Respiratory Syncytial Virus Prefusion F Vaccination: Antibody Persistence and Revaccination

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Background: Respiratory syncytial virus (RSV) causes substantial respiratory disease. Bivalent RSV prefusion F (RSVpreF) vaccine is licensed in ≥60-year-olds. RSVpreF was well-tolerated and immunogenic in a phase 1/2 study. We evaluated antibody persistence after initial vaccination and safety and immunogenicity after revaccination from this study.

Methods: Healthy adults were randomized to receive both initial vaccination and revaccination 12 months later with either placebo or RSVpreF 240 μg (±Al(OH)3). RSV-A and RSV-B geometric mean neutralizing titers (GMTs) were measured through 12 months after both vaccinations. Tolerability/safety was assessed.

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Results: There were 263 participants revaccinated (18–49-years-old, n=134; 65–85-years-old, n=129). Among 18–49-year-olds and 65–85-year-olds, respectively, geometric mean fold rises (GMFRs) for both RSV subgroups (RSV-A; RSV-B) 1 month after initial RSVpreF vaccination were 13.3–20.4 and 8.9–15.5 compared with levels before initial vaccination; corresponding GMFRs 12 months after initial vaccination were 4.1–5.0 and 2.6–4.1. GMFRs 1 month after revaccination compared with levels before revaccination were 1.4–2.3 and 1.4–2.2 for 18–49-year-olds and 65–85-year-olds, respectively. Peak GMTs after revaccination were lower than those after initial vaccination. GMTs 12 months after initial vaccination and revaccination were similar, with GMFRs ranging from 0.7–1.6. No safety signals occurred.

Conclusions: RSVpreF revaccination was immunogenic and well-tolerated among adults. NCT03529773

Keywords: immunogenicity; neutralizing responses; respiratory syncytial virus; RSVpreF; safety; vaccine

INTRODUCTION

Respiratory syncytial virus (RSV) infection is the predominant cause of acute lower respiratory tract illness (LRTI) in infants and young children and an important cause of respiratory disease in older adults [1-7]. Among US adults ≥65 years old, RSV is associated with approximately 178–267 annual hospitalizations per 100,000 [8]. Adults in this age group and those with underlying conditions or immunocompromise are at increased risk of severe RSV-associated illness [1,9]. RSV-associated illness is also associated with functional decline and impaired quality of life among older adults; the socioeconomic burden of disease is substantial [7,10-12].

RSVpreF is a bivalent stabilized prefusion F protein vaccine currently licensed for prevention of RSV-associated LRTI in ≥60-year-olds and for maternal vaccination for prevention of RSV-associated LRTI in infants from birth to 6 months of age [13,14]. The protein sequence is based on RSV-A and RSV-B strains, which are the 2 cocirculating antigenic subgroups [13,15,16]. In the phase 1/2 first-in-human study in adults, RSVpreF was well-tolerated and elicited robust RSV-A and RSV-B neutralizing titers 1 month after vaccination [13,16].

Based on these study results, a 120-µg dose level was selected for further investigation of RSVpreF in a human RSV challenge model and in the phase 3 efficacy trial. In the human challenge study in 70 healthy 18–50-year-olds, RSVpreF was associated with 86.7% and 100% reduction in symptomatic RSV infection based on any detectable viral RNA and on measurement of quantifiable viral RNA, respectively [17]. In the primary analysis of the pivotal phase 3 study (RENOIR) in 34,284 adults ≥60 years old, vaccine efficacy (VE) of RSVpreF was 66.7% and 85.7% against RSV-associated LRTI with ≥2 and ≥3 symptoms, respectively [18]. RSVpreF maintained a VE of 65.1% and 88.9%, respectively, at the end of the first RSV season, with 56.8%
and 84.4% VE by mid-season 2 [19]. Information on persistence of antibody responses and potential revaccination intervals are critical to recommending bodies and prescribers. Therefore, this report presents antibody persistence approximately 12 months after primary dosing and safety and immunogenicity after revaccination with RSVpreF 240 μg among those participating in the phase 1/2 first-in-human study of 18–49-year-olds and 65–85-year-olds [13,16].

