MAJOR ARTICLE

Safety, Tolerability, and Immunogenicity of a 20-Valent Pneumococcal Conjugate Vaccine (PCV20) in Adults 60 to 64 Years of Age

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Background. Pneumococcal conjugate vaccines (PCVs) have significantly decreased pneumococcal disease worldwide; however, expanding serotype coverage may further reduce disease burden. A 20-valent PCV (PCV20) containing capsular polysaccharide conjugates of serotypes present in the 13-valent PCV (PCV13) and 7 new serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) is currently in development. This phase 2 study evaluated safety, tolerability, and immunogenicity of PCV20 in adults without prior pneumococcal vaccination.

Methods. In this randomized, active-controlled, double-blinded trial, 444 adults 60 through 64 years of age were randomized to receive either a single dose of PCV20 followed 1 month later by saline placebo or a single dose of PCV13 followed 1 month later by 23-valent polysaccharide vaccine. Local injection site reactions, select systemic symptoms, and adverse events (AEs) were recorded. Immunogenicity was assessed by measuring serotype-specific opsonophagocytic activity (OPA) titers before and approximately 1 month after each vaccination.

Results. Local reaction and systemic event rates were similar after vaccination with PCV20 or PCV13; no serious vaccine-related AEs were reported. In the PCV20 group, functional immune responses as measured by OPA were robust for all 20 serotypes included in the vaccine, with geometric mean fold rises from baseline ranging from 6.0 to 113.4.

Conclusions. PCV20 was well tolerated in adults 60 to 64 years of age, with a safety profile consistent with historical experience of PCVs in this age group. Substantial OPA responses were elicited against all serotypes. Results demonstrate the potential for PCV20 to expand pneumococcal disease protection.

Clinical Trials Registration. NCT03313037.

Keywords. adult; immunogenicity and safety; 20-valent pneumococcal conjugate vaccine; *Streptococcus pneumoniae*; clinical trial.

Streptococcus pneumoniae infection is a major cause of morbidity and mortality, manifesting either as invasive pneumococcal disease (IPD; eg, meningitis, bacteremia, bacteremic pneumonia) or noninvasive disease (eg, otitis media, nonbacteremic pneumonia) [1–3]. Young children and adults > 65 years of age are at greatest risk [1]. Disease burden is considerable, with the mean cost per IPD episode in otherwise healthy US adults 19–64 years of age as high as US$48 000 [4]. More than 90 pneumococcal serotypes exist, each characterized by a unique polysaccharide capsule; however, the majority of disease is caused by a limited serotype subset [1, 3, 5]. Furthermore, the distribution of disease-causing serotypes varies by age and geographic region and can shift over time [1].

The 23-valent pneumococcal polysaccharide vaccine (PPSV23) is recommended for routine vaccination in adults ≥65 years of age in many countries [6], including the United States [7], but provides relatively transient protection due to a lack of immunological memory [8]. Conversely, pneumococcal conjugate vaccines (PCVs) generally induce more robust immune responses and subsequent memory responses that are associated with longer-term protection, including in adults; moreover, PCV13 has demonstrated efficacy against pneumococcal pneumonia, including nonbacteremic pneumonia, in adults [8–10]. Introduction of PCVs has resulted in major reductions of pneumococcal disease burden worldwide [11–14]. Specifically, US introduction of the 7-valent PCV (PCV7) in 2000 was associated with a 76% reduction in all IPD among children <5 years of age and 45% reduction across all ages [15]. In

the first 3 years following subsequent 13-valent PCV (PCV13) introduction in 2010, the nationwide incidence of IPD decreased by a further 64% among children <5 years of age and by 12%–32% (depending on age) among adults [12]. Despite these reductions, vaccine coverage of non-PCV13 serotypes constitutes a significant unmet need [13, 14, 16–19], with the majority of US pediatric IPD cases in the post-PCV13 era caused by these serotypes [12].

