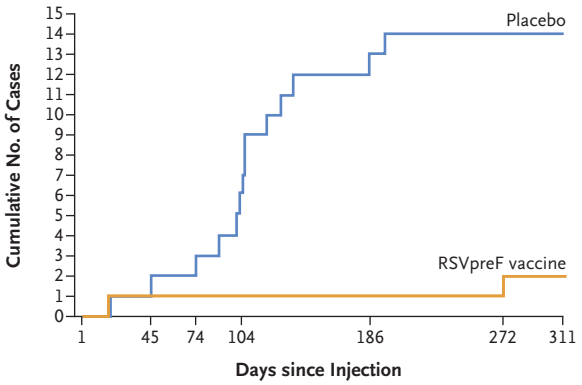
A RSV-Associated Lower Respiratory Tract Illness with ≥2 Signs or Symptoms



Vaccine Efficacy (96.66% CI)
percent
66.7 (28.8–85.8)

Cumulative No. of Cases								
Placebo	0	7	12	17	27	29	33	33
RSVpreF vaccine	0	3	5	8	8	10	11	11

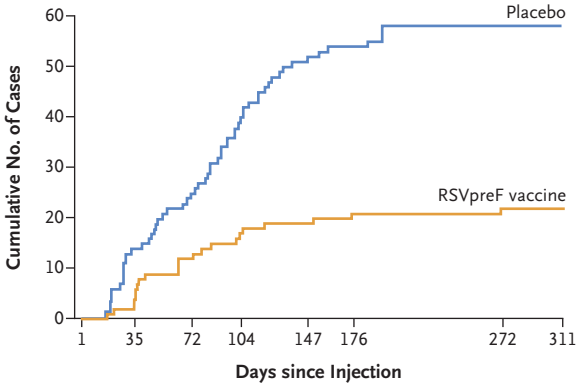
B RSV-Associated Lower Respiratory Tract Illness with ≥3 Signs or Symptoms



Vaccine Efficacy (96.66% CI)
percent
85.7 (32.0–98.7)

Cumulative No. of Cases								
Placebo	0	2	3	7	13	14	14	
RSVpreF vaccine	0	1	1	1	1	2	2	

C RSV-Associated Acute Respiratory Illness



Vaccine Efficacy (95% CI)
percent
62.1 (37.1–77.9)

Cumulative No. of Cases								
Placebo	0	14	25	40	52	54	58	58
RSVpreF vaccine	0	4	12	17	19	21	22	22

Figure 2 (facing page). Vaccine Efficacy.

Shown is the vaccine efficacy with respect to a first episode of RSV-associated lower respiratory tract illness with at least two signs or symptoms (Panel A) or at least three signs or symptoms (Panel B) and RSV-associated acute respiratory illness (Panel C). Data are for the evaluable efficacy population (16,306 participants in the RSVpreF vaccine group and 16,308 participants in the placebo group). The cumulative case accrual curve begins on the day of injection. Data are based on the first episode of RSV-associated lower respiratory tract illness with an onset of signs and symptoms from day 15 (14 days after injection) through July 8, 2022 (i.e., to allow collection of nasal swabs within 7 days after the onset of signs and symptoms of acute respiratory illness up to the data-cutoff date of the interim analysis, which was July 14, 2022. The 96.66% confidence intervals were calculated with the use of the conditional exact test based on the binomial distribution of P, adjusted according to Pocock error spending for the interim analysis (type I error, 3.34%). The widths of the 95% confidence intervals have not been adjusted for multiplicity and cannot be used in place of a hypothesis test.

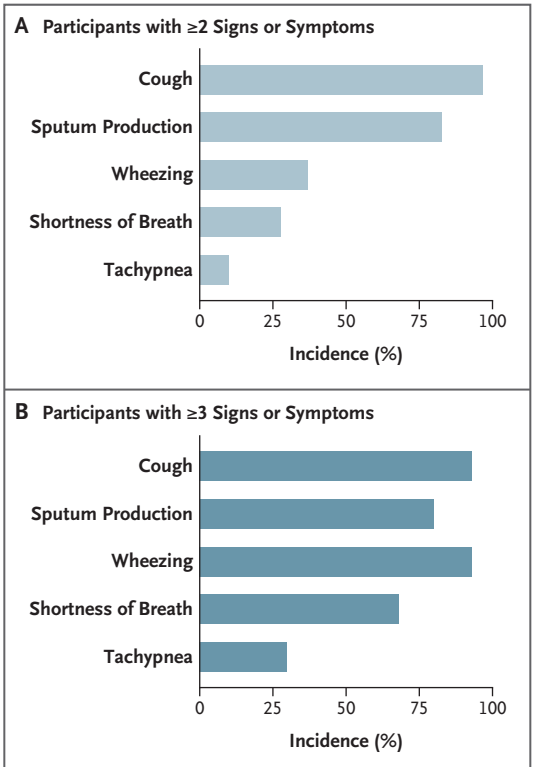


Figure 3. Incidence of Signs or Symptoms of RSV-Associated Lower Respiratory Tract Illness.