METHODS

Study design

As previously reported, a phase 1/2 randomized, placebo-controlled, observer-blinded, dose-finding study (NCT03529773; registration date: 2018-04-17) was conducted at 36 US sites between April 2018 and December 2020 [13,16]. The study comprised 3 stages: a phase 1 dose-escalation stage with a sentinel cohort (Stage 1; hereafter referred to as sentinel cohort), a phase 2 initial vaccination stage with an expanded cohort (Stage 2; hereafter referred to as expanded cohort), and a phase 2 extension revaccination stage (Stage 3; hereafter referred to as expanded cohort for revaccination).

Safety and immunogenicity methods for the sentinel and expanded cohorts, including details of concomitant seasonal inactivated influenza vaccine (SIIV) schedule in the expanded cohort, were reported previously [13,16]. In the expanded cohort, participants were randomized within age groups (18–49 or 65–85 years) to receive initial vaccination with RSVpreF with or without Al(OH)₃ at 1 of 3 RSVpreF dose levels (60 μg, 120 μg, 240 μg) or placebo in the left deltoid muscle; SIIV or placebo were administered into the right deltoid muscle. A control group received 2 placebo doses, 1 each in the left and right deltoid muscle. Approximately 1 month later, participants randomized to receive RSVpreF were given either placebo or SIIV and participants randomized to receive placebo were given an additional placebo dose into the deltoid muscle of the nondominant arm.

Participants from the expanded cohort who had received either an initial dose of RSVpreF 240 μg with or without Al(OH)₃ or who had received placebo and completed all primary vaccinations before the Northern Hemisphere RSV season (September 2018/19) were invited to enroll in the expanded cohort for the revaccination phase of the trial. Notably, the 240-μg dose was selected for revaccination before the 120-μg dose level without Al(OH)₃ was selected for the phase 3 efficacy trial. Participants were revaccinated 12 months after receiving their first dose with the same dose level and formulation of RSVpreF with or without concomitant SIIV and followed for up for 12 months after revaccination and into the same deltoid muscle as used for the initial vaccination (Figure 1).
Participants

Participants in the expanded cohort for revaccination met the same eligibility criteria for the expanded cohort, which have been previously published [13]. Briefly, participants included healthy nonpregnant 18–49-year-olds or 65–85-year-olds. Individuals could also be included if they had preexisting stable disease not requiring any significant change in therapy or hospitalization for worsening disease during the past 6 weeks, and were excluded if they had received influenza vaccine within 6 months before study vaccine administration.

The protocol and informed consent documents were approved by institutional review board(s) and/or independent ethics committee(s) for each site. The study was conducted in compliance with ethical principles of the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines and followed all local regulatory requirements.

Procedures

Participants were allocated to vaccine groups using interactive response. Participants, study and sponsor team members, and laboratory personnel remained blinded as appropriate throughout the study; site dispensers and administrators were unblinded because the physical appearances of the vaccines differed.

Participants in the expanded cohort for revaccination received identical injections and schedules of injections to those received at the initial vaccination. The injection (revaccination) was either placebo or RSVpreF 240 μg (120 μg each of stabilized recombinant prefusion F antigens from RSV-A and-B) with or without 0.2 mg Al(OH)₃ and with or without SIIV; administration occurred approximately 12 months after initial vaccination (Figure 1). Lyophilized RSVpreF was reconstituted in either sterile water or Al(OH)₃ and administered in a 0.5-mL injection volume. Participants 18–49-years-old received commercially available quadrivalent SIIV (Fluzone Quadrivalent, Sanofi Pasteur, Swiftwater, PA) [20] and 65–85-year-old participants received high-dose trivalent SIIV (Fluzone High-Dose, Sanofi Pasteur, Swiftwater, PA) [21] either concomitantly with RSVpreF or separated by 1 month. The placebo was a sterile 0.9% NaCl solution administered in a 0.5-mL injection volume.

Blood was collected 1, 2, 3, 6, and 12 months after initial vaccination in the expanded cohort and before and 1, 2, 6, and 12 months after revaccination in the expanded cohort for revaccination. Serum was assayed for RSV-A and RSV-B neutralizing antibody levels as described previously [16]. Although serum testing was not all conducted concurrently because of the greater than 24-month study period, the critical assay reagents were consistent throughout. Immunoglobulin (Ig) levels against nonvaccine RSV antigens (ie, matrix, nucleoprotein, and Ga or Gb peptide) were tested using a direct-binding Luminex immunoassay as described previously [13].
Outcomes

All endpoints in the expanded cohort for revaccination were exploratory. Safety endpoints included local reactions and systemic events within 14 days after revaccination; and adverse events (AEs), medically attended AEs (MAEs), and serious AEs (SAEs) within 1 and 12 months after revaccination. Antibody persistence through 12 months after initial vaccination was evaluated by measuring RSV-A and RSV-B neutralizing antibody titers before and 1, 2, 3, 6, and 12 months after revaccination.