An investigational 20-valent PCV (PCV20) that includes all components of PCV13 plus polysaccharide conjugates of 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) is being developed to broaden pneumococcal disease coverage beyond that of currently licensed PCVs. These additional serotypes were included based on their generalized geographic distribution as causes of IPD and other factors such as association of these serotypes with antibiotic resistance or greater disease severity [12, 13, 16–18, 20–24]. These 7 serotypes are also present in PPSV23 but only as unconjugated polysaccharides [25]. Therefore, PCV20 is anticipated to provide more robust protection than PPSV23 for the serotypes in common between PCV20 and PPSV23, thus further reducing the global pneumococcal disease burden. A first-in-human study performed in 66 healthy adults 18–49 years of age indicated that PCV20 was well tolerated and induced immune responses against all 20 vaccine serotypes [26]. The current phase 2 study evaluated safety, tolerability, and immunogenicity of PCV20 in adults 60–64 years of age without previous pneumococcal vaccination. Immunogenicity results through 1 month postvaccination and safety data through 12 months postvaccination are presented.

METHODS

Study Design and Subjects

This phase 2, randomized, active-controlled, double-blind study conducted at 14 US sites evaluated PCV20 safety and immunogenicity in healthy pneumococcal vaccine-naive adults 60–64 years of age. This age group was selected to approximate those ≥65-year-olds who receive PPSV23 and PCV13 vaccination according to current US recommendations [7]. However, as the study population was slightly younger, they were less likely than those ≥65 years of age to have already been vaccinated with a pneumococcal vaccine.

Men and women were eligible for inclusion if they were generally healthy, including those with a diagnosis of preexisting stable disease (disease not requiring change in therapy or hospitalization ≤3 months before receipt of the investigational product). Key exclusion criteria included diagnosis of a serious, unstable, chronic medical condition (eg, metastatic malignancy, clinically unstable cardiac disease; further described in the Supplementary Appendix); severe acute or chronic psychiatric condition that could potentially increase risk associated with study participation as judged by the investigator; previous or planned vaccination with a pneumococcal vaccine; history of a severe adverse reaction to a vaccine and/ or any component of any vaccine used in the current study; previous laboratory-confirmed IPD diagnosis; known or suspected immunocompromising condition (including current or planned treatment with immunosuppressive therapy).

Subjects were randomly assigned in a 1:1 ratio to receive a single 0.5-mL dose of either PCV20 or PCV13 (vaccination 1; Figure 1). One month after vaccination 1, PCV20 recipients were given saline placebo (0.5 mL), and PCV13 recipients were given PPSV23 (0.5 mL; vaccination 2). In this study, PCV13 served as a control for immunogenicity of the 13 serotypes in common with PCV20 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) as well as for safety, whereas PPSV23 served as a control for immunogenicity of the 7 additional serotypes in PCV20 (8, 10A, 11A, 12F, 15B, 22F, 33F). All vaccines were administered intramuscularly into the deltoid muscle.

The study was conducted in accordance with all legal and regulatory requirements and with the principles set forth in
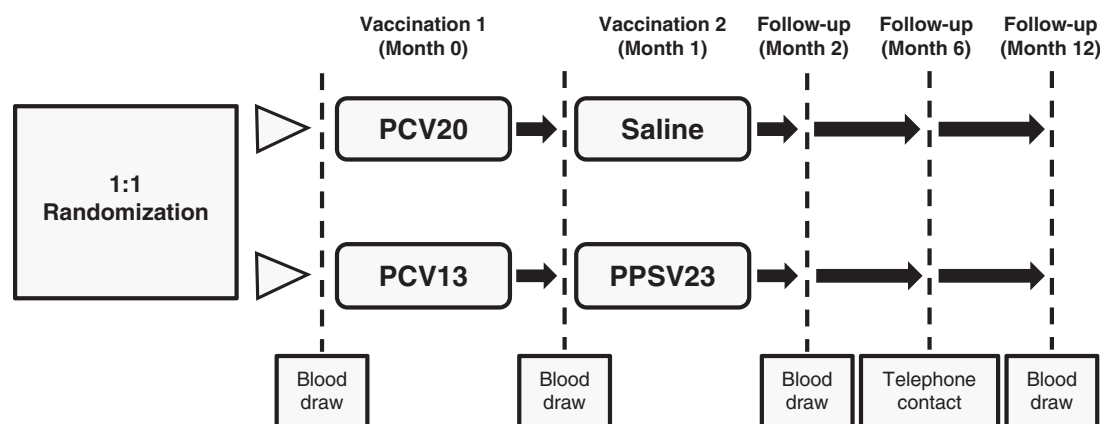

Figure 1. Study design. Immune responses measured at 12 months following vaccination 1 are not reported here. Abbreviations: PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

Figure 2. Subject disposition. Abbreviations: PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.
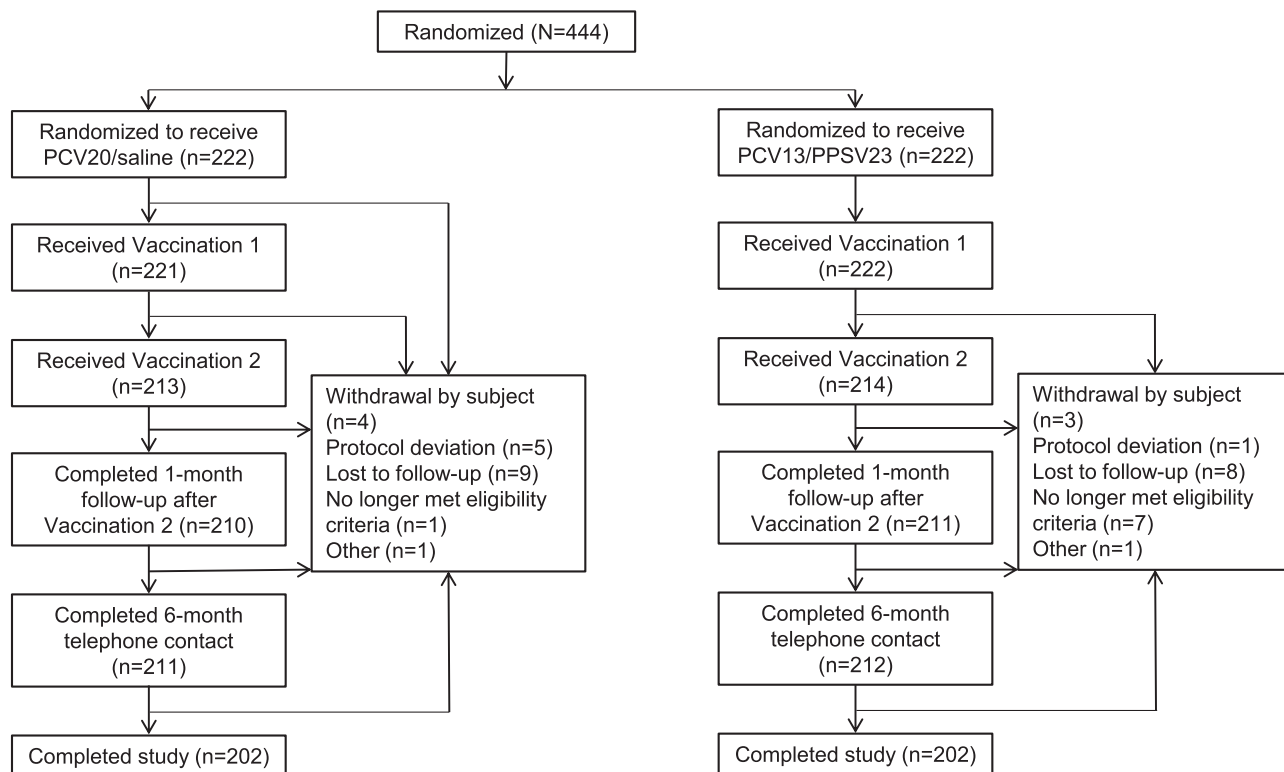
Table 1. Demographics (Safety Population)

	PCV20/Saline (n = 221)	PCV13/PPSV23 (n = 222)	Total (N = 443)
Sex, n (%)			
Male	106 (48.0)	89 (40.1)	195 (44.0)
Female	115 (52.0)	133 (59.9)	248 (56.0)
Race, n (%)			
White	169 (76.5)	165 (74.3)	334 (75.4)
Black	37 (16.7)	46 (20.7)	83 (18.7)
Asian	8 (3.6)	7 (3.2)	15 (3.4)
Native American or Native Alaskan	1 (0.5)	2 (0.9)	3 (0.7)
Native Hawaiian or other Pacific Islander	1 (0.5)	0	1 (0.2)
Multiracial	4 (1.8)	2 (0.9)	6 (1.4)
Not reported	1 (0.5)	0	1 (0.2)
Ethnicity, n (%)			
Hispanic/Latino	27 (12.2)	25 (11.3)	52 (11.7)
Non-Hispanic/non-Latino	192 (86.9)	195 (87.8)	387 (87.4)
Unknown	2 (0.9)	2 (0.9)	4 (0.9)
Age at vaccination 1, y			
Mean ± SD	62.0 ± 1.4	62.0 ± 1.4	62.0 ± 1.4
Median (range)	62 (60–64)	62 (60–64)	62 (60–64)

Abbreviations: PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Council for Harmonisation Guideline for Good Clinical Practice, and the Declaration of Helsinki. The protocol was approved by institutional review boards, and all subjects were required to provide written informed consent.

Assessments

Safety assessments included local reactions, systemic events, adverse events (AEs), serious AEs (SAEs), and newly diagnosed chronic medical conditions (NDCMCs). Prompted local reactions and systemic events were recorded in an electronic diary for 10 and 7 days, respectively, after vaccination 1. Local reactions (ie, redness, swelling, pain at injection site) and systemic events (ie, fatigue, headache, muscle pain, joint pain) were graded as mild (grade 1), moderate (grade 2), severe (grade 3), or grade 4 based on increasing severity levels; for redness and swelling, grading was based on size or description of the affected area, whereas for pain and all systemic events, grading was based on degree to which the event interfered with activity. Data on AEs were collected through 1 month following each vaccination and on SAEs and NDCMCs through 12 months after vaccination 1, including during a telephone follow-up at the 6-month time point and a visit at the 12-month time point.

Blood samples for immunogenicity assessments were collected before vaccination 1, approximately 1 month after each vaccination, and approximately 1 year after vaccination 1. The current report includes immunogenicity data through 1 month after vaccination 2.
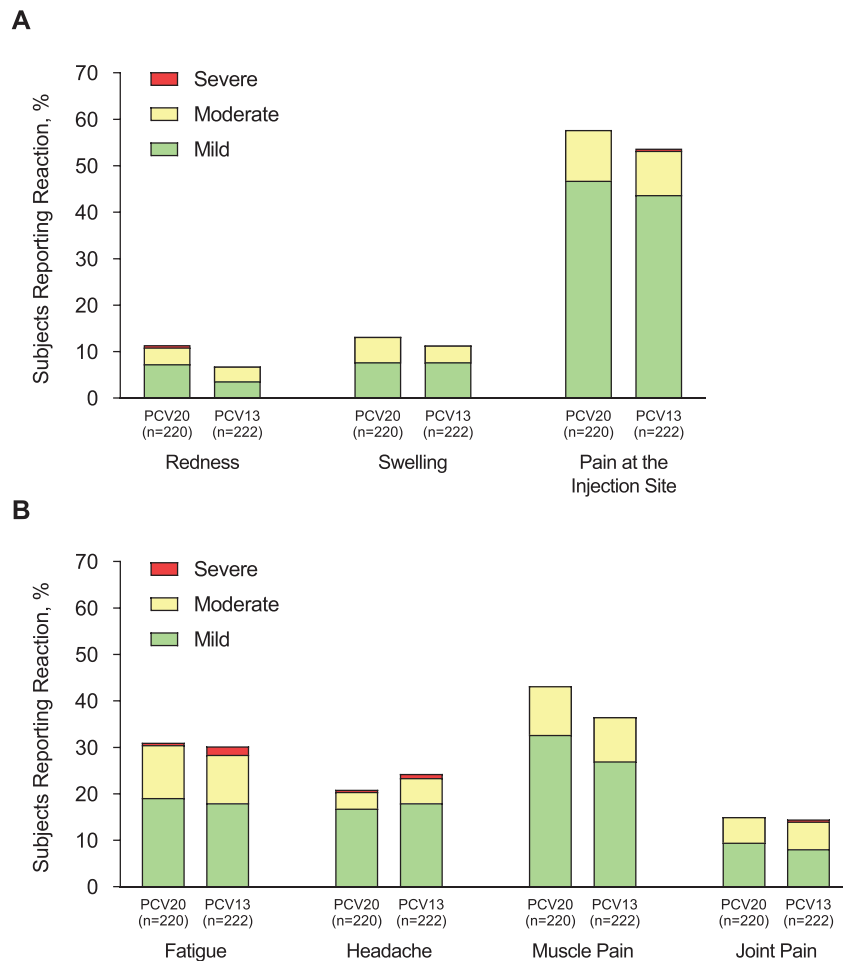
Figure 3. Prompted reactogenicity events including (*A*) local reactions within 10 days of vaccination, and (*B*) systemic events within 7 days of vaccination. The single report of fever is not included. Abbreviations: PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine.

Endpoints

Primary endpoints were the percentages of subjects reporting prompted local reactions within 10 days after vaccination 1, prompted systemic events within 7 days after vaccination 1, AEs within 1 month after vaccination 1, and SAEs and NDCMCs within 6 and 12 months after vaccination 1.

Secondary endpoints included pneumococcal serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) [27] 1 month after vaccination and OPA geometric mean fold rises (GMFRs) from before vaccination to 1 month after vaccination. Percentages of subjects with ≥4-fold rises in OPA titers from baseline were also evaluated. Exploratory endpoints were pneumococcal serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) 1 month after vaccination and IgG GMFRs from before to 1 month after vaccination.

Analyses

This was a descriptive study with no hypothesis testing. The study planned to enroll approximately 440 subjects (220 per group) to provide a sample size sufficient to detect infrequent local reactions, systemic events, and AEs (probability of 0.89 and > 0.999 of detecting ≥1 event with a true rate of 1% and ≥ 5%, respectively, in a group of 200 subjects).

The safety population was used for all primary endpoints and included all subjects who received 1 PCV13 or PCV20 dose; subjects were assigned to vaccine groups corresponding to the vaccine actually received. Safety data were summarized using descriptive statistics.

The evaluable immunogenicity population included all eligible subjects who received the assigned vaccine as randomized, had a blood collection within 27–49 days after either vaccination, had OPA titers for ≥1 serotype postvaccination, and had no other major protocol deviations.

Descriptive summaries of geometric means and corresponding 95% confidence intervals (CIs) were calculated for OPA titers and IgG concentrations at each time point by vaccine group, with each serotype analyzed separately. Assay results below the serotype-specific lower limits of quantitation (LLOQs) were set to 0.5 × LLOQ in the analysis. For OPA and IgG results, GMFRs were calculated as the fold change in titer

from before vaccination 1 (baseline) to 1 month after vaccination 1 and from baseline to 1 month after vaccination 2. OPA GMTs and GMFRs were calculated by log transformation of titers or titer ratios. The 95% CIs were calculated with reference to the t distribution, and the mean and limits were exponentiated. IgG GMCs and GMFRs were calculated similarly.

RESULTS

Study Population

Among 444 subjects randomized (n = 222, PCV20/saline; n = 222, PCV13/PPSV23), 443 received vaccination 1 and 427 received vaccination 2 (Figure 2). Overall, 94.8% of subjects completed the visit occurring 1 month after vaccination 2, 95.3% completed the 6-month telephone visit, and 91.0% completed the study. Reasons for withdrawal were decision to withdraw by subject, no longer meeting eligibility criteria, lost to follow-up, protocol deviations, and other; no subjects withdrew due to an AE.

Subject demographics were similar between study groups (Table 1). The majority of subjects were women (56.0%) and White (75.4%); subjects had a mean ± standard deviation (SD) age of 62.0 ± 1.4 years.

Safety

The frequency and severity of prompted local reactions within 10 days of vaccination were similar following receipt of PCV20 or PCV13 (Figure 3A). For both vaccines, injection site pain was the most commonly reported local reaction (reported by 57.7% and 53.6% of PCV20 and PCV13 recipients, respectively). Most local reactions were mild or moderate in severity and generally resolved after a median duration of 1–2 days.

The frequency and severity of prompted systemic events within 7 days of vaccination were similar following vaccination with PCV20 or PCV13 (Figure 3B). The most commonly reported systemic event was muscle pain, experienced by 43.2% of PCV20 recipients and 36.5% of PCV13 recipients, which typically resolved with median durations of 1–2 days. A single subject (PCV13 recipient) experienced fever that was 38.0°C–38.4°C. Most systemic events were mild or moderate in severity.

Percentages of subjects reporting AEs within 1 month of vaccination 1 were similar following PCV20 and PCV13 vaccination (12.2% vs 13.1%, respectively) and were most commonly infections and infestations (6.3% in each group; Table 2; Supplementary Table 1). Among these AEs, 1.4% in each vaccine group were graded as severe. AEs occurred more commonly in PPSV23 recipients compared with saline recipients following vaccination 2 (18.7% vs 7.0%), particularly for events in the general disorders and administration site conditions category (6.5% vs 0.5%); infections and infestations were also most commonly reported at this time point (Supplementary Table 1). Among these AEs, 0.5% in the saline group and 2.8% in the

PPSV23 group were graded as severe. No AEs occurring within 30 minutes after vaccination were reported in either group.

Rates of SAEs and NDCMCs within 1 month after vaccination were ≤1.9% in each group (Table 2). Throughout the study, 9 and 11 SAEs occurred in the PCV20/saline and PCV13/PPSV23 groups, respectively; 13 and 8 NDCMCs occurred in these groups, respectively. No identical NDCMCs occurred in >1 subject in either study group, and no SAEs or NDCMCs were considered related to the vaccine. No deaths occurred during the study.

Immunogenicity

Baseline serotype-specific OPA GMTs were low in all groups and usually close to the LLOQs for each assay (Figures 4 and 5). OPA GMFRs from baseline to 1 month after vaccination 1 for the 13 serotypes contained in both PCV20 and PCV13 were somewhat lower for PCV20 compared with PCV13, ranging from 6.0 to 58.6 in the PCV20 group and from 7.1 to 68.6 in the PCV13 group depending on serotype (Figure 4; Supplementary Table 2). Among PCV20 recipients, 53.5%–87.2% exhibited ≥4-fold rises from baseline in PCV13-serotype OPA titers at 1 month following vaccination (Supplementary Figure 1). A slight booster

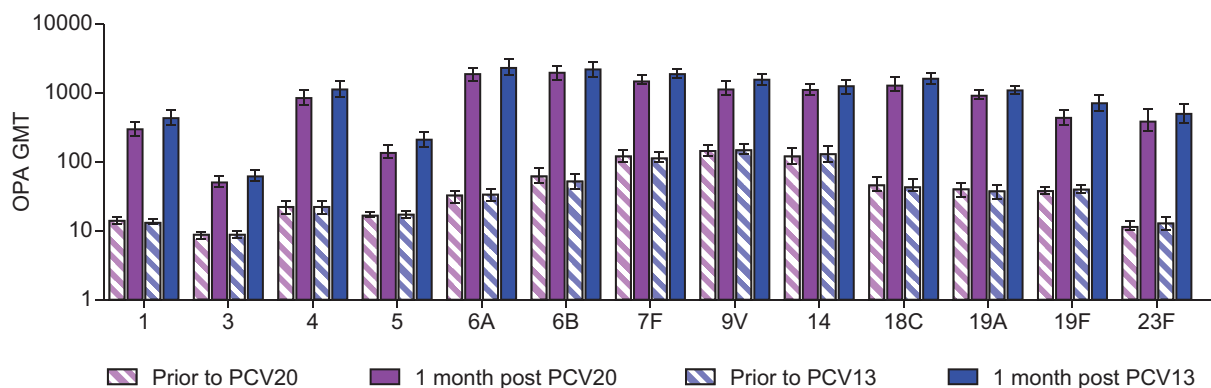**Table 2. Summary of Adverse Events (Safety Population)**

Time Point Type of AE	PCV20/Saline (n = 221[a]/213[b])		PCV13/PPSV23 (n = 222[a]/214[b])	
	n (%)	(95% CI)	n (%)	(95% CI)
Following PCV20 or PCV13 administration through 1 month of follow-up				
Any AE	27 (12.2)	(8.2, 17.3)	29 (13.1)	(8.9, 18.2)
Severe AE	3 (1.4)	(.3, 3.9)	3 (1.4)	(.3, 3.9)
SAE	0	(.0, 1.7)	1 (0.5)	(.0, 2.5)
NDCMC	2 (0.9)	(.1, 3.2)	1 (0.5)	(.0, 2.5)
Following saline or PPSV23 administration through 1 month of follow-up				
Any AE	15 (7.0)	(4.0, 11.3)	40 (18.7)	(13.7, 24.6)
Severe AE	1 (0.5)	(.0, 2.6)	6 (2.8)	(1.0, 6.0)
SAE	0	(.0, 1.7)	4 (1.9)	(.5, 4.7)
NDCMC	2 (0.9)	(.1, 3.4)	4 (1.9)	(.5, 4.7)
From 1 month following saline or PPSV23 administration through 12 months of follow-up				
SAE	9 (4.2)	(2.0, 7.9)	7 (3.3)	(1.3, 6.6)
NDCMC	9 (4.2)	(2.0, 7.9)	3 (1.4)	(.3, 4.0)
Throughout the study				
SAE	9 (4.1)	(1.9, 7.6)	11 (5.0)	2.5, 8.7
NDCMC	13 (5.9)	(3.2, 9.8)	8 (3.6)	(1.6, 7.0)

Abbreviations: AE, adverse event; CI, confidence interval; NDCMC, newly diagnosed chronic medical condition; PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; SAE, serious adverse event.

[a]Safety population reporting AEs from vaccination 1 to 1 month after vaccination 1.
[b]Safety population reporting AEs from vaccination 2 to 1 month after vaccination 2.

A

B

GMFRs in Functionality Antibody From Baseline to 1 Month After Vaccination													
Serotype		1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
PCV20	GMFR	21.2	6.0	37.8	8.3	58.6	29.6	12.2	7.7	8.5	26.8	23.3	11.8	33.6
	95% CI	16.96, 26.60	5.02, 7.23	27.4, 52.10	6.55, 10.54	44.15, 77.73	22.56, 38.96	9.86, 15.22	6.15, 9.57	6.35, 11.26	19.96, 35.85	17.96, 30.19	8.93, 15.47	24.19, 46.54
PCV13	GMFR	33.5	7.1	51.0	11.6	68.6	38.8	15.8	10.1	9.6	35.2	30.9	18.4	39.8
	95% CI	25.77, 43.65	5.85, 8.60	36.04, 72.27	9.09, 14.86	49.49, 95.20	28.52, 52.66	12.57, 19.82	7.95, 12.74	7.20, 12.89	26.02, 47.50	23.70, 40.37	14.19, 23.87	28.85, 54.88

Figure 4. OPA (*A*) GMTs and (*B*) GMFRs for the PCV13 serotypes before and 1 month after vaccination. LLOQs for individual serotypes were as follows: serotype 1, 18; serotype 3, 12; serotype 4, 21; serotype 5, 29; serotype 6A, 37; serotype 6B, 43; serotype 7F, 113; serotype 9V, 141; serotype 14, 35; serotype 18C, 31; serotype 19A, 18; serotype 19F, 48; serotype 23F, 13. Abbreviations: GMFR, geometric mean fold rise; GMT, geometric mean titer; LLOQ, lower limit of quantitation; OPA, opsonophagocytic activity; PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine.

response to most PCV13 serotypes was observed 1 month post-PPSV23 (Supplementary Table 2).

OPA GMFRs from baseline to 1 month after PCV20 or PPSV23 vaccination for the 7 serotypes unique to PCV20 and PPSV23 ranged from 11.2 to 113.4 in the PCV20 group and from 8.9 to 77.0 in the PPSV23 group (Figure 5; Supplementary Table 2). For 6 of these 7 serotypes, OPA GMFRs were higher in the PCV20 group compared with PPSV23. For PCV20 recipients, 63.2%–90.2% exhibited ≥4-fold rises from baseline in OPA titers for these 7 serotypes at 1 month following vaccination (Supplementary Figure 1).

Evaluation of IgG GMCs for the 13 serotypes included in PCV13 and the 7 additional serotypes in PCV20 demonstrated consistency with OPA results (Supplementary Table 3).

DISCUSSION

Despite major reductions in global pneumococcal burden following PCV13 introduction, serotypes beyond those included in the vaccine continue to cause disease [18]. In the United States, following PCV7 introduction in 2000, IPD among those ≥65 years of age caused by PCV13 serotypes decreased from 43 cases to 14 cases per 100 000 by 2010 [28]. Further decreases occurred after PCV13

was introduced in 2010 for children, with only 5–6 annual cases per 100 000 of PCV13-type IPD incidence reported during 2015 and 2016. Despite this reduction, overall IPD in 2016 in individuals ≥65 years of age remained at 24 cases per 100 000, 75% of which were attributed to non-PCV13 serotypes. Recent findings from an observational study of adults hospitalized with suspected pneumonia detected non-PCV13 serotypes in 23% of cases with known serotype among adults ≥65 years of age [19]. The ongoing development of multivalent PCVs targeting additional disease-causing serotypes is therefore essential to improving public health through both direct and indirect vaccination effects, particularly among older adults and those at increased risk.

Immune responses induced by PCV20 are preferable to those associated with PPSV23. Conjugate vaccines such as PCV13 induce robust T-cell–dependent immune responses associated with immunological memory [8, 10] and thus have the potential to provide substantial and prolonged protection against pneumococcal disease [9]. Conversely, polysaccharide vaccines such as PPSV23 induce T-cell–independent immune responses that are short-lived and deplete peripheral B cells, which may explain why subsequent ("booster") administration elicits an attenuated immune response [8, 29]. Furthermore, multiple studies have demonstrated statistically greater OPA

A

B
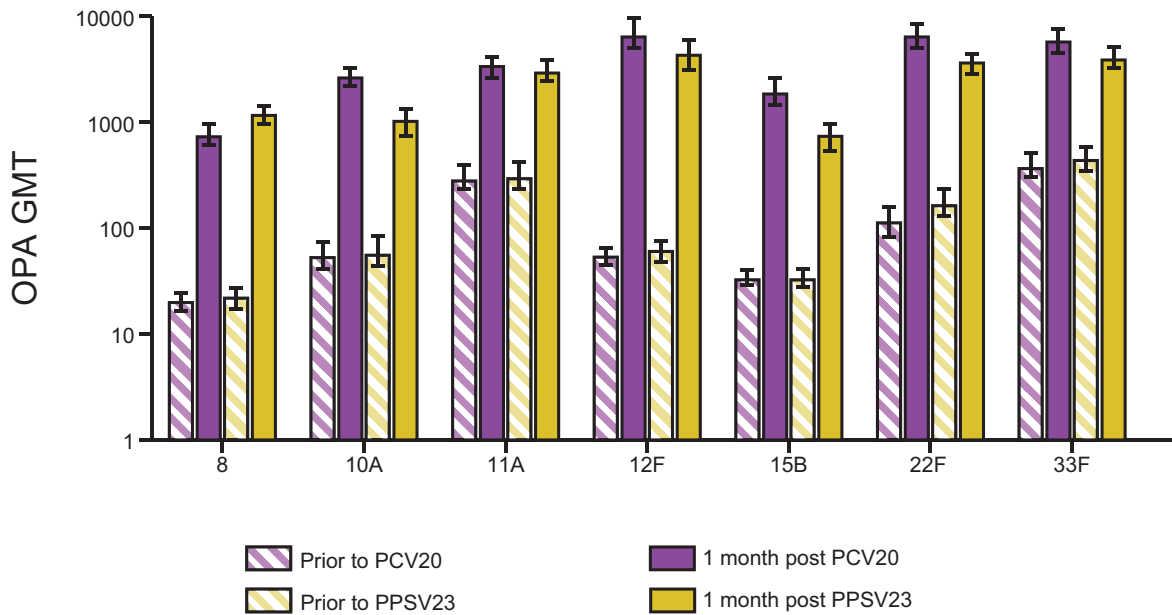
GMFRs in Functionality Antibody From Baseline to 1 Month After Vaccination							
Serotype		8	10 A	11 A	12 F	15 B	22 F	33 F
PCV20	GMFR	37.1	49.3	11.2	113.4	57.1	55.4	14.0
	95% CI	27.71, 49.71	35.18, 68.95	8.16, 15.31	81.47, 157.90	41.74, 78.07	38.88, 79.01	9.96, 19.62
PPSV23	GMFR	56.9	17.1	9.8	77.0	21.3	20.3	8.9
	95% CI	42.90, 74.46	12.15, 24.15	7.41, 13.06	55.04, 107.64	15.30, 29.71	14.69, 27.96	6.67, 11.84

Figure 5. OPA (*A*) GMTs and (*B*) GMFRs for the 7 additional serotypes before and 1 month after vaccination. LLOQs for individual serotypes were as follows: serotype 8, 16; serotype 10A, 14; serotype 11A, 32; serotype 12F, 51; serotype 15B, 36; serotype 22F, 28; serotype 33F, 49. Abbreviations: CI, confidence interval; GMFR, geometric mean fold rise; GMT, geometric mean titer; LLOQ, lower limit of quantitation; OPA, opsonophagocytic activity; PCV20, 20-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

GMTs elicited by PCV13 compared with PPSV23 for many of the 12 serotypes shared by both vaccines [30–34]. The 4 serotypes in PPSV23 that are not included in PCV20 (ie, 2, 9N, 17F, 20) are less commonly associated with IPD in the United States or other regions [12, 20]. Thus, PCV20 may represent an important advance in pneumococcal disease prevention by facilitating broader serotype coverage similar to PPVS23 coupled with the advantages of a conjugate vaccine.

In the current study, PCV20 was well tolerated in adults 60–64 years of age, exhibiting a safety profile that was comparable to PCV13 and consistent with expectations of PCV receipt in this age group. Overall AE and SAE rates were low and similar following vaccination with PCV20 and PCV13. Moreover, similