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Influence of initial vaccination with 13-valent pneumococcal conjugate vaccine or 23-valent pneumococcal polysaccharide vaccine on anti-pneumococcal responses following subsequent pneumococcal vaccination in adults 50 years and older

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ABSTRACT

Background: Unlike free polysaccharide vaccines, pneumococcal polysaccharide conjugate vaccines (PCVs) induce a T cell-dependent immune response and have the potential to provide an extended duration of protection with repeated vaccinations.
Methods: This was an extension of a previous study in pneumococcal vaccine-naïve adults aged 50–64 years in which adults 60–64 years of age were given 13-valent PCV (PCV13) or 23-valent pneumococcal polysaccharide vaccine (PPSV23) and adults aged 50–59 were given PCV13. In this follow up study conducted about 4 years later, the 60–64 year olds initially given PCV13 received PCV13 or PPSV23, and those initially given PPSV23 received another PPSV23. All adults aged 50–59 years were re-vaccinated with PCV13. Anti-pneumococcal opsonophagocytic activity (OPA) titers were measured before and 1 month after vaccination.
Results: A second PCV13 given about 4 years after a first vaccination induced OPA titers that were significantly higher than those following the initial vaccination for 7 of 13 serotypes in the older group, and 6 of 13 serotypes in the younger group, and responses to the remaining serotypes were largely non-inferior. In contrast, OPA titers following revaccination with PPSV23 were statistically significantly lower for 9 of the 13 serotypes, and non-inferior for the remaining serotypes, when compared to the responses to the first PPSV23. OPA titers in the older adults who received PPSV23 after initial PCV13 were significantly higher than those following a first PPSV23 for 10 of the 13 serotypes.
Conclusion: In adults 50 to 64 years of age, initial vaccination with PCV13 establishes an immune state that results in recall anti-pneumococcal responses upon subsequent vaccination with either conjugated or free polysaccharide vaccine. In contrast, initial vaccination with PPSV23 results in an immune state in which subsequent PPSV23 administration yields generally lower responses compared with the initial responses.

Abbreviations: ACIP, United States Advisory Committee on Immunization Practices; AE, adverse event; CI, confidence interval; CRM_{197}, cross-reactive material 197; GMR, geometric mean ratio; GMT, geometric mean titer; OPA, opsonophagocytic activity; PCV, pneumococcal polysaccharide conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent polysaccharide vaccine; RCDC, reverse cumulative distribution curve; SAE, serious adverse event.

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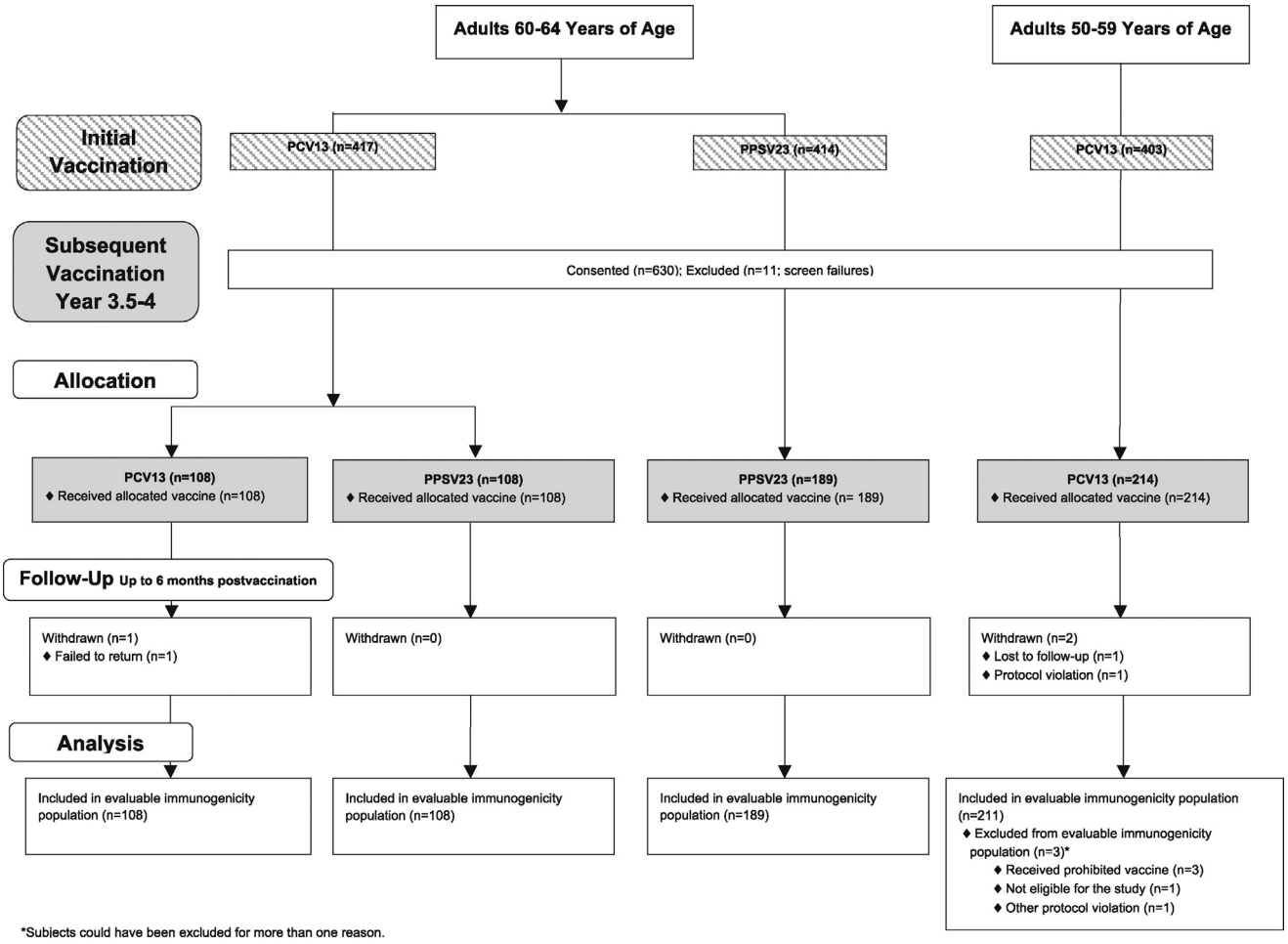

Fig. 1. Study design and disposition of subjects.
Vaccinations received as part of the initial study are shown in the striped boxes [5]. Abbreviations: PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

1. Introduction

The incidence and mortality of pneumococcal disease in adults increase with advancing age [1,2]. A 23-valent pneumococcal vaccine containing free (unconjugated) polysaccharides (PPSV23) has been available for 30 years and a single vaccination is recommended for adults ≥65 years and for younger adults with certain chronic medical conditions or other indications [2]. Revaccination is not routinely indicated in part due to the diminished immune responses that have been observed following revaccination, which may be due to the T cell independent nature of the immune response [2,3]. In contrast to PPSV23, the 13-valent pneumococcal conjugate vaccine (PCV13) was designed to engender T cell-dependent immunity, inducing a recall response on subsequent bacterial exposure or revaccination with the potential to significantly prolong the protection afforded by the vaccine.[4]

A previous clinical study of pneumococcal vaccine-naïve adults 50 through 64 years of age evaluated the functional opsonophagocytic activity (OPA) anti-pneumococcal immune responses elicited by a first vaccination with PCV13 or PPSV23. PCV13 was immunogenic and, in adults 60–64 years of age that were randomized to receive PCV13 or PPSV23, PCV13 elicited significantly higher OPA titers than those elicited by PPSV23 for 9 of 12 serotypes common to both vaccines. Adults 50–59 years of age all received PCV13, and had generally higher OPA titers than observed in adults 60–64 years of age who received PCV13 [5].

This follow-up study was conducted 3.5–4 years after the previous study in order to evaluate the immune responses to a second PCV13 and to a second PPSV23, and to determine the influence of initial PCV13 immunization on the responses to a subsequent PPSV23 vaccination in the adults 60–64 years of age who received PCV13.

2. Methods

2.1. Study design and populations

This was an extension of a previous study in pneumococcal vaccine-naïve adults 50 through 64 years of age, conducted at 23 medical centers in the United States [5]. Both studies were undertaken in accordance with the Declaration of Helsinki and Good Clinical Practice [6,7]. In the initial study, adults 60–64 years of age were randomly assigned with equal probability to receive PCV13 or PPSV23 and those 50–59 years of age received open label PCV13. In this extension study conducted 3.5–4 years after the start of the previous study, informed consent was obtained as for a new study and adults in the 60–64 year old age group who had initially received PCV13 were randomized 1:1 to receive PCV13 or PPSV23, and those who had received PPSV23 received another PPSV23 vaccination. Adults in the 50–59 year old age group received a second PCV13 (Fig. 1).

Table 1
Baseline characteristics.

Characteristic	60–64 Year age group			50–59 Year age group
	PCV13/PCV13 *N* = 108	PCV13/PPSV23 *N* = 108	PPSV23/PPSV23 *N* = 189	PCV13/PCV13 *N* = 214
Female, %	57.4	50.0	64.0	63.1
Race, %				
White	98.1	96.3	94.7	94.9
Black	0.0	0.9	1.6	3.7
Asian	0.0	0.9	0.5	1.4
Other	0.9	0.0	2.1	0.0
Indian or Alaska Native	0.9	1.9	0.5	0.0
Native Hawaiian or Other Pacific Islander	0.0	0.0	0.5	0.0
Hispanic or Latino, %	0.9	2.8	3.2	0.0
Mean age at vaccination 1, years (SD)	61.6 (1.4)	61.7 (1.3)	61.6 (1.4)	54.4 (2.9)
Time since vaccination 1, years (SD)	3.7 (0.1)	3.7 (0.1)	3.7 (0.1)	3.5 (0.1)
Mean age at vaccination 2, years (SD)	65.3 (1.4)	65.3 (1.4)	65.3 (1.4)	57.9 (2.9)

The study populations for both studies included persons with stable pre-existing underlying chronic conditions (e.g., cardiovascular, pulmonary, renal, liver diseases including alcoholic liver disease and alcoholism, and diabetes mellitus). Disease had to be stable, defined as not requiring significant change in therapy or hospitalization for worsening disease 12 weeks prior to vaccination. Participants were excluded if they had serious chronic disorders including metastatic malignancy, severe chronic obstructive pulmonary disease requiring supplemental oxygen, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, impaired immune function, or had previously received a PPSV23 dose or any prior PCV.

Non-study medications were permitted. Licensed vaccines, except pneumococcal vaccines, could be given according to local or national recommendations, and could be administered concomitantly. Receipt of influenza vaccine was permitted, if it was given at least 14 days before or after study vaccination.

Clinic visits occurred at vaccination and 1 month (29–43 days) after vaccination with a telephone visit for a safety assessment at 6 months after vaccination. Blood samples were obtained before and 1 month after vaccination.

2.2. Vaccines and administration

PCV13 (Prevnar 13/Prevenar 13®, Wyeth Vaccines; Lot Number 7-5095-010A) contains polysaccharides of pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, and 23F individually conjugated to a nontoxic mutant form of diphtheria toxin cross-reactive material 197 (CRM_{197}). Each 0.5 mL dose contains 2.2 μg of each serotype, except type 6B, which is included at 4.4 μg. Each dose is formulated in 5.0 mM succinate and 0.85% sodium chloride at pH 5.8 with 0.125 mg aluminum as aluminum phosphate and 0.02% polysorbate 80. The vaccine is supplied in single-dose syringes without preservatives and stored at 2–8 °C.

PPSV23 (Pneumovax 23®, Merck & Company, Inc; Lot Number A08071-003L) consists of a purified capsular polysaccharide from 12 of the serotypes included in PCV13 (all except 6A), as well as 11 additional serotypes (2, 8, 9 N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F). The vaccine is formulated to contain 25 μg of each of the 23 purified polysaccharide serotypes per 0.5 mL dose of vaccine, contains phenol as a preservative and stored at 2–8 °C.

Vaccines were administered by intramuscular injection in the deltoid using 25 G 1 in. needles.

2.3. Study objectives

In the older age group, the primary study objective was to evaluate the response to PPSV23 after an initial dose of PCV13 or PPSV23 for the 12 serotypes common to both vaccines and for serotype 6A which is unique to PCV13.Secondary objectives were to evaluate the ability of PCV13 to maintain or enhance OPA responses when given 3.5–4 years after an initial dose of PCV13 in both age groups, and describe the immune responses following 2 consecutive doses of PPSV23 in the older age group for the 12 serotypes common to both vaccines and for serotype 6A. Additionally, various immune response comparisons were performed as described in the Results section.

2.4. Analysis populations

The evaluable immunogenicity population was the primary population for immunogenicity analyses and consisted of eligible subjects who had at least one valid and determinate assay result in this extension study, received both study vaccines as assigned and no prohibited vaccines, and had no other major protocol violation.

2.5. Immunogenicity assessments

Primary endpoints were the functional antibacterial OPA titers for the 13 serotypes in PCV13 measured using serotype-specific validated OPA assays in samples obtained immediately before and approximately 1 month after each vaccination [8].

2.6. Safety assessments

Participants recorded local reactions (redness, swelling, pain and limitation of arm movement of the injected arm), and systemic events (chills, fatigue, headache, vomiting, decreased appetite, rash, new generalized muscle pain, aggravated generalized muscle pain, new generalized joint pain, and aggravated generalized joint pain), and oral temperature in an electronic diary on the evening of vaccination and for the next 13 days. Adverse events (AEs) were collected from enrollment through the month 1 postvaccination visit, serious adverse events (SAEs) from enrollment through the month 6 follow-up phone contact, and deaths through the end of the study.

2.7. Statistical analysis

2.7.1. Sample size considerations

All subjects who received the first vaccination and satisfied eligibility criteria to receive a second vaccination were included in the analyses. No formal power calculation was done.

2.7.2. Immunogenicity analyses

All analyses were descriptive and were done using the SAS software package. The non-inferiority criterion used in the previous study was applied in this study. No imputations were done for

missing data. For the comparison of post-vaccination OPA GMTs between vaccine groups or sequences, the 2-sided 95% confidence interval (CI) on the geometric mean ratio (GMR) for each serotype was calculated (back-transformed 95% CI for mean difference on the logarithmic scale computed using the Student *t* distribution). For comparisons within a vaccine sequence, analyses were performed using data only from those subjects who had OPA assessments after both vaccinations. Noninferiority was declared if the lower limit of the 2-sided 95% CI for the GMR was greater than 0.5 (2-fold criterion). This value was selected based on matching immunogenicity to efficacy results from several infant 7-valent Pneumococcal polysaccharide conjugate vaccine (PCV) or 9-valent PCV efficacy trials [9]. A secondary analysis assessed statistically significantly greater or lower responses; a statistically greater response was declared if the lower limit of the 95% CI for the GMR was >1.0, and a statistically lower response was declared if the upper limit of the 95% CI for the GMR was <1.0.

Reverse cumulative distribution curves (RCDC) for key comparisons were generated to permit comparisons of immune response throughout the full range of OPA responses

2.7.3. Safety analyses

Comparisons of the incidence of local reactions and systemic events between vaccine groups were performed with corresponding 95% CIs and *p*-values based on Chan and Zhang methodology [10].

3. Results

3.1. Baseline characteristics and disposition of subjects

A total of 405 subjects 60–64 years of age at enrollment in the initial study participated in the extension study. Of those, 216 had received PCV13 in the initial study and were randomized to receive PCV13 ($N = 108$) or PPSV23 ($N = 108$) in the extension study, and 189 had received PPSV23 in the initial study and received PPSV23 in the extension study, with all being evaluable. Additionally, 214 of subjects 50–59 years of age at initial study enrollment participated in the extension study and received a second PCV13 vaccination, with 211 being evaluable. In total, 50.1% of subjects who received vaccination 1 in the initial study returned for this extension study (Table 1, Fig. 1).

The mean ages of subjects in the 60–64 year age group and in the 50–59 year age group were 65.3 years and 57.9 years, respectively, at vaccination 2. The mean intervals since initial vaccination were 3.7 (range 3.6–3.9) and 3.5 (range 3.3–3.6) years, respectively.

The race and ethnicity of subjects was similar across the total study population with the majority of subjects being white (94.7–98.1%). In adults aged 60–64 years, more females were vaccinated in the PCV13/PCV13 and PPSV23/PPSV23 groups (57.4% and 64.0% respectively) compared to the PCV13/PPSV23 group (50.0%), and in the younger cohort, who all received PCV13/PCV13, 63.1% of subjects were female (Table 1).

In the older and younger age groups 25.9% and 19.2%, respectively, reported chronic underlying diseases.

3.2. Immune responses

3.2.1. PPSV23 following initial PCV13 (PCV13/PPSV23) compared to initial PPSV23

OPA geometric mean titers (GMTs) following PPSV23 administered after PCV13 were statistically significantly greater for 10 of 13 serotypes (1, 3, 5, 6A, 6B, 7F, 18C, 19A, 19F, 23F) and non-inferior for the remainder (4, 9V, 14), when compared to responses following initial PPSV23 administered in the previous study (Table 2).

Table 2
Comparison of pneumococcal OPA GMTs following revaccination in the 60–64 year age group initially vaccinated with PCV13.

Serotype	PCV13/PPSV23 vs. PPSV23			PCV13/PPSV23 vs. PCV13			PCV13/PCV13 vs PCV13		
	PCV13/PPSV23 n^a = 99–107 GMT[b]	PPSV23 n^a = 167–184 GMT[b]	Ratio GMT ratio[c] (95% CI)	PCV13/PPSV23 n^a = 88–100 GMT[b]	PCV13 n^a = 88–100 GMT[b]	Ratio GMT ratio[c,d] (95% CI)	PCV13/PCV13 n^a = 92 – 102 GMT[b]	PCV13 n^a = 92–102 GMT[b]	Ratio GMT ratio[c,d] (95% CI)
1	398	116	3.4 (2.32–5.09)	377	172	2.2 (1.64–2.94)	334	155	2.2 (1.59–2.92)
3	164	105	1.6 (1.13–2.16)	162	102	1.6 (1.23–2.03)	87	102	0.9 (0.68–1.08)
4	1875	1420	1.3 (0.88–1.98)	1997	2894	0.7 (0.51–0.94)	1194	1626	0.7 (0.53–1.01)
5	476	149	3.2 (2.04–4.97)	445	239	1.9 (1.37–2.53)	277	180	1.5 (1.09–2.16)
6A[e]	832	274	3.0 (1.61–5.73)	812	2884	0.3 (0.21–0.37)	2126	2411	0.9 (0.64–1.21)
6B	2670	1088	2.5 (1.50–4.00)	2707	2664	1.0 (0.79–1.31)	4357	2312	1.9 (1.42–2.50)
7F	1895	403	4.7 (2.76–7.99)	1818	971	1.9 (1.25–2.80)	1226	928	1.3 (0.89–1.95)
9V	1089	654	1.7 (0.93–2.97)	909	1474	0.6 (0.42–0.91)	855	1163	0.7 (0.46–1.17)
14	1268	824	1.5 (0.99–2.39)	1367	655	2.1 (1.43–3.04)	1040	746	1.4 (1.01–1.93)
18C	2489	1135	2.2 (1.37–3.50)	2503	2136	1.2 (0.92–1.49)	1837	1529	1.2 (0.93–1.55)
19A	966	377	2.6 (1.78–3.68)	976	765	1.3 (1.05–1.55)	791	591	1.3 (1.06–1.68)
19F	1653	621	2.7 (1.77–4.01)	1670	675	2.5 (1.69–3.61)	989	467	2.1 (1.48, 3.04)
23F	299	86	3.5 (1.99–6.13)	333	432	0.8 (0.56–1.07)	918	448	2.1 (1.40–3.01)

[a] n = Number of subjects with determinate OPA titer for the specified serotype.
[b] GMTs calculated using all evaluable subjects with data for a given blood draw.
[c] Ratio of GMTs calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
[d] For within group comparisons the GMT ratio (95% CI) accounts for each subject as their own control across time and GMTs are derived for subjects with data at both time points.
[e] Serotype 6A is not included in PPSV23.

Table 3
Pneumococcal OPA GMTs following revaccination with PCV13 in 50–59 year old subjects initially vaccinated with PCV13 and comparison of pneumococcal OPA GMTs following vaccination with 13vPnC/13vPnC in 60–64 year old subjects and 50–59 year old subjects.

Serotype	PCV13/PCV13 vs PCV13 (Adults 50–59 years of age)			PCV13/PCV13 (Adults 50–59 years of age vs. Adults 60–64 years of age)		
	PCV13/PCV13 n[a] = 181–202 GMT[b]	PCV13 n[a] = 181–202 GMT[b]	Ratio GMT ratio[c,d] (95% CI)	50–59 years of age n[a] = 196–205 GMT[b]	60–64 years of age n[a] = 100–104 GMT[b]	Ratio GMT ratio[c] (95% CI)
1	296	198	1.5 (1.20–1.86)	292	334	0.9 (0.63–1.22)
3	85	91	0.9 (0.80–1.08)	83	87	1.0 (0.73–1.26)
4	1685	2817	0.6 (0.49–0.73)	1657	1175	1.4 (1.07–1.86)
5	291	235	1.2 (1.02–1.50)	293	276	1.1 (0.71–1.58)
6A[e]	3143	4347	0.7 (0.6–0.87)	3104	2064	1.5 (1.05–2.16)
6B	4886	3085	1.6 (1.29–1.95)	4885	4184	1.2 (0.88–1.54)
7F	1659	1596	1.0 (0.83–1.30)	1654	1223	1.4 (1.06–1.73)
9V	1492	1933	0.8 (0.61–0.98)	1421	770	1.8 (1.23–2.77)
14	1278	865	1.5 (1.15–1.90)	1186	1031	1.1 (0.85–1.55)
18C	2156	1742	1.2 (0.96–1.59)	2066	1918	1.1 (0.79–1.46)
19A	1048	959	1.1 (0.94–1.27)	1039	789	1.3 (1.01–1.72)
19F	1182	633	1.9 (1.51–2.32)	1171	958	1.2 (0.88–1.70)
23F	1188	563	2.1 (1.63–2.73)	1158	867	1.3 (0.90–1.99)

[a] n = Number of subjects with determinate OPA titer for the specified serotype.
[b] GMTs calculated using all evaluable subjects with data for a given blood draw.
[c] Ratio of GMTs calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
[d] For within group comparisons the GMT ratio (95% CI) accounts for each subject as their own control across time and GMTs are derived for subjects with data at both time points.
[e] Serotype 6A is not included in PPSV23.

3.2.2. PCV13/PPSV23 compared to initial PCV13

OPA GMTs following PPSV23 administered after PCV13 were statistically significantly greater for 7 of 13 serotypes (1, 3, 5, 7F, 14, 19A, 19F) and met non-inferiority criteria for 4 of the remaining 6 serotypes (4, 6B, 18C, 23F) when compared to responses following initial PCV13 administered in the previous study (Table 2). The OPA GMTs were significantly lower for 3 serotypes (4, 6A, 9V); nonetheless, the 95% CI upper bounds for 2 of these serotypes (4 and 9V) were ≥0.91 suggesting generally comparable responses when comparing the first and second vaccine administrations. Only the serotype 6A response following PPSV23 administration was clearly lower than after initial PCV13, reflecting the absence of this serotype in PPSV23 (Table 2).

3.2.3. PCV13/PCV13 compared to initial PCV13

OPA GMTs following 2 administrations of PCV13 were statistically significantly greater compared to a single administration of PCV13 for 7 of 13 serotypes (1, 5, 6B, 14, 19A, 19F, 23F) in adults 60–64 years of age (Table 2), and 6 of 13 serotypes (1, 5, 6B, 14, 19F, 23F) in adults 50–59 years of age (Table 3). Responses to the remaining serotypes were largely non-inferior, although 3 serotypes (4, 6A, 9V) yielded statistically inferior responses in the younger age group.

3.2.4. PPSV23/PPSV23 compared to initial PPSV23

OPA GMTs following 2 doses of PPSV23 were statistically significantly lower for 9 of the 13 serotypes (3, 4, 5, 6A, 9V, 14, 18C, 19F, 23F), and non-inferior for the remaining 4 serotypes (1, 6B, 7F, 19A) (Table 4).

3.2.5. PCV13/PPSV23 compared to PPSV23/PPSV23

OPA GMTs following administration of PPSV23 to persons who had previously received PCV13 were statistically significantly greater for all serotypes compared to the responses to PPSV23 given to persons who had previously received PPSV23 (Table 4).

3.2.6. PCV13/PCV13 compared to PPSV23/PPSV23

OPA GMTs following a second dose of PCV13 were statistically significantly greater for all common serotypes compared to responses following a second dose of PPSV23 (Table 4).

3.2.7. PCV13/PCV13 in younger adults compared to PCV13/PCV13 in older adults

OPA GMTs after 2 doses of PCV13 in the younger age group were statistically significantly greater for 5 serotypes (4, 6A, 7F, 9V, 19A) (Table 3).

3.3. Population responses

RCDCs showing the population anti-pneumococcal OPA responses in adults 60–64 years of age for the vaccination sequences PCV13/PCV13, PCV13/PPSV23, and PPSV23/PPSV23 confirm the results obtained when comparing OPA GMTs (Supplemental Figs. S1, S2, S3). Depending on serotype, responses throughout the vaccinated population were higher or comparable following administration of PPSV23 or PCV13 given after an initial administration of PCV13. In contrast, population responses were consistently lower following 2 consecutive doses of PPSV23.

3.4. Safety

Local reactions were generally mild across all groups. Incidences of local reactions in subjects receiving 2 sequential doses of PCV13, or PCV13 followed by PPSV23, were generally lower than for subjects receiving 2 doses of PPSV23 (Table 5). An increase in local reactions was seen after a second dose of PPSV23 compared to a first (Table 5). Muscle pain, fatigue, and headache were the most common systemic events after each vaccination (Table 5). Fever was rare and no severe fever was reported. Most adverse events (AEs) were conditions commonly observed among older adults, and no vaccine related serious adverse events (SAEs) or deaths were reported.

4. Discussion

Although the incidence and mortality of pneumococcal disease increase with age among older adults, the current recommended use of PPSV23 does not allow for maintenance of the vaccine-elicited protective immune response over the period of risk. This vaccine is not generally recommended for adults 50–64 years of age and, in the United States, only a single administration is

Table 4
Comparison of pneumococcal OPA immune responses following revaccination in the 60–64 year age group initially vaccinated with PPSV23.

Serotype	PPSV23/PPSV23 vs PPSV23 (Adults 60–64 years of age)			PCV13/PPSV23 vs. PPSV23/PPSV23 (Adults 60–64 years of age)			PCV13/PCV13 vs. PPSV23/PPSV23 (Adults 60–64 years of age)		
	PPSV23/PPSV23 n^a = 157–181 GMT[b]	PPSV23 n^a = 157–181 GMT[b]	Ratio GMT ratio[c,d] (95% CI)	PCV13/PPSV23 n^a = 99–107 GMT[b]	PPSV23/PPSV23 n^a = 174–186 GMT[b]	Ratio GMT ratio[c] (95% CI)	PCV13/PCV13 n^a = 100–104 GMT[b]	PPSV23/PPSV23 n^a = 174–186 GMT[b]	Ratio GMT ratio[c] (95% CI)
1	95	115	0.8 (0.68–1.02)	398	95	4.2 (2.87–6.08)	334	95	3.5 (2.39–5.14)
3	53	103	0.5 (0.44–0.59)	164	53	3.1 (2.26–4.30)	87	53	1.6 (1.19–2.28)
4	725	1437	0.5 (0.40–0.64)	1875	733	2.6 (1.72–3.80)	1175	733	1.6 (1.05–2.44)
5	71	152	0.5 (0.39–0.56)	476	74	6.5 (4.09–10.19)	276	74	3.7 (2.32–6.04)
6A[e]	133	286	0.5 (0.35–0.62)	832	123	6.8 (3.72–12.33)	2064	123	16.8 (9.45–29.87)
6B	915	1133	0.8 (0.62–1.04)	2670	916	2.9 (1.83–4.63)	4184	916	4.6 (2.92–7.15)
7F	466	440	1.1 (0.81–1.37)	1895	497	3.8 (2.41–6.03)	1223	497	2.5 (1.56–3.89)
9V	181	669	0.3 (0.18–0.41)	1089	187	5.8 (3.13–10.82)	770	187	4.1 (2.22–7.65)
14	619	823	0.8 (0.60–0.95)	1268	661	1.9 (1.30–2.84)	1031	661	1.6 (1.07–2.26)
18C	822	1096	0.8 (0.60–0.94)	2489	802	3.1 (2.02–4.78)	1918	802	2.4 (1.54–3.72)
19A	361	374	1.0 (0.83–1.12)	966	364	2.7 (1.87–3.76)	789	364	2.2 (1.52–3.08)
19F	405	596	0.7 (0.57–0.81)	1653	374	4.4 (2.97–6.58)	958	374	2.6 (1.68–3.92)
23F	56	91	0.6 (0.50–0.76)	299	54	5.5 (3.20–9.41)	867	54	15.9 (9.33–27.19)

[a] n = Number of subjects with determinate antibody titer to the specified serotype.
[b] GMTs calculated using all evaluable subjects with available data for a given blood draw.
[c] Ratio of GMTs calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
[d] For within group comparisons the GMT ratio (95% CI) accounts for each subject as their own control across time and GMTs are derived for subjects with data at both time points.
[e] Serotype 6A is not included in PPSV23.

recommended for adults ≥65 years [2,3,11]. Although not invariantly observed, re-immunization with PPSV23 has been repeatedly shown to elicit lower antibody responses following revaccination, compared to the responses after initial administration [11,12]. Of interest, similar observations have been made with other free polysaccharide vaccines, such as *Neisseria meningitidis* capsular polysaccharide vaccines [4,14,15]. The underlying mechanism for the blunting of the immune response with revaccination is not fully understood, but may be due to the loss of memory B cells upon initial or follow-on administration of free polysaccharides [16–18].

By contrast, an efficient recall response is seen with PCVs like PCV13 in which the polysaccharide is covalently attached to an immunological "carrier" protein converting the T cell-independent immune response elicited by PPSV23 to a T cell-dependent immune response [17–20]. Therefore, PCV13 may induce a qualitatively different immune response than that elicited by PPSV23, resulting in immunological memory and an improved immune response upon subsequent vaccine administration of PCV13 or PPSV23 with the potential for re-immunization to provide protection for a lifetime of risk. ACIP recently recommended that certain immunocompromized populations be vaccinated with PCV13 first followed by a dose of PPSV23 [21].

In this study, subjects in both age groups who received PCV13 in the previous study generally had robust responses to either PCV13 or PPSV23 given in the current study. Among persons who received a second dose of PCV13, responses to the second vaccination were generally at least comparable to initial PCV13 responses and statistically significantly greater for many of the serotypes. Among persons who received PCV13 in the original study and PPSV23 in this extension study, the responses following the PPSV23 were significantly greater for most of the serotypes common to both vaccines than those observed in persons who received an initial dose of PPSV23 in the original study.

The recall immune responses seen after re-vaccination with PCV13 in the current study are in contrast to previously reported results. In previous studies, neither administration of a second dose of PCV13 one year after an initial dose of PCV13 nor a dose of PPSV23 administered 3–6 months after a dose of PCV7 demonstrated an apparent immunological recall [22–25]. It is possible that a longer interval between PCV13 administration and a second dose of PCV13 or a dose of PPSV23 is required to optimize immune responses to subsequent doses of pneumococcal vaccine after an initial dose of conjugated vaccine. These results support the perspective that the conjugate vaccine is capable of eliciting polysaccharide-specific immunological memory.

In contrast, administration of a second dose of PPSV23 to persons who had received PPSV23 in the original study led to notably lower immune responses than those observed following the initial PPSV23. The lack of immunological memory elicited by PPSV23 stands in contrast to the apparent memory elicited by PCV13, and reflects previously reported observations with similar vaccines [26]. The immunological advantage of the PCV compared to the free (unconjugated) polysaccharide vaccine is most notable when comparing the OPA responses after 2 doses of PCV13 with those following 2 doses of PPSV23. An OPA threshold for protection has not been identified, but the population responses as reflected by the RCDCs demonstrate the immunologic advantage of the PCV13 throughout the full distribution of OPA responses for a number of serotypes. Hence, whatever the threshold, PCV13 alone or as a successive dose is likely to improve protection, compared to single or successive doses of PPSV23 for serotypes common to both vaccines.

Finally, responses after 2 PCV13 doses in 50–59 year olds were noninferior to the responses in the older age group and statistically significantly greater for 5 serotypes, demonstrating a not unexpected greater immune response in younger compared to older adults.

Table 5
Local reactions and systemic events reported up to day 14 after vaccination 1 and vaccination 2.

		Adults 60–64 years of age									Adults 50–59 years of age		
		PPSV23/PPSV23 vs. PPSV23			PCV13/PPSV23 vs. PCV13			PCV13/PCV13 vs. PCV13			PCV13/PCV13 vs. PCV13		
		PPSV23/PPSV23%	PPSV23%	Difference[d] (95% CI)	PCV13/PPSV23%	PCV13%	Difference[d] (95% CI)	PCV13/PCV13%	PCV13%	Difference[d] (95% CI)	PCV13/PCV13%	PCV13%	Difference[d] (95% CI)
Local reactions													
Redness[a]	Any	**30.5**	**13.6**	**16.9** (3.0;29.8)	**28.0**	**20.0**	**8.0** (−14.2;29.0)	**20.6**	**26.5**	**−5.9** (−19.8;8.0)	**26.5**	**18.4**	**8.2** (−5.8;21.5)
	Mild	**24.1**	**9.3**	**14.8** (1.3;27.3)	**17.4**	**13.0**	**4.3** (−18.1;26.0)	**20.6**	**23.5**	**−2.9** (−16.1;10.3)	**23.4**	**17.0**	**6.4** (−7.6;19.9)
	Moderate	**16.3**	**4.1**	**12.2** (0.7;22.8)	**14.3**	**9.5**	**4.8** (−16.4;25.6)	**6.1**	**9.1**	**−3.0** (−16.5;10.2)	**2.6**	**2.6**	**0.0** (−8.5;8.5)
	Severe	**4.4**	**0.0**	**4.4** (−2.9;11.4)	**4.8**	**4.8**	**0.0** (−14.8;14.8)	**0.0**	**0.0**	**0.0** (−5.9;5.9)	**0.0**	**2.6**	**−2.6** (−9.4;4.4)
Swelling	Any	**31.0**	**12.1**	**19.0** (6.1;30.5)	**26.9**	**15.4**	**11.5** (−8.7;30.2)	**24.3**	**32.4**	**−8.1** (−26.3;10.2)	**31.5**	**26.5**	**−2.0** (−15.3;11.3)
	Mild	**18.9**	**11.3**	**7.5** (−4.4;18.9)	**24.0**	**8.0**	**16.0** (−3.6;33.1)	**17.1**	**25.7**	**−8.6** (−24.7;8.2)	**22.4**	**26.5**	**−4.1** (−17.7;9.9)
	Moderate	**16.3**	**2.0**	**14.3** (3.5;23.9)	**9.5**	**9.5**	**0.0** (−19.1;19.1)	**11.8**	**14.7**	**−2.9** (−20.0;14.0)	**0.0**	**5.4**	**−5.4** (−13.7;3.4)
	Severe	**2.3**	**0.0**	**2.3** (−3.8;8.2)	**4.8**	**0.0**	**4.8** (−7.6;16.3)	**0.0**	**0.0**	**0.0** (−5.9;5.9)	**0.0**	**0.0**	**0.0** (−5.0;5.0)
Pain[b]	Any	**88.3**	**78.1**	**10.2** (3.1;16.9)	**86.3**	**84.9**	**1.4** (−9.1;11.8)	**77.8**	**81.9**	**−4.2** (−14.6;6.9)	**95.2**	**93.2**	**2.0** (−2.5;6.6)
	Mild	**83.8**	**73.5**	**10.3** (2.1;18.1)	**86.4**	**81.8**	**4.5** (−7.1;15.9)	**76.5**	**80.9**	**−4.4** (−15.4;6.9)	**92.8**	**90.6**	**2.2** (−3.8;8.1)
	Moderate	**52.4**	**28.6**	**23.8** (9.4;36.7)	**45.2**	**29.0**	**16.1** (−2.9;33.2)	**23.8**	**33.3**	**−9.5** (−23.6;5.6)	**56.5**	**35.5**	**21.0** (6.2;34.5)
	Severe	**12.2**	**8.2**	**4.1** (−6.2;14.0)	**17.4**	**4.3**	**13.0** (−3.0;27.0)	**0.0**	**0.0**	**0.0** (−5.9;5.9)	**0.0**	**5.4**	**−5.4** (−13.7;3.4)
Limitation of arm movement[c]	Any	**47.2**	**30.6**	**16.7** (3.5;28.9)	**37.9**	**24.1**	**13.8** (−9.4;35.2)	**26.2**	**35.7**	**−9.5** (−24.9;6.3)	**32.9**	**50.0**	**2.9** (−7.7;13.3)
	Mild	**45.7**	**30.0**	**15.7** (2.4;28.1)	**34.5**	**24.1**	**10.3** (−12.0;31.2)	**22.0**	**34.1**	**−12.2** (−28.3;5.4)	**47.0**	**47.0**	**0.0** (−11.9;11.9)
	Moderate	**2.3**	**0.0**	**2.3** (−3.8;8.2)	**13.6**	**0.0**	**13.6** (−3.0;28.0)	**3.1**	**3.1**	**0.0** (−5.8;5.8)	**5.3**	**2.6**	**2.6** (−4.4;9.4)
	Severe	**8.3**	**4.2**	**4.2** (−4.7;12.7)	**10.0**	**0.0**	**10.0** (−5.9;54.0)	**0.0**	**0.0**	**0.0** (−5.9;5.9)	**2.6**	**2.6**	**0.0** (−8.3;8.3)
Any local reaction[e]		**88.7**	**79.7**	**9.0** (2.4;15.4)	**89.3**	**86.7**	**2.7** (−7.2;12.8)	**82.4**	**81.1**	**1.4** (−8.3;11.0)	**95.4**	**94.7**	**0.7** (−3.8;5.1)
Systemic Events													
Fever													
	Any (≥38 °C)	**2.3**	**9.1**	**−6.8** (−16.8;3.7)	**4.8**	**0.0**	**4.8** (−7.6;16.3)	**0.0**	**0.0**	**0.0** (−5.9;5.9)	**2.6**	**0.0**	**2.6** (−4.4;9.4)
	Mild (≥38 °C but <38.5 °C)	**2.3**	**2.3**	**0.0** (−7.5;7.5)	**4.8**	**0.0**	**4.8** (−7.6;16.3)	**0.0**	**0.0**	**0.0** (−5.9;5.9)	**2.6**	**0.0**	**2.6** (−4.4;9.4)
	Moderate (≥38.5 °C but <39 °C)	**0.0**	**0.0**	**0.0** (−4.4;4.4)	**0.0**	**0.0**	**0.0** (−8.9;8.9)	**0.0**	**0.0**	**0.0** (−5.9;5.9)	**0.0**	**0.0**	**0.0** (−5.0;5.0)
	Severe (≥39 °C but ≤40 °C)	**0.0**	**0.0**	**0.0** (−4.4;4.4)	**0.0**	**0.0**	**0.0** (−8.9;8.9)	**0.0**	**0.0**	**0.0** (−5.9;5.9)	**0.0**	**0.0**	**0.0** (−5.0;5.0)
	>40 °C	**0.0**	**6.8**	**−6.8** (−14.8;1.8)	**0.0**	**0.0**	**0.0** (−8.9;8.9)	**0.0**	**0.0**	**0.0** (−5.9;5.9)	**0.0**	**0.0**	**0.0** (−5.0;5.0)
Fatigue		**56.4**	**64.9**	**−8.5** (−19.2;2.6)	**53.6**	**68.6**	**0.0** (−13.3;13.3)	**49.1**	**62.3**	**−13.2** (−27.5;2.0)	**65.6**	**65.6**	**0.0** (−10.7;10.7)
Headache		**57.3**	**61.0**	**−3.7** (−15.4;8.3)	**52.4**	**54.8**	**−2.4** (−18.9;14.2)	**47.2**	**51.2**	**−14.0** (−27.2;0.6)	**61.4**	**72.7**	**−11.4** (−21.3;−0.9)
Chills		**32.8**	**25.9**	**6.9** (−7.5;20.8)	**26.7**	**33.3**	**−6.7** (−24.5;12.2)	**20.2**	**22.2**	**0.0** (−13.6;13.6)	**22.6**	**24.5**	**−1.9** (−15.1;11.5)
Rash		**32.7**	**9.1**	**23.6** (9.5;36.1)	**17.2**	**27.6**	**−10.3** (−29.4;10.2)	**20.2**	**12.1**	**12.1** (−2.9;25.8)	**7.3**	**9.8**	**−2.4** (−15.2;10.5)
Vomiting		**2.3**	**0.0**	**2.3** (−3.8;8.2)	**4.8**	**0.0**	**4.8** (−7.6;16.3)	**6.5**	**3.2**	**3.2** (−5.3;11.4)	**7.1**	**7.1**	**0.0** (−10.0;10.0)
Decreased appetite		**21.6**	**19.6**	**2.0** (−9.8;13.8)	**14.5**	**31.0**	**3.4** (−12.2;18.1)	**14.7**	**20.6**	**−5.9** (−21.8;10.0)	**26.4**	**28.3**	**−1.9** (−15.1;11.5)
New generalized muscle pain		**70.5**	**57.9**	**12.6** (2.2;22.6)	**71.7**	**56.5**	**15.2** (−0.1;29.5)	**30.0**	**47.7**	**2.3** (−15.9;20.6)	**67.8**	**69.0**	**−1.1** (−12.8;10.5)
Aggravated generalized muscle pain		**40.0**	**25.0**	**15.0** (0.1;28.9)	**38.7**	**32.3**	**6.5** (−9.5;21.8)	**22.9**	**22.9**	**0.0** (−19.1;19.1)	**36.1**	**42.6**	**−6.6** (−20.5;7.8)
New generalized joint pain		**23.2**	**25.0**	**−1.8** (−12.4;9.0)	**20.7**	**31.0**	**−10.3** (−21.9;2.2)	**14.3**	**21.6**	**2.7** (−13.3;18.8)	**41.5**	**35.2**	**−3.7** (−18.0;10.8)
Aggravated generalized joint pain		**17.0**	**11.3**	**5.7** (−5.7;16.8)	**25.0**	**20.8**	**4.2** (−11.2;18.6)	**16.7**	**19.4**	**−2.8** (−18.9;13.2)	**25.0**	**25.0**	**0.0** (−14.1;14.1)
Any systemic event[f]		**86.4**	**84.8**	**1.5** (−4.9;7.9)	**82.8**	**87.5**	**−4.7** (−15.6;6.3)	**77.6**	**79.1**	**−1.5** (−13.5;10.6)	**88.3**	**92.0**	**−3.6** (−8.8;1.6)

[a] Redness and swelling were categorized as absent if <2.5 cm, mild if ≥2.5 cm and ≤5.0 cm, moderate if >5.0 cm and ≤10.0 cm, and severe if >10.0 cm.

[b] If pain at the injection site was present, subjects were asked to enter the severity as mild if the symptom was easily tolerated, moderate if there was discomfort sufficient to interfere with usual activity, and severe if the pain was incapacitating.

[c] If limitation of arm movement was present, subjects were asked to enter the severity as mild if there was some limitation of arm movement, moderate if the subject was unable to move his or her arm above the head but able to move it above the shoulder, and severe if the subject was unable to move the arm above the shoulder.

[d] Difference in proportions expressed as a percentage.

[e] Any local reaction = any pain, any swelling, any redness, or any limitation of arm movement.

[f] Any systemic event = any fever ≥38 °C, any fatigue, any headache, any chills, any rash, any vomiting, any decreased appetite, any new or aggravated generalized muscle pain, and any new or aggravated joint pain.

An acceptable safety profile was seen when PCV13 was followed 3.5–4 years later by PCV13 or PPSV23, irrespective of subject age. Subsequent vaccination with PPSV23 gave rise to more local reactions in those previously administered PCV13 or PPSV23 than did revaccination with PCV13.

A potential limitation is that the study was a non-prospective open label extension of a reported parent study [5]. However, all serological evaluations remained blinded throughout all stages of the study, and vaccine allocation in subjects aged 60–64 years was maintained through an electronic randomization system. Subjects that returned for the extension study did not differ in terms of baseline demographics, medical history or response to initial vaccination, when compared to subjects that did not return. The study also did not include a study arm evaluating the sequence of PPSV23 followed by PCV13 at a 3.5–4 year interval to evaluate the potential longer term impact of PPSV23 on subsequent PCV13 immune response. However, PPSV23 has been shown to dramatically decrease response to subsequent PCV7 or PCV13 administered 1 year later and results from this study demonstrate that the negative impact of PPSV23 on subsequent PPSV23 persists for at least 3.5–4 years, consistent with the inability of this T cell independent vaccine to prompt a recall response to antigens in common [19,20,23,27].

5. Conclusion

The present study documents the potential advantage of initial PCV administration, which permits the establishment of an immune state that results in appropriate recall responses upon subsequent immunization with either PCV13 or PPSV23. The study further demonstrates that PCV13 in a younger adult population results in higher responses compared to older adults. These responses can be sustained with a subsequent PCV13 dose when delivered at an appropriate interval, and can likely be expanded to include responses to the non-PCV13 serotypes with administration of PPSV23 later in life. Such an approach has the potential to provide protective immunity against significant disease-associated pneumococcal serotypes throughout an extended at-risk period of later adult life.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.04.084.

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