To further characterize immune responses to RSVpreF and to concurrent RSV infection, including whether intercurrent RSV infections may have contributed to potential blunting of immune response with revaccination and interfered with true antibody decay rates, Ig titers to nonvaccine RSV antigens were assessed before and after initial vaccination and revaccination. Baseline was considered before the RSV season and 6 months after initial vaccination or revaccination was considered the end of the RSV season. Seroconversion was defined as ≥4-fold rise in any of the 3 anti-RSV nonvaccine antigen Ig titers from before to after the RSV season.

Statistical analysis

Sample size determination was not based on formal testing of statistical hypotheses. Data were analyzed separately for each age group (younger age group, 18–49 years; older age group, 65–85 years). Safety results were reported for the safety population (all participants who received ≥1 study vaccine dose and were analyzed according to vaccine administered). These data were summarized descriptively using counts and percentages with 2-sided 95% CIs. Immunogenicity analyses were conducted for the evaluable RSV immunogenicity population (all participants who received the initial vaccination and revaccination as randomized; had ≥1 valid and determinate assay result at 1 month after revaccination; and had no major protocol violations). Geometric mean titers (GMTs) at each time point and geometric mean fold rises (GMFRs) from before to each time point after initial vaccination and revaccination were determined for each vaccine group. A Student t distribution of log-transformed data followed by back transformation to the original scale was used to calculate 95% CIs for GMTs and GMFRs. Missing data were not imputed.

RESULTS

Participants

A total of 267 participants (younger age group [18–49 years], n=134; older age group [65–85 years], n=133) completed the expanded cohort stage of the study and consented for the expanded cohort for revaccination stage (Figure 2). Of these, all 134 participants in the younger age group and 129 of 133 participants in the older age group completed revaccination with RSVpreF 240 μg or placebo and therefore comprised the expanded cohort for revaccination (safety population). The evaluable RSV immunogenicity population included 128 participants in the younger age group.
and 118 participants in the older age group. Reasons for exclusion in the younger age group were blood draws not within 27–42 days after revaccination (n=5) and lack of ≥1 valid and determinate assay result 1 month after revaccination (n=1). Participants in the older age group were excluded for the same reasons (n=7 and n=1, respectively) or because they were no longer eligible (n=4), did not receive vaccination as randomized (n=4), or had major protocol violations (n=3). Among all participants completing revaccination, demographic characteristics were generally similar across age and vaccine groups (Table 1).

**Immunogenicity**

Among RSVpreF recipients, GMTs for either RSV-A or RSV-B increased from before to all time points after initial vaccination (Figure 3; Supplementary Table S1). GMFRs for RSV-A from before to 1 month after initial vaccination were 13.3 to 18.3 and 8.9 to 13.3 for younger and older adults, respectively; corresponding GMFRs for RSV-B were 16.0 to 20.4 and 10.8 to 15.5 (Supplementary Table S2). Twelve months after initial vaccination, GMFRs were 4.2 to 5.0 and 2.6 to 3.6 for RSV-A for younger and older adults, respectively, and 4.1 to 4.5 and 2.8 to 4.1, respectively, for RSV-B compared with before initial vaccination. GMFRs 1 month after revaccination compared with levels before revaccination ranged between 1.4 to 2.3 and 1.4 to 2.2 for RSV-A for younger and older adults, respectively, and between 1.4 to 2.2 and 1.5 to 2.1 for RSV-B, respectively (Supplementary Table S3). GMTs 1 month after revaccination were lower than 1 month after initial vaccination (Figure 3; Supplementary Table S1). However, differences became smaller and GMTs 2 and 6 months after revaccination were similar or almost the same as the corresponding time points after initial vaccination, with GMFRs across both age groups and both subgroups ranging between 0.5 to 1.1 from 2 or 6 months after revaccination compared with 2 or 6 months after initial vaccination. Notably, GMTs 1 and 2 months after revaccination were generally similar to those 2 and 3 months after initial vaccination. RSV-A and RSV-B GMTs at 12 months after both initial vaccination and revaccination were similar, with GMFRs ranging from 0.7 to 1.6 from 12 months after revaccination compared with 12 months after initial vaccination.

For RSV-A and RSV-B in both age groups, GMT decay rates were slower after revaccination compared with rates after initial vaccination, as evidenced by the observation that final GMFRs from baseline were similar despite a more robust response to initial vaccination versus revaccination. This was the case for both formulations of RSVpreF (with or without Al(OH)₃).

The seroconversion rate of anti-RSV nonvaccine antigens from before the RSV season (ie, before initial vaccination) to the end of the RSV season (ie, 6 months after initial vaccination) ranged from 2.6% to 7.5% for RSVpreF and 10.5% for placebo among the younger age group and 0.0% to 15.8% for RSVpreF and 13.2% for placebo among the older age group (Supplementary Table S4). Corresponding seroconversion rates after revaccination were 0.0% to 6.9% for RSVpreF and 4.2% for placebo among the younger age group and 0.0% to 7.1% for RSVpreF and 4.8% for placebo among the older age group.
Safety

In both age groups, the percentages of participants reporting local reactions were similar after revaccination with RSVpreF compared with initial vaccination and trended higher in the Al(OH)₃ vaccine groups and in the younger age group (Figure 4). The most common local reaction was mild injection-site pain, which was reported more frequently among younger versus older participants. Injection-site pain trended slightly higher after revaccination but was generally mild. Most local reactions were mild or moderate in severity. One participant in the younger group who received RSVpreF + Al(OH)₃ + SIIV reported severe injection-site pain after revaccination. Median duration and median time to onset of local reactions were 1.0−12.0 days and 1.0−9.0 days, respectively, across vaccine and age groups.

The percentages of participants reporting systemic events were also similar after revaccination compared with initial vaccination in both age groups (Figure 5). After revaccination, percentages of participants with systemic events were generally similar across vaccine groups but were higher in the younger compared with the older age group. The most frequently reported systemic events were headache, muscle pain, and fatigue/tiredness; most events occurring after revaccination were mild or moderate in severity. In the younger group, severe muscle pain and severe fatigue/tiredness were reported after revaccination by 1 participant each in the RSVpreF + Al(OH)₃ + SIIV group. No participants in the older age group experienced a severe systemic event following revaccination. Three participants in the younger age group reported fever after revaccination; 2 had mild fever (≥38.0°C−38.4°C) and 1 had moderate fever (≥38.4°C−38.9°C). Two participants in the older age group reported mild fever (≥38.0°C−38.4°C) after revaccination; fever >40.0°C was not reported. One participant in the older age group who received RSVpreF 240 µg + placebo was diagnosed with influenza 2 days after initial vaccination and reported fever >40.0°C. Median time to onset and median duration of systemic events were 1.0−14.0 days and 1.0−9.0 days, respectively, across vaccine and age groups.

The percentages of participants reporting any AE, MAE, or SAE within 1 month were similar after revaccination compared with initial vaccination (Figure 6). Across vaccine groups, 16 (14.8%) and 8 (7.7%) participants who received RSVpreF in the younger and older age groups, respectively, reported ≥1 AE within 1 month after revaccination; the corresponding values in the placebo groups were 1 (3.8%) and 3 (12.0%) participants. MAEs 1 month after revaccination among younger and older age groups, respectively, were reported by 9 (8.3%) and 7 (6.7%) participants who received RSVpreF and by 1 (3.8%) and 2 (8.0%) participants who received placebo. One SAE (lactic acidosis that was not considered related to vaccination) was reported in an older participant who received RSVpreF + placebo. Severe AEs 1 month after revaccination were reported by 1 (0.9%) and 2 (1.9%) participants who received RSVpreF in the younger and older age groups, respectively, and none were reported among participants who received placebo. No vaccine-related AEs, life-threatening AEs, or AEs leading to study withdrawal were reported by 1 month after revaccination.
Percentages of participants reporting any AE, MAE, or SAE within 12 months after initial vaccination were generally higher compared with percentages within 12 months after revaccination (Figure 6). By 12 months after revaccination, AEs among the younger and older age groups, respectively, were reported by 33 (30.6%) and 24 (23.1%) participants who received RSVpreF, and by 7 (26.9%) and 5 (20.0%) participants who received placebo. Among the younger and older age groups, respectively, MAEs were reported by 23 (21.3%) and 17 (16.3%) participants who received RSVpreF and by 4 (15.4%) and 3 (12.0%) participants who received placebo; none were considered related to vaccination. SAEs were reported by 2 (1.9%) and 4 (3.8%) participants who received RSVpreF in the younger and older age groups, respectively, and by 1 participant in each age group (3.8% and 4.0%, respectively) among those who received placebo. None were considered related to vaccination. Among participants who received RSVpreF, severe AEs were reported by 5 (4.6%) and 6 (5.8%) participants in the younger and older age groups, respectively. No life-threatening AEs, AEs leading to study withdrawal, or deaths were reported in either age group up to 12 months after revaccination.

DISCUSSION

Both initial vaccination and revaccination after 12 months with RSVpreF 240 μg elicited robust RSV-A and RSV-B neutralizing antibody responses among healthy younger 18–49-year-old and older 65–85-year-old adults. The highest RSV neutralizing GMTs in both age groups were observed 1 month after initial vaccination; GMTs gradually declined over time but remained higher than levels before initial vaccination after 12 months. In both age groups, RSVpreF revaccination 12 months after initial vaccination induced robust increases in RSV-A and RSV-B GMTs that were less pronounced than the increases observed after initial vaccination but were still higher than levels before initial vaccination. Despite this, GMTs by 2 months and through 12 months were generally similar after revaccination and after initial vaccination, providing evidence of potentially comparable protection after revaccination. These results were consistent across both RSVpreF formulations (with or without Al(OH)₃) and regardless of whether RSVpreF was administered with concomitant SIIV. Similar trends following revaccination approximately 1 year later have also been observed for seasonal influenza vaccines in consecutive years when ≥1 of the antigenic components were the same [22]. Other studies have further demonstrated a reduced serologic response following repeated influenza vaccination albeit an overall increase from prevaccination levels [23-25]. Additionally, an RSV prefusion F monovalent vaccine, which is also US licensed in older adults, showed similar immunogenicity trends up to 12 months after initial vaccination and up to 6 months after revaccination administered 12 months after initial vaccination, and did not provide improved efficacy in the second RSV season compared with those who were not revaccinated [26-28].

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Across both age groups, formulations, and coadministration groups, initial vaccination and revaccination with RSVpreF were well-tolerated. There were no observed increases in reactogenicity or AE rates after revaccination compared with initial vaccination, and most local reactions, systemic events, and AEs were mild or moderate in severity. No vaccine-related SAEs or AEs leading to study withdrawal occurred within 12 months after initial vaccination and revaccination.

This study showed robust RSV neutralizing responses compared with prior RSV F-based vaccines [16,29] and demonstrated high efficacy in the pivotal phase 3 study [18]. The primary analysis of the RENOIR phase 3 pivotal trial in adults ≥60 years old demonstrated that RSVpreF 120 µg (without Al(OH)₃) was 66.7% and 85.7% efficacious in preventing RSV-associated LRTI with ≥2 and ≥3 symptoms, respectively [18]. Taken together, these data suggest that robust RSV-A and RSV-B neutralizing GMTs observed after administration of RSVpreF are likely to be associated with real-world protection against severe outcomes of RSV. The relationship between antibody response and duration of protection will be assessed as further data become available from RENOIR. A preliminary analysis of data in the second RSV season has shown persistent vaccine efficacy against more severe RSV-associated LRTI with ≥3 symptoms [19].

A major strength of our study was the analysis of 2 age groups encompassing a wide range of ages among adults, including those at highest risk because of advanced age. The design also provided important information regarding safety and immunogenicity of 2 vaccine formulations. Limitations of this study include a sample size that did not provide sufficient power for statistical comparisons between vaccine groups. Notably, a separate study with RSVpreF 120 µg and powered for noninferiority evaluations demonstrated that RSVpreF and influenza vaccine can be coadministered [30]. Additionally, the present study evaluated RSVpreF 240 µg as it was conducted before selection of the final dose level and formulation for the efficacy trial and licensed vaccine (RSVpreF 120 µg). However, as previously reported, overall RSV neutralizing responses at the 120-µg and 240-µg dose levels were generally similar [13,15,16]. Despite selecting a lower dose level for the efficacy study, changes to the overall observations with revaccination are not expected. Additionally, although seroconversion of nonvaccine RSV antigen Ig titers from before to the end of the RSV season was assessed to investigate whether intercurrent RSV infections may have contributed to potential blunting of immune response with revaccination and interfered with true antibody decay rates, the small numbers included in this assessment precluded definitive interpretation of findings. Finally, a study arm with participants who received RSVpreF for initial vaccination and placebo for revaccination was not included, limiting assessment of antibody persistence of RSVpreF neutralizing titers beyond 12 months after initial vaccination.

**CONCLUSION**

Revaccination with RSVpreF 240 µg 12 months after initial vaccination was well-tolerated and immunogenic in healthy adults. Increases in RSV neutralizing titers persisted for at least 12
months. Further study is required to determine the duration of protection and potential optimal interval for RSVpreF revaccination.

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**Data sharing statement**

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

**FOOTNOTE PAGE**

**Conflict of interest statement:** Dr. Walsh reports receiving grants from Pfizer, Merck Sharpe and Dohme, and Janssen and serving in unpaid consultancy roles for Janssen, Merck, Moderna, and Pfizer. Ann R. Falsey reports receiving grant funding from Pfizer Inc, Merck, Janssen, BioFire Diagnostics, Vax Co, and CyanVac and consulting fees from Gilead, GlaxoSmithKline, Icosavax, and Novavax. Agnieszka M. Zareba, Qin Jiang, Alejandra Gurtman, David Radley, Emily Gomme, David Cooper, Kathrin U. Jansen, William C. Gruber, Kena A. Swanson, and Beate Schmoele-Thoma are current or former employees of Pfizer Inc and may hold stock or stock options.

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### TABLES

#### Table 1. Demographics of Participants in the Expanded Cohort for Revaccination

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RSVpreF 240 μg + SIIV (N=32)</th>
<th>RSVpreF 240 μg + Placebo (N=31)</th>
<th>RSVpreF 240 μg with Al(OH)₃ + SIIV (N=22)</th>
<th>RSVpreF 240 μg with Al(OH)₃ + Placebo (N=23)</th>
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<td>3 (9.7)</td>
<td>4 (18.2)</td>
<td>3 (13.0)</td>
<td>0</td>
<td>12 (9.0)</td>
</tr>
<tr>
<td>Not reported</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (4.3)</td>
<td>0</td>
<td>1 (0.7)</td>
</tr>
</tbody>
</table>

DOI: 10.1093/infdis/jiae185
### Older Age Group (65–85 Years) by Vaccination Group (as Administered)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RSVpreF 240 μg + SIIV (N=22)</th>
<th>RSVpreF 240 μg + Placebo (N=24)</th>
<th>RSVpreF 240 μg with Al(OH)$_3$ + SIIV (N=29)</th>
<th>RSVpreF 240 μg with Al(OH)$_3$ + Placebo (N=29)</th>
<th>Placebo + Placebo (N=25)</th>
<th>Total (N=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>16 (72.7)</td>
<td>14 (58.3)</td>
<td>17 (58.6)</td>
<td>14 (48.3)</td>
<td>19 (76.0)</td>
<td>80 (62.0)</td>
</tr>
<tr>
<td>Male</td>
<td>6 (27.3)</td>
<td>10 (41.7)</td>
<td>12 (41.4)</td>
<td>15 (51.7)</td>
<td>6 (24.0)</td>
<td>49 (38.0)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>19 (86.4)</td>
<td>20 (83.3)</td>
<td>27 (93.1)</td>
<td>22 (75.9)</td>
<td>23 (92.0)</td>
<td>111 (86.0)</td>
</tr>
<tr>
<td>Black or African</td>
<td>3 (13.6)</td>
<td>3 (12.5)</td>
<td>2 (6.9)</td>
<td>6 (20.7)</td>
<td>2 (8.0)</td>
<td>16 (12.4)</td>
</tr>
<tr>
<td>American</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
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<td>0</td>
<td>0</td>
<td>1 (3.4)</td>
<td>0</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Multiracial</td>
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<td>1 (4.2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic/non-Latino</td>
<td>22 (100.0)</td>
<td>22 (91.7)</td>
<td>28 (96.6)</td>
<td>26 (89.7)</td>
<td>21 (84.0)</td>
<td>119 (92.2)</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>0</td>
<td>2 (8.3)</td>
<td>1 (3.4)</td>
<td>1 (3.4)</td>
<td>4 (16.0)</td>
<td>8 (6.2)</td>
</tr>
<tr>
<td>Not reported</td>
<td>0</td>
<td>0</td>
<td>2 (6.9)</td>
<td>0</td>
<td>2 (1.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Age at revaccination, y, mean (SD)</strong></td>
<td>72.8 (4.0)</td>
<td>72.8 (5.5)</td>
<td>70.8 (4.1)</td>
<td>71.7 (5.3)</td>
<td>72.2 (4.5)</td>
<td>72.0 (4.7)</td>
</tr>
</tbody>
</table>

Al(OH)$_3$, aluminum hydroxide; RSVpreF, respiratory syncytial virus prefusion F vaccine; SIIV, seasonal inactivated influenza vaccine.

*Revaccinated with placebo or RSVpreF 240 μg formulated with or without Al(OH)$_3$ and concomitantly with either placebo or SIIV.
FIGURE LEGENDS

Figure 1. Study design. Left deltoid, right deltoid, and deltoid of non-dominant arm refer to the deltoid muscle. Al(OH)₃, aluminum hydroxide; RSVpreF, respiratory syncytial virus prefusion F vaccine; SIIV, seasonal inactivated influenza vaccine.

<table>
<thead>
<tr>
<th>Expanded cohort</th>
<th>Expanded cohort for revaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 0</td>
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<tr>
<td>Initial vaccination</td>
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<tr>
<td><strong>Left deltoid</strong></td>
<td>RSVpreF 240 µg</td>
</tr>
<tr>
<td><strong>Right deltoid</strong></td>
<td>SIIV</td>
</tr>
<tr>
<td><strong>Deltoid of non-dominant arm</strong></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>RSVpreF 240 µg with Al(OH)₃</td>
</tr>
<tr>
<td></td>
<td>SIIV</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
</tr>
</tbody>
</table>
Figure 2. Disposition of participants (A) 18–49 and (B) 65–85 years of age. Al(OH)₃, aluminum hydroxide; RSVpreF, respiratory syncytial virus prefusion F vaccine; SIIV, seasonal inactivated influenza vaccine.
Figure 3. RSV-A and RSV-B neutralizing titers. (A) RSV-A titers in participants 18–49 years of age; (B) RSV-B titers in participants 18–49 years of age; (C) RSV-A titers in participants 65–85 years of age; and (D) RSV-B titers in participants 65–85 years of age. Samples from different time points were tested separately. GMT and 95% CIs are also provided in Supplementary Table S1. Associated GMFRs are provided in Supplementary Table S2 and Supplementary Table S3. Different reagents were used between M1 and the subsequent time points. Revaccination was administered 12 months after initial vaccination (the x-axis is not to scale). Al(OH)₃, aluminum hydroxide; GMFR, geometric mean fold rise; GMT, geometric mean titer; M, month; revax, revaccination; RSV-A, respiratory syncytial virus subgroup A; RSVpreF, respiratory syncytial virus prefusion F vaccine; SIIV, seasonal inactivated influenza vaccine; vax1, initial vaccination.
Figure 4. Local reactions within 14 days after initial vaccination and revaccination in participants (A) 18–49 and (B) 65–85 years of age. Al(OH)₃, aluminum hydroxide; D1, initial vaccination; D3, revaccination; RSVpreF, respiratory syncytial virus prefusion F vaccine; SIIV, seasonal inactivated influenza vaccine.
Figure 5. Systemic events within 14 days after initial vaccination and revaccination in participants (A) 18–49 and (B) 65–85 years of age. Al(OH)$_3$, aluminum hydroxide; D1, initial vaccination; D3, revaccination; RSVpreF, respiratory syncytial virus prefusion F vaccine; SIIV, seasonal inactivated influenza vaccine.
Figure 6. Summary of adverse events occurring (A) 1 month and (B) 12 months after vaccination in participants 18–49 and 65–85 years of age. Al(OH)$_3$, aluminum hydroxide; RSVpreF, respiratory syncytial virus prefusion F vaccine; SIIIV, seasonal inactivated influenza vaccine.