Shown are the incidences of signs and symptoms of RSV-associated lower respiratory tract illness in participants with at least two signs or symptoms (Panel A) and at least three signs or symptoms (Panel B).

tant unmet clinical need. Although RSV has historically been considered to be a pathogen infecting children, RSV disease is increasingly recognized as an important cause of illness and death among older adults.[2,3,5,20] For instance, annual rates of RSV-associated hospitalizations and deaths among older adults may approach approximately 25 to 50% of those attributed to influenza type A (subtype H3N2) and are similar to yearly rates of influenza type A (subtype H1N1) and influenza type B.[21-23]

The development of an efficacious, safe, immunogenic, and broadly protective RSV vaccine for at-risk populations, including older adults, has previously been unsuccessful. Several RSV vaccine candidates have failed in development, generally owing to lack of immunogenicity.[9,24-26] In some efficacy trials, F protein–based vaccines did not protect against RSV illness in adults.[27-29] Recognition that F protein transitions from a metastable prefusion form to a stable but antigenically suboptimal postfusion form may explain these failures.[11,30] A major target of virus neutralizing antibodies and a key vaccine antigen is preF, which is the metastable prefusion form of the F protein; thus, stabilization and purification of preF have been important in accelerating the development of RSV vaccine.[11,12]

In this worldwide, phase 3 trial, RSVpreF vaccine was effective in preventing RSV-associated lower respiratory tract illness in older adults through one RSV season. The success criteria for vaccine efficacy with respect to both primary end points were met, with vaccine efficacy of 66.7% against RSV-associated lower respiratory tract illness with at least two signs or symptoms and 85.7% against this illness with at least three signs or symptoms. The higher efficacy observed with respect to the latter primary end point was consistent with that observed with other vaccines in which efficacy increased with increasing severity of respiratory disease (e.g., influenza and Covid-19).[31-33]

In this interim analysis of vaccine efficacy, an insufficient number of cases of severe lower respiratory tract illness, as defined in the protocol (e.g., hospitalization and illness warranting the use of oxygenation or mechanical ventilation), had accrued for evaluation. However, the higher vaccine efficacy values observed with an increas-

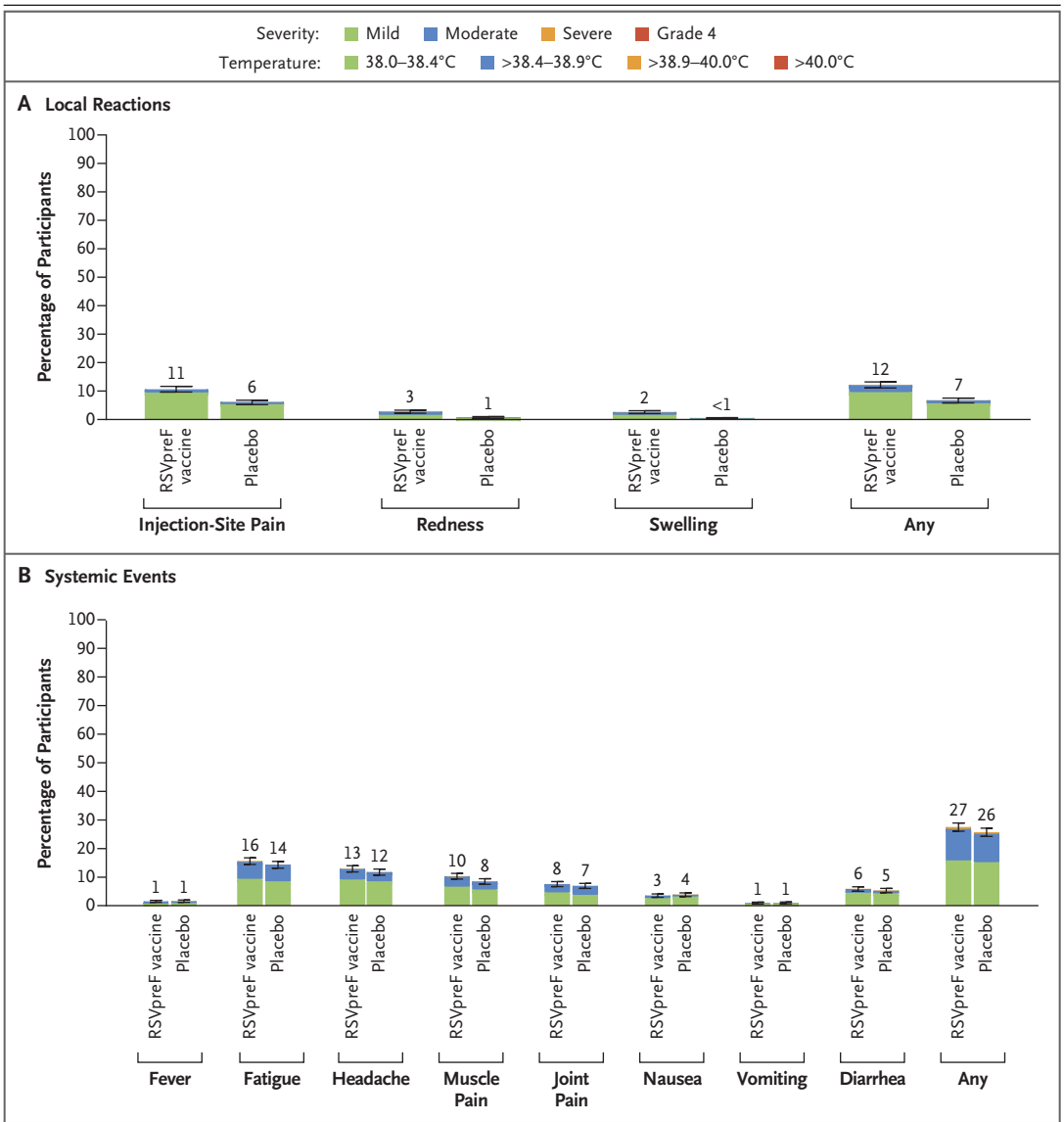


Figure 4. Local Reactions and Systemic Events.

Panel A shows local reactions and Panel B shows systemic events reported within 7 days after administration of RSVpreF vaccine (3621 recipients) or placebo (3539 participants). Data are from the electronic diary subgroup of the safety population (a subgroup of participants at selected U.S. and Japanese sites who recorded reactogenicity events in an electronic diary), the demographic characteristics of which are shown in Table S9. Severity scales are summarized in Table S10. I bars denote 95% confidence intervals. The percentages of participants with fever, redness, and swelling do not include 2 participants in the RSVpreF vaccine group and 7 participants in the placebo group because they did not receive a thermometer or caliper.

ingly severe symptom profile of RSV-associated lower respiratory tract illness (with at least three signs or symptoms) suggest that high efficacy against protocol-defined severe lower respiratory tract illness outcomes may be anticipated.

In addition, vaccine efficacy of 62.1% against RSV-associated acute respiratory illness (the secondary end point) was observed. The efficacy of RSVpreF vaccine against RSV-associated lower respiratory tract illness (both with at least two signs or symptoms and with at least three signs or symptoms) and RSV-associated

acute respiratory illness was consistent against illness due to RSV A and RSV B, the two major cocirculating antigenic variants.[14] Vaccine efficacy was also consistent among various assessed subgroups, including adults who were 80 years of age or older and those with conditions that placed them at particularly high risk for adverse outcomes from RSV illness. However, case numbers for these subgroup assessments were small.

The safety and side-effect profiles of RSVpreF vaccine were also consistent with those in previous phase 1–2 clinical studies involving adults.[13,15,16] The incidence of reactogenicity events among participants who received RSVpreF vaccine was low, and these events were predominantly mild. The incidence of severe adverse events was low, and no safety concerns were identified by the data monitoring committee. One case of Guillain–Barré syndrome and one case of Miller–Fisher syndrome were reported in the RSVpreF vaccine group; both cases occurred in an age group at increased risk for these syndromes,[34] and in both cases, there were confounding factors that make it difficult to discern the potential relatedness to RSVpreF vaccine. If RSVpreF vaccine is approved and recommended, these adverse events warrant close monitoring in future studies and with real-world data and postmarketing surveillance.

Additional cases of RSV-associated lower respiratory tract illness occurred during the first RSV season in the Southern Hemisphere, where enrollment was completed on September 16, 2022. These cases may provide important data regarding outcomes of interest, including the incidences of hospitalization, RSV-attributed complications, adverse events, and death. Such data, coupled with the results of studies of vaccine outcomes, are expected to inform the implementation of RSVpreF vaccine in vaccination programs for adults. Although it is likely that prevention of RSV-associated acute respiratory illness would translate into prevention of more serious complications,[35] data are lacking on whether the efficacy of RSVpreF vaccine will decrease the number of outpatient visits and adults who present with severe disease. In the current trial, the assessment of vaccine efficacy against severe RSV-associated lower respiratory tract illness at the end of the first RSV season — including health care resource utilization related to RSV-associated lower respiratory tract illness and a reduction in the incidence of lower respiratory tract illness — is under way. The number of cases of lower respiratory tract illness in this trial was undoubtedly impeded by altered epidemiologic characteristics of RSV, as well as those of other respiratory viruses, because of the Covid-19 pandemic.[36]

A limitation of our trial was the exclusion of immunocompromised persons. RSV-associated lower respiratory tract illness, which can progress to severe disease with substantial morbidity and mortality, has a considerable effect on this population,[37,38] and further study in this vulnerable population is warranted. In the prespecified interim analysis, participants were evaluated during a single RSV season. Additional analyses may add to our knowledge of whether the protection of RSVpreF vaccine persists for more than one season or whether additional doses of vaccine may be needed.

At this interim analysis involving adults who were at least 60 years of age, the success criterion for vaccine efficacy was met with respect to RSV-associated lower respiratory tract illness with at least two signs or symptoms and at least three signs or symptoms (the two primary end points) and RSV-associated acute respiratory illness. RSVpreF vaccine had an acceptable safety profile.

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APPENDIX

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