Published in final edited form as:

Vaccine. 2018 January 29; 36(5): 606–614. doi:10.1016/j.vaccine.2017.12.061.

Randomized clinical trial of a single versus a double dose of 13-valent pneumococcal conjugate vaccine in adults 55 through 74 years of age previously vaccinated with 23-valent pneumococcal polysaccharide vaccine

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Conflict of Interest Disclosures: The University of Alabama at Birmingham (UAB) has IP rights to several reagents developed in M.H.N.'s laboratory, and M.H.N. and R.L.B. are UAB employees. M.H.N. and R.L.B. declare no other conflicts of interest. RB reports grant funding from Pfizer for projects not related to this study. Other co-authors reported no conflicts of interest.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Prior presentations: None

Additional Contributions: The study investigators wish to thank our study participants and the study teams at each enrollment site.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01654263

Abstract

INTRODUCTION—In older adults, prior administration of 23-valent pneumococcal polysaccharide vaccine (PPSV23) blunts the opsonophagocytic antibody (OPA) response to subsequent administration of 13-valent pneumococcal conjugate vaccine (PCV13). To determine whether a higher dose of PCV13 could mitigate this effect in adults 55 through 74 years of age, we compared OPA responses to a double dose of PCV13 in persons previously vaccinated with PPSV23 with responses to a single dose of PCV13 in previously vaccinated persons, and with a single dose in PPSV23 naïve persons.

METHODS—Subjects previously vaccinated with PPSV23 were randomly assigned to receive either a single injection or two concurrent injections of 0.5 mL PCV13. Naïve subjects received a single injection of 0.5 mL PCV13. Serotype-specific OPA responses to 12 of the PCV13 serotypes were assessed on samples collected on Day 29 and Day 181. Comparisons of the OPA titers between study groups were based on the lower bound of the 95% confidence interval of the log geometric mean ratio to define superiority (> 1) and non-inferiority (> 0.5).

RESULTS—At Day 29, the OPA responses to one dose in previously vaccinated ($n = 284$) versus one dose in naïve subjects ($n = 311$) achieved the threshold for non-inferiority for only 3 of the 12 serotypes. In previously vaccinated subjects, responses to a double dose ($n = 288$) versus a single dose met the threshold for superiority for 7 serotypes. The responses to a double dose in previously vaccinated subjects versus a single dose in naïve subjects met the threshold for non-inferiority for 9 serotypes.

CONCLUSIONS—There is a dose response to PCV13 in older adults and the higher response to a double dose in previously vaccinated adults is non-inferior to that of a single dose in naïve adults for 9 of the 12 PCV13 serotypes evaluated.

Keywords

pneumococcal vaccine

INTRODUCTION

In 2014, the Advisory Committee on Immunization Practices (ACIP) modified the longstanding recommendation for routine use of 23 valent pneumococcal polysaccharide vaccine (PPSV23) in adults 65 years of age and older to add routine administration of 13 valent pneumococcal conjugate vaccine (PCV13).⁽¹⁾ This decision was based in part on the results of a landmark randomized placebo controlled trial of PCV13 in approximately 85,000 pneumococcal vaccine naïve, immunocompetent adults 65 years of age and older in the Netherlands (CAPITA trial),⁽²⁾ which found that PCV13 was effective in reducing the risks of vaccine-type community acquired pneumonia (efficacy 46%) and invasive pneumococcal disease (efficacy 75%).

The 2014 ACIP recommendation specifies that, for immunocompetent adults 65 years of age who have not previously received either PPSV23 or PCV13, PCV13 should be given first, followed at least one year later by PPSV23. This sequence is recommended due to the

evidence that prior administration of PPSV23 blunts the immune response to subsequent doses of PCVs, including PCV13, in adults.(3, 4)

For immunocompetent adults 65 years who have received PPSV23 but not PCV13, a dose of PCV13 is recommended, to be given at least one year after the most recent dose of PPSV23. For those given the PPSV23-PCV13 sequence, the benefits of PCV13 vaccination observed in the CAPITA population of PPSV23 naïve persons may not be realized, due to the blunting of the immune response to PCV13 induced by the prior PPSV23 vaccination. An estimated 25% of immunocompetent adults 50 through 64 years of age in the United States have an indication for PPSV23 vaccination (5) and so could receive PPSV23 before they are recommended to receive PCV13.

We conducted a large dose ranging study of PCV13 vaccine that enrolled two groups of adults 55 through 74 years of age – those who had received PPSV23 three through seven years prior to enrollment and those who had never received PPSV23. The previously vaccinated subjects were randomized to receive either two 0.5 mL doses of PCV13 given concurrently or a single 0.5 mL dose of PCV13 and the OPA responses to the double dose were compared with the single dose to evaluate a dose effect. The vaccine naïve group received a single 0.5 mL dose of PCV13. The OPA responses to the double dose in the previously vaccinated group were compared with the responses to the single dose in the vaccine naïve group to evaluate the extent to which the higher dose could mitigate the effect of hyporesponsiveness due to prior PPSV23 exposure.

METHODS

Vaccine and administration

Each dose of PCV13 (Prevnar 13[®], Pfizer, Philadelphia, PA), composed of saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to nontoxic diphtheria toxin cross-reactive material 197 (CRM197), was supplied in a single 0.5 mL dose prefilled syringe and was administered by intramuscular injection in the deltoid. Subjects received either one 0.5 mL injection or two 0.5 mL injections, one in each arm, at the enrollment visit.

Study design

This open-label phase IIb study evaluated medically stable adults 55 through 74 years of age who had either never received PPSV23 or who had previously received exactly one prior dose of PPSV23, which was administered 3 and 7 years prior to enrollment. Enrollment into both groups was stratified by age group (55 through 64 years and 65 through 74 years) (Supplemental Figure 1 [flowchart, pending]). The presence or absence of prior PPSV23 vaccination may have been presumptively ascertained by subject report but for all subjects was confirmed by review of primary source information, such as medical records or primary care or other provider report, covering at least the previous 10 years. All subjects provided written informed consent for study participation. Complete eligibility criteria are listed on clinicaltrials.gov. Subjects were enrolled at seven US sites between September 26, 2012 and March 3, 2015.

All PPSV23 naïve subjects received one 0.5 mL injection of PCV13. Previously vaccinated subjects were randomized within each age stratum with equal probability to receive one or two 0.5 mL injections of PCV13. The randomization sequence was generated using permuted block randomization with randomly selected block sizes of 2 or 4. Upon enrollment, each subject was assigned a randomization number from the electronic data entry system that corresponded to a treatment on a randomization list available at the study site.

After vaccination, subjects recorded oral temperature and solicited local and systemic reactogenicity information for 8 days (Day 1 [day of vaccination] through Day 8), using a memory aid. Unsolicited adverse events (AEs) were collected from the time of vaccination through Day 29 and serious adverse events (SAEs) were collected from the time of vaccination until the end of follow-up on Day 181.

Immunogenicity assays

Functional antibody titers were assessed by a fourfold multiplexed OPA killing assay performed at the University of Alabama at Birmingham as previously described (6) on samples obtained at baseline and on Days 29 and 181. Samples were identified only by specimen number to maintain blinding of laboratory personnel. OPA titers were determined for all of the PCV13 serotypes except serotype 3, which was not included in the testing because it is less immunogenic than other serotypes, and so a difference between study groups for this serotype was not likely to be seen, and because the OPA testing was done in batches of 4 serotypes so omitting one of the 13 serotypes allowed testing three batches instead of four. All PCV13 serotypes except serotype 6A are also contained in PPSV23.

Objectives

The safety objectives were to evaluate the acceptability of the safety profile of the single and double doses of PCV13 among subjects previously vaccinated with PPSV23, as measured by the frequency of solicited and unsolicited adverse events (AEs), and to specifically compare the frequency of injection site pain, tenderness, redness, and swelling between the two dose groups. For subjects who received a double dose, local reactogenicity was collected separately for each injected arm, and comparisons were based on the highest reported grade across both arms. An additional objective was to compare the frequency of injection site pain, tenderness, redness, and swelling following a single dose between subjects previously vaccinated with PPSV23 and vaccine naïve subjects.

The first of two primary immunogenicity objectives was to determine if, among subjects previously vaccinated with PPSV23, a double dose of PCV13 was statistically significantly more immunogenic at Day 29 than a single dose for at least some of the vaccine serotypes and was non-inferior for all of the 12 vaccine serotypes evaluated. The second primary immunogenicity objective was to determine if a double dose of PCV13 administered to subjects previously vaccinated with PPSV23 was non-inferior to a single dose administered to vaccine naïve subjects for the 12 vaccine serotypes at Day 29. The two secondary immunogenicity objectives included the same comparisons for samples obtained at Day 181.

Exploratory objectives included assessing the relationship between factors such as age and gender with vaccine response and with decline in antibody levels over time, by study group.

Data analysis

Sample size and analysis subsets—The two primary immunogenicity objectives for this study were each based on testing 12 related hypotheses, one for each serotype selected. Based on simulations that assumed at least one serotype was superior and a standard deviation of 2.0 on the natural log scale, a sample size of 280 evaluable subjects per group for each of the primary comparisons provided at least 80% power to meet the study objectives. Assuming a 5% drop out rate, the final planned sample size was 294 for each of the three study groups (Group I [vaccine naïve, 0.5 mL PCV13], Group IIA [previously vaccinated, 0.5 mL PCV13], and Group IIB [previously vaccinated, two 0.5 mL doses of PCV13]), for a total of 882 subjects.

All immunogenicity analyses reported are based on the intent-to-treat (ITT) analysis subset (n=883) which includes subjects who were vaccinated and had OPA results at baseline and at one or more post-vaccination time points.

Statistical analysis

Proportions of subjects reporting solicited AEs were compared using Fisher's Exact Test. Comparisons of post-vaccination OPA titers between study groups were based on the lower bound of the 95% confidence interval (CI) of the log geometric mean ratio (GMR), with superiority defined by a lower bound > 1 and non-inferiority by a lower bound > 0.5 . An analysis of variance tested for possible associations of Day 29 responses and covariates of interest such as gender, race, and age.

RESULTS

Demographics and characteristics

Demographic and baseline characteristics of subjects in the ITT subgroup are summarized in Table 1 and did not appreciably differ among the three study groups.

Safety

Solicited AEs—In general, systemic AEs were infrequent and most were reported as mild (Table 2). Local AEs, particularly injection site pain and tenderness, were not uncommon and the highest proportions of moderate pain and tenderness were reported in Group IIB. All AEs were self-limited.

The percentage of subjects reporting solicited AEs was compared between groups. For Group I versus Group IIA, no statistically significant differences were identified. In contrast, in comparisons of Group IIA versus Group IIB, Group IIB was significantly more likely to report malaise, headache, chills, local pain, and local tenderness, as well as any systemic symptom, any local symptom, any moderate or severe systemic symptom and any moderate or severe local symptom.

Unsolicited AEs—Eight severe unsolicited non-serious AEs were reported. Only one of these, exacerbation of plantar fasciitis, with onset on the day of vaccination, was judged related to vaccination by the study investigator. There were 27 SAEs reported for 25 subjects, none of which were considered related to study vaccine.

Immunogenicity

Within each study group there were substantial variations in both baseline geometric mean titer (GMT) and in the magnitude of the OPA responses by serotype (Table 3). Baseline titers were consistently higher in previously vaccinated compared with naïve subjects.

Group IIA versus Group I at Day 29—The OPA responses to a single dose of PCV13 were consistently lower in Group IIA (previously vaccinated) compared with Group I (naïve) for the 11 serotypes common to PCV13 and PPSV23, which is reflective of hyporesponsiveness induced by prior receipt of PPSV23. Among all subjects (both age groups), the non-inferiority threshold for Group IIA versus Group I was met for only 3 of the 12 serotypes tested (6A [not included in PPSV23], 14, and 19A) (Figure 1 and Supplemental Table 1). Restricting to the younger age subgroup, the non-inferiority threshold was also met for serotype 6B while in the older age subgroup the non-inferiority threshold was not met for any serotype.

Group IIB versus Group IIA at Day 29—Among previously vaccinated subjects, OPA GMTs were consistently higher in Group IIB (double dose) than in Group IIA (single dose), indicating a dose response. Among all subjects, and in each of the age subgroups, the responses in Group IIB compared to Group IIA met the non-inferiority threshold for all 12 serotypes (Figure 2 and Supplemental Table 2). Among all subjects, the response in Group IIB also met the superiority threshold for 7 serotypes, while in the younger age subgroup this threshold was met for only 1 serotype and in the older age subgroup this threshold was met for 9 serotypes.

Group IIB versus Group I at Day 29—The OPA GMTs in Group IIB were consistently lower than in Group I. Among all subjects, the responses in Group IIB were non-inferior to those in Group I for the 9 serotypes: the 3 serotypes that met the non-inferiority threshold for Group IIA versus Group I and an additional 6 serotypes (Figure 3 and Supplemental Table 3). In both the younger and older age subgroups the non-inferiority threshold was met for the same 8 serotypes. Thus, a double dose in previously vaccinated subjects produced responses that were more comparable to a single dose in naïve subjects than a single dose but that were not non-inferior for all tested serotypes.

Day 181 Responses—OPA GMTs declined substantially from Day 29 through Day 181 in all study groups but the patterns of between-group comparisons at Day 181 tended to correspond with those observed at Day 29 (Supplemental Tables 1–3 and Supplemental Figures 2–4). When comparing Day 181 responses among all subjects, Group IIA was non-inferior to Group I for 8 serotypes, Group IIB was non-inferior to Group IIA for all 12 serotypes and was superior for 5 serotypes, and Group IIB was non-inferior to Group I for 10 serotypes.

Multivariate analyses—The multivariate analyses of variance for each of the Day 29 serotype specific OPA responses included the covariates of study group, age stratum, gender, and race (white vs non-white). In those analyses, Group I had significantly greater GMTs than Group IIA for all serotypes, Group I had significantly greater GMTs than Group IIB for all serotypes except 6A, and Group IIB had significantly greater GMTs than Group IIA for 9 serotypes. There was also an independent age effect, with the younger stratum having significantly higher titers for 9 serotypes, as well as a gender effect, with women having significantly higher titers for 10 serotypes, but not a race effect, with non-whites having higher titers for only one serotype.

DISCUSSION

In this large clinical trial evaluating both the effect of prior vaccination with PPSV23 on the immune response to subsequent PCV13 vaccination and the response to a double versus a single dose of PCV13 in previously vaccinated persons, we found, as with previous evaluations, that prior administration of PPSV23 blunts the OPA response to PCV13, a phenomenon known as hyporesponsiveness induced by plain polysaccharide antigens.⁽⁷⁾ Among the subjects who received a single dose of PCV13, the Day 29 OPA responses in Group IIA (previously vaccinated) compared with Group I (vaccine naïve) achieved the threshold for non-inferiority for only 3 of the 12 serotypes among all subjects and for none of the serotypes in the older age subgroup. Among the previously vaccinated subjects there was evidence of a dose effect, with the Day 29 OPA responses in Group IIB (double dose of PCV13) compared to Group IIA (single dose) meeting the threshold for superiority for 7 serotypes among all subjects and for 9 serotypes in the older age subgroup. This dose effect led to greater comparability of responses between Group IIB and Group I than between Group IIA and Group I. The Day 29 responses in Group IIB compared to Group I met the threshold for non-inferiority for 9 serotypes among all subjects and for 8 serotypes in the older age subgroup, suggesting that the higher dose could mitigate the effect of hyporesponsiveness.

Among previously vaccinated subjects, the double dose of PCV13 was associated with a higher frequency of solicited local and systemic AEs than the single dose, but the AEs tended to be mild or moderate and were self-limited.

The dose effect we observed is consistent with the findings of another, relatively small, dose ranging study of 7-valent PCV (PCV7) vaccine in adults 70 through 79 years of age previously vaccinated with PPSV23. That study evaluated PCV7 dosages of 0.5 mL, 1.0 mL, and 2.0 mL with 44 subjects per group.⁽⁸⁾ In that study, the point estimates of the Day 29 OPA GMTs were higher after a dose of 1.0 mL than after the standard dose of 0.5 mL for five of the seven serotypes, although these differences were statistically significant for only two of those five. There was no further increase in OPA GMTs between the 1.0 mL and 2.0 mL dose groups.

The CAPITA study evaluated the standard dose of PCV13 in pneumococcal vaccine naïve adults 65 years of age and older. The use of the same formulation of PCV13 for both children and older adults was supported by a dose-ranging study in pneumococcal vaccine

naïve older adults that found no consistent or statistically significant differences in OPA responses with doses higher than the pediatric dose.(9) There is no defined immunologic correlate of protection against pneumococcal infection in adults; therefore, it is not possible to determine whether the lower OPA responses observed in older adults previously vaccinated with PPSV23 are associated with diminished protection against vaccine-type pneumococcal infections. However, the validity of bridging from the CAPITA results to the likely benefit of the standard dose of PCV13 in previously vaccinated older adults is lessened by the demonstrably lower OPA responses to the standard dose of PCV13 in subjects previously vaccinated with PPSV23 (Group IIA) compared with PPSV23-naïve older adults (Group I).

The implication of these findings for consideration of alternate strategies for the use of PCV13 in adults is uncertain. First, the herd immunity effect from routine vaccination of children with PCVs (10) has greatly reduced the incidence of invasive pneumococcal disease due to PCV13 serotypes in persons 65 years of age or older — from 45 per 100,000 persons in 1999 to 6 per 100,000 persons in 2015.(11) In light of the known herd immunity effect, the 2014 ACIP recommendations indicated that routine use of PCV13 among adults aged 65 years will be reevaluated in 2018 and revised as needed, so it is possible that PCV13 may no longer be generally recommended for older adults.(1) Second, administration of a double dose of PCV13 for persons previously vaccinated with PPSV23 would be off-label and more expensive, which cannot be justified by a known benefit at this time. These findings do, however, have implications for vaccine development strategies, by highlighting limitations of a “one-size-fits-all” approach to adult vaccination, when vaccination benefits demonstrated in one group are not necessarily generalizable to other important population subgroups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support: This study was conducted by the following Vaccine and Treatment Evaluation Unit (VTEU) sites and collaborating institutions: HHSN272201200005C University of Alabama at Birmingham (contract HHSN272201200005C), Kaiser Permanente Washington (contract HHSN272200800004C), Baylor College of Medicine (contract HHSN272200800002C), St Louis University (contract HHSN272200800003C), Emory University (contract HHSN272201300018I), University of Iowa (contract), Cincinnati Children’s Hospital Medical Center (contract HHSN272200800006C), Vanderbilt University (contract HHSN2722012000031), and the Emmes Corporation (contract HHSN272200800013C). The network of VTEUs is supported by the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health.

Role of the Funders/Sponsors: The funders/sponsors participated in the design and monitoring of the study and the review and approval of the manuscript. The funders/sponsors did not participate in the collection, management, analysis, and interpretation of the data; the preparation of the manuscript; or the decision to submit the manuscript for publication.

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A.

B.

Figure 1.

Comparison of serotype specific geometric mean ratios at Day 29, Group IIA (previously vaccinated, 0.5 mL PCV13) versus Group I (naïve, 0.5 mL PCV13), overall (A) and by age group (B).

A.

B.

Figure 2.

Comparison of serotype specific geometric mean ratios at Day 29, Group IIB (previously vaccinated, 1.0 mL PCV13) versus Group IIA (previously vaccinated, 0.5 mL PCV13), overall (A) and by age group (B).

A.

B.

Figure 3.

Comparison of serotype specific geometric mean ratios at Day 29, Group IIB (previously vaccinated, 1.0 mL PCV13) versus Group I (naïve, 0.5 mL PCV13), overall (A) and by age group (B).

Table 1

Demographic characteristics by study group, all enrolled subjects.

	All Subjects (N=883)	Group I - Naïve, Age 55-64 (N=164)	Group I - Naïve, Age 65-74 (N=147)	Group IIA - Previously Vaccinated, Age 55-64 (N=139)	Group IIA - Previously Vaccinated, Age 65-74 (N=145)	Group IIB - Previously Vaccinated, Age 55-64 (N=139)	Group IIB - Previously Vaccinated, Age 65-74 (N=149)
Gender — n(%)							
Male	371 (42)	36 (22)	77 (52)	52 (37)	76 (52)	59 (42)	71 (48)
Ethnicity — n(%)							
Non-Hispanic	862 (98)	159 (97)	144 (98)	132 (95)	143 (99)	137 (99)	147 (99)
Race — n(%)							
American Indian/Alaskan Native	1 (0)	0	0	0	1 (1)	0	0
Asian	14 (2)	0	2 (1)	1 (1)	5 (3)	4 (3)	2 (1)
Black/African American	61 (7)	8 (5)	4 (3)	18 (13)	6 (4)	17 (12)	8 (5)
White	793 (90)	154 (94)	140 (95)	114 (82)	132 (91)	115 (83)	138 (93)
Multi-Racial	10 (1)	2 (1)	1 (1)	4 (3)	0	2 (1)	1 (1)
Other/Unknown	4 (0)	0	0	2 (1)	1 (1)	1 (1)	0
Age (years)							
Mean (STD)	65.0 (5.3)	59.7 (2.8)	67.6 (2.6)	60.8 (2.7)	70.5 (2.0)	61.0 (2.8)	70.3 (2.0)
Median	65.0	59.6	66.4	61.1	70.5	61.8	70.1
Min, Max	(55, 74)	(55, 64)	(65, 74)	(55, 64)	(65, 74)	(55, 64)	(65, 74)
Time since prior PPSV23 (years)							
Mean (STD)	n/a	n/a	n/a	4.5 (1.2)	4.8 (1.2)	4.7 (1.3)	4.6 (1.1)
Median				4.4	4.4	4.4	4.4
Min, Max				3.0, 7.9	3.0, 7.5	3.0, 7.8	3.0, 7.3

Groups I and IIA received a 0.5 mL dose of PCV13. Group IIB received two 0.5 mL doses of PCV13.

Table 2

Maximum reported severity of solicited local and systemic adverse events by study group, all enrolled subjects.

Reactogenicity	Group I N=311				Group IIA N=284				Group IIB N=288			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
Systemic												
Elevated Oral Temp. ¹	98	<1	<1	0	99	1	0	0	98	1	<1	<1
Feverishness ²	94	5	<1	<1	91	8	1	0	90	7	3	<1
Malaise ²	83	13	4	<1	80	14	6	<1	70*	21	8	<1
Headache ²	86	11	2	<1	85	13	2	0	78*	16	6	0
Nausea ²	96	4	<1	0	95	3	1	<1	95	5	0	0
Chills ²	95	4	2	<1	96	3	1	0	91*	6	3	0
New muscle pain ²	92	6	2	<1	91	6	2	<1	88	9	3	0
Aggravated muscle pain ²	97	2	<1	<1	96	3	1	0	93	4	3	0
New joint pain ²	96	3	<1	<1	95	3	2	0	94	3	2	0
Aggravated joint pain ²	96	3	<1	<1	95	5	<1	<1	93	4	3	0
Any Systemic Reaction	68	23	8	<1	66	24	9	1	52*	30	17	<1**
Local												
Pain ³	52	39	9	0	46	43	11	0	35*	49	16	0
Tenderness ⁴	32	60	8	0	37	55	8	0	26*	60	14	0
Redness ⁵	87	10	<1	2	83	14	1	1	82	14	1	3
Swelling ⁵	87	8	2	2	83	12	2	2	84	11	2	2
Swelling (functional) ²	87	11	2	0	83	15	1	<1	84	14	2	0
Any Local Reaction	23	62	12	3	22	62	13	3	15*	63	19	4**

Group I (naïve) and Group IIA (previously vaccinated) received one 0.5 mL dose of PCV13; Group IIB (previously vaccinated) received two 0.5 mL doses of PCV13.

* Fisher's exact p value < 0.05 for comparison of the risk of any reaction between Group IIB and Group IIA. For comparisons of Group IIA with Group I, no statistically significant differences were observed.

** Fisher's exact p value < 0.05 for comparison of the frequency of moderate or severe reactions between Group IIB and Group IIA.

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- 1 Mild, 38.0°C and 38.4°C; Moderate, 38.5°C and 38.9°C; Severe, 39.0°C
- 2 Mild, No interference with activity; Moderate, Some interference with activity; Severe, Significant interference, prevents daily activity
- 3 Mild, Subject is aware of pain but it does not interfere with daily activity and no pain medication is taken; Moderate, Subject is aware of pain, there is interference with daily activity or it requires use of pain medication; Severe, Subject is aware of pain and it prevents daily activity
- 4 Mild, The area immediately surrounding the injection site hurts only when touched and it does not interfere with daily activity; Moderate, The area immediately surrounding the injection site hurts when touched and it interferes with daily activity; Severe, The area immediately surrounding the injection site hurts when touched **and** it prevents daily activity
- 5 Mild, maximum diameter 1-25 mm; Moderate, 26-50 mm; Severe, 51 mm

Serotype specific opsonophagocytic geometric mean titers at Days 1, 29, and 181, by age group and study group, intent to treat population.

Table 3

Serotype	Age Group	Study Group	Day 1 N	Day 1 GMT (95% CI)	Day 29 N	Day 29 GMT (95% CI)	Day 181 N	Day 181 GMT (95% CI)
1	55 – 64	I	164	6.3 (5.4, 7.4)	163	237.2 (183.7, 306.2)	163	97.3 (74.4, 127.3)
		IIA	138	23.0 (16.9, 31.3)	137	96.6 (72.0, 129.5)	137	52.7 (38.8, 71.6)
		IIIB	139	16.5 (12.8, 21.4)	137	99.7 (75.6, 131.4)	139	47.6 (36.4, 62.3)
	65 – 74	I	147	7.5 (6.1, 9.1)	146	191.6 (142.1, 258.3)	147	88.8 (65.9, 119.6)
		IIA	145	18.1 (13.8, 23.9)	144	58.2 (44.3, 76.6)	143	38.5 (29.1, 50.9)
		IIIB	149	24.1 (18.5, 31.5)	149	90.2 (69.6, 116.9)	148	59.4 (45.7, 77.2)
	All	I	311	6.8 (6.0, 7.7)	309	214.4 (176.5, 260.4)	310	93.1 (76.4, 113.6)
		IIA	283	20.4 (16.6, 25.0)	281	74.5 (60.9, 91.2)	280	44.9 (36.5, 55.1)
		IIIB	288	20.1 (16.7, 24.2)	286	94.6 (78.4, 114.2)	287	53.4 (44.2, 64.3)
4	55 – 64	I	164	19.8 (14.7, 26.8)	163	2180.0 (1810.0, 2625.6)	163	804.3 (662.8, 976.1)
		IIA	138	128.1 (91.7, 178.9)	137	1221.6 (1002.1, 1489.3)	137	646.0 (535.3, 779.7)
		IIIB	138	84.7 (58.7, 122.2)	137	1600.9 (1347.8, 1901.5)	139	769.8 (641.3, 923.9)
	65 – 74	I	147	21.7 (16.0, 29.4)	145	1454.8 (1180.6, 1792.7)	147	636.5 (509.4, 795.2)
		IIA	143	71.1 (50.4, 100.3)	144	716.2 (561.0, 914.3)	143	373.9 (283.9, 492.4)
		IIIB	149	78.5 (57.0, 108.3)	149	1300.6 (1079.7, 1566.7)	148	703.3 (577.8, 856.2)
	All	I	311	20.7 (16.7, 25.6)	308	1802.0 (1566.3, 2073.2)	310	719.8 (621.8, 833.3)
		IIA	281	94.9 (74.6, 120.8)	281	929.2 (791.6, 1090.6)	280	488.6 (412.2, 579.2)
		IIIB	287	81.4 (64.0, 103.7)	286	1436.7 (1265.2, 1631.4)	287	734.8 (642.7, 840.0)
5	55 – 64	I	164	8.4 (6.9, 10.2)	163	584.7 (438.4, 780.0)	163	255.5 (189.7, 344.0)
		IIA	138	66.0 (46.3, 94.1)	137	365.9 (271.0, 493.9)	137	228.4 (167.5, 311.3)
		IIIB	139	38.8 (28.0, 53.7)	137	368.1 (278.2, 487.1)	139	191.0 (143.4, 254.3)
	65 – 74	I	147	9.4 (7.6, 11.6)	146	432.4 (326.3, 573.0)	147	213.8 (161.0, 284.0)
		IIA	145	42.8 (31.3, 58.5)	144	223.6 (176.2, 283.7)	143	150.9 (117.3, 193.9)
		IIIB	149	33.8 (24.8, 45.9)	149	252.3 (193.7, 328.8)	148	146.9 (109.9, 196.3)
	All	I	311	8.8 (7.7, 10.2)	309	507.0 (414.5, 620.3)	310	234.8 (191.2, 288.3)
		IIA	283	52.9 (41.8, 66.9)	281	284.3 (234.7, 344.3)	280	184.8 (151.5, 225.4)
		IIIB	288	36.1 (28.9, 45.1)	286	302.4 (249.4, 366.6)	287	166.8 (136.1, 204.4)
6A	55 – 64	I	163	21.8 (15.9, 29.9)	163	3630.8 (2844.0, 4635.4)	163	1600.9 (1272.1, 2014.5)

Serotype	Age Group	Study Group	Day 1 N	Day 1 GMT (95% CI)	Day 29 N	Day 29 GMT (95% CI)	Day 181 N	Day 181 GMT (95% CI)
6B	65 – 74	IIA	137	53.4 (35.7, 79.8)	137	2982.2 (2318.4, 3836.1)	136	1577.4 (1252.3, 1986.8)
		IIB	139	58.2 (39.7, 85.3)	137	3814.3 (2870.8, 5067.8)	139	1645.8 (1260.7, 2148.7)
		I	147	27.2 (19.0, 38.8)	146	2814.2 (2178.4, 3635.4)	147	1534.2 (1191.6, 1975.3)
		IIA	144	41.3 (28.0, 60.9)	144	1678.1 (1280.2, 2199.5)	143	873.7 (665.5, 1147.1)
	All	IIB	148	51.5 (35.1, 75.5)	149	2261.1 (1696.0, 3014.5)	148	1176.0 (876.9, 1577.2)
		I	310	24.2 (19.1, 30.7)	309	3219.0 (2698.6, 3839.8)	310	1568.9 (1324.6, 1858.2)
		IIA	281	46.8 (35.4, 61.8)	281	2221.1 (1842.0, 2678.2)	279	1165.3 (971.8, 1397.2)
		IIB	287	54.7 (41.8, 71.5)	286	2904.7 (2369.9, 3560.3)	287	1383.9 (1134.5, 1688.2)
	55 – 64	I	163	48.4 (34.4, 68.3)	163	3444.6 (2700.7, 4393.3)	163	1574.5 (1241.3, 1997.0)
		IIA	138	123.3 (84.0, 181.0)	137	2525.3 (1942.6, 3282.7)	137	1394.5 (1079.5, 1801.5)
		IIB	139	157.9 (108.8, 229.0)	137	3272.7 (2474.7, 4327.9)	139	1615.5 (1229.4, 2122.8)
		I	146	48.5 (33.4, 70.4)	146	2498.3 (1893.2, 3296.8)	147	1284.5 (977.7, 1687.7)
7F	65 – 74	IIA	145	92.7 (63.0, 136.3)	144	1224.1 (879.0, 1704.6)	143	734.3 (532.9, 1011.9)
		IIB	149	136.9 (93.0, 201.6)	149	2047.4 (1544.2, 2714.5)	148	1110.3 (816.4, 1509.9)
		I	309	48.5 (37.7, 62.3)	309	2959.5 (2464.0, 3554.8)	310	1429.6 (1195.0, 1710.4)
		IIA	283	106.5 (81.3, 139.7)	281	1742.4 (1404.6, 2161.3)	280	1005.0 (816.0, 1237.8)
	55 – 64	IIB	288	146.7 (112.3, 191.6)	286	2563.2 (2099.7, 3129.0)	287	1331.4 (1083.1, 1636.6)
		I	163	58.7 (40.1, 85.8)	163	5628.0 (4694.3, 6747.5)	163	2586.9 (2178.1, 3072.6)
		IIA	138	355.1 (263.1, 479.3)	137	2258.3 (1812.4, 2813.9)	137	1353.9 (1108.8, 1653.3)
		IIB	139	352.4 (252.9, 491.2)	137	2309.4 (1914.3, 2785.9)	139	1447.4 (1221.0, 1715.9)
	65 – 74	I	147	102.6 (71.2, 148.0)	146	3836.6 (3115.9, 4724.0)	147	2090.1 (1739.6, 2511.2)
		IIA	144	234.1 (165.8, 330.5)	144	1309.5 (1056.6, 1622.9)	143	865.7 (694.6, 1079.0)
		IIB	149	276.0 (203.4, 374.5)	149	1992.4 (1637.7, 2424.0)	148	1331.8 (1113.5, 1592.8)
		I	310	76.5 (58.7, 99.7)	309	4696.0 (4090.3, 5391.5)	310	2338.1 (2062.5, 2650.5)
9V	All	IIA	282	287.0 (228.3, 361.0)	281	1708.0 (1461.4, 1996.3)	280	1077.5 (927.0, 1252.4)
		IIB	288	310.6 (248.2, 388.5)	286	2138.4 (1867.4, 2448.8)	287	1386.6 (1226.0, 1568.2)
		I	163	83.5 (59.8, 116.5)	163	2476.9 (2077.1, 2953.7)	162	1184.3 (1001.1, 1400.9)
		IIA	137	247.8 (172.2, 356.7)	137	1421.2 (1126.0, 1793.8)	137	965.7 (764.3, 1220.0)
	55 – 64	IIB	138	216.3 (151.0, 309.9)	137	1818.4 (1458.8, 2266.6)	139	1021.3 (807.8, 1291.3)
		I	147	98.5 (69.8, 139.0)	146	2178.9 (1681.6, 2823.5)	147	1210.7 (918.8, 1595.3)
		IIA	144	183.3 (131.2, 256.0)	144	840.4 (653.7, 1080.3)	142	559.8 (428.3, 731.8)

Serotype	Age Group	Study Group	Day 1 N	Day 1 GMT (95% CI)	Day 29 N	Day 29 GMT (95% CI)	Day 181 N	Day 181 GMT (95% CI)
14	All	IIB	149	272.2 (196.4, 377.3)	149	1813.1 (1467.7, 2239.7)	148	1210.9 (978.6, 1498.4)
		I	310	90.3 (71.1, 114.6)	309	2331.4 (2000.7, 2716.6)	309	1196.8 (1022.7, 1400.4)
		IIA	281	212.3 (166.1, 271.5)	281	1085.7 (912.9, 1291.2)	279	731.7 (611.1, 876.0)
		IIB	287	243.7 (191.5, 310.1)	286	1815.6 (1560.2, 2112.8)	287	1115.1 (952.7, 1305.1)
	55 – 64	I	163	107.9 (76.5, 152.2)	163	1929.4 (1568.4, 2373.5)	163	1084.3 (883.2, 1331.1)
		IIA	138	451.3 (323.8, 628.9)	137	1420.6 (1119.8, 1802.2)	137	1067.5 (844.0, 1350.2)
		IIB	139	452.5 (325.9, 628.2)	137	1400.8 (1125.2, 1743.8)	139	1041.5 (838.7, 1293.4)
		I	147	132.1 (91.9, 189.9)	146	1414.4 (1065.4, 1877.7)	147	895.3 (697.4, 1149.5)
	65 – 74	IIA	145	306.5 (213.2, 440.7)	144	894.5 (678.7, 1179.0)	143	665.6 (497.4, 890.7)
		IIB	149	470.6 (340.6, 650.1)	149	1299.3 (1042.8, 1618.9)	148	1079.5 (875.3, 1331.4)
18C	All	I	310	118.8 (92.6, 152.3)	309	1666.1 (1401.9, 1980.2)	310	990.2 (844.0, 1161.6)
		IIA	283	370.2 (289.4, 473.4)	281	1120.8 (932.6, 1347.1)	280	838.7 (694.3, 1013.1)
		IIB	288	461.7 (367.2, 580.5)	286	1347.0 (1154.1, 1572.0)	287	1061.0 (913.4, 1232.4)
		I	164	37.4 (28.0, 50.1)	163	2237.3 (1772.0, 2824.9)	163	916.9 (716.0, 1174.3)
	55 – 64	IIA	138	208.3 (148.9, 291.2)	137	1066.8 (833.5, 1365.3)	137	651.8 (500.2, 849.3)
		IIB	139	220.1 (156.7, 309.2)	137	1468.8 (1189.4, 1813.9)	139	793.9 (620.8, 1015.2)
		I	147	45.5 (33.4, 61.9)	146	2014.0 (1578.8, 2569.0)	147	1030.2 (796.6, 1332.2)
		IIA	145	206.9 (152.3, 281.1)	144	834.1 (655.2, 1061.9)	143	537.4 (416.0, 694.1)
	65 – 74	IIB	149	189.5 (133.9, 268.2)	149	1277.7 (1032.5, 1581.1)	148	770.8 (605.3, 981.5)
		I	311	41.0 (33.2, 50.7)	309	2128.9 (1800.4, 2517.2)	310	969.0 (811.5, 1157.1)
19A	All	IIA	283	207.5 (165.7, 260.0)	281	940.4 (791.7, 1117.0)	280	590.6 (491.7, 709.4)
		IIB	288	203.7 (159.9, 259.5)	286	1365.9 (1176.3, 1586.1)	287	781.9 (658.8, 928.0)
	55 – 64	I	163	135.4 (101.8, 180.1)	163	2942.2 (2473.9, 3499.2)	163	1406.8 (1188.9, 1664.6)
		IIA	138	570.0 (431.5, 752.8)	137	2186.9 (1835.7, 2605.2)	137	1525.7 (1280.7, 1817.7)
		IIB	139	566.1 (429.6, 745.9)	137	2524.8 (2148.5, 2966.9)	139	1539.4 (1306.1, 1814.5)
		I	145	188.1 (146.9, 241.0)	146	3045.7 (2484.2, 3734.1)	147	1681.7 (1389.6, 2035.2)
	65 – 74	IIA	145	517.4 (400.3, 668.7)	144	1563.3 (1305.3, 1872.4)	143	1090.6 (913.1, 1302.5)
		IIB	149	441.9 (328.1, 595.1)	149	2120.1 (1762.7, 2549.9)	148	1465.6 (1206.5, 1780.4)
	All	I	308	158.1 (130.7, 191.3)	309	2990.7 (2620.7, 3412.9)	310	1531.0 (1349.5, 1737.0)
		IIA	283	542.4 (449.5, 654.5)	281	1841.3 (1622.3, 2089.8)	280	1285.3 (1133.6, 1457.3)
19B	All	IIB	288	498.0 (406.5, 610.0)	286	2305.1 (2038.2, 2607.0)	287	1500.9 (1321.5, 1704.8)

Serotype	Age Group	Study Group	Day 1 N	Day 1 GMT (95% CI)	Day 29 N	Day 29 GMT (95% CI)	Day 181 N	Day 181 GMT (95% CI)
19F	55 – 64	I	164	62.6 (47.3, 82.8)	163	1534.6 (1294.5, 1819.4)	163	717.6 (611.0, 842.9)
		IIA	138	175.8 (129.3, 239.0)	137	870.2 (695.4, 1089.0)	137	601.6 (487.2, 742.8)
		IIB	139	154.7 (114.5, 208.9)	137	1162.0 (957.6, 1410.2)	139	622.3 (511.2, 757.6)
	65 – 74	I	147	65.9 (48.2, 90.3)	145	1291.3 (1044.1, 1597.0)	147	687.5 (548.1, 862.2)
		IIA	144	137.2 (102.0, 184.5)	142	624.7 (506.1, 771.2)	143	394.2 (316.9, 490.2)
		IIB	149	181.2 (140.0, 234.6)	149	934.5 (761.9, 1146.2)	148	581.2 (470.5, 717.9)
23F	All	I	311	64.1 (52.1, 79.0)	308	1414.8 (1237.2, 1618.0)	310	703.2 (613.8, 805.6)
		IIA	282	154.9 (125.2, 191.6)	279	735.1 (630.2, 857.5)	280	484.7 (416.0, 564.8)
		IIB	288	167.9 (138.0, 204.3)	286	1037.3 (901.1, 1194.2)	287	600.8 (520.2, 693.7)
	55 – 64	I	163	16.7 (12.2, 23.0)	163	1219.6 (910.5, 1633.6)	163	594.8 (445.6, 794.0)
		IIA	138	58.1 (40.6, 83.3)	137	888.5 (641.4, 1230.7)	136	503.1 (357.5, 707.9)
		IIB	139	56.1 (38.6, 81.5)	137	986.4 (732.5, 1328.3)	139	468.0 (338.7, 646.7)
	65 – 74	I	147	18.4 (13.3, 25.6)	146	704.6 (512.7, 968.2)	147	395.2 (284.4, 549.0)
		IIA	145	48.4 (33.8, 69.3)	143	474.9 (340.9, 661.4)	143	254.3 (181.4, 356.5)
		IIB	149	43.5 (30.8, 61.3)	149	683.7 (505.0, 925.7)	148	394.9 (292.4, 533.3)
	All	I	310	17.5 (14.0, 22.0)	309	941.1 (758.1, 1168.2)	310	490.0 (394.1, 609.1)
		IIA	283	52.9 (41.1, 68.2)	280	645.2 (510.6, 815.3)	279	354.6 (278.4, 451.8)
		IIB	288	49.2 (38.2, 63.3)	286	814.9 (658.9, 1007.9)	287	428.7 (344.3, 533.8)

Group I (naïve) and Group IIA (previously vaccinated) received one 0.5 mL dose of PCV13; Group IIB (previously vaccinated) received two 0.5 mL doses of PCV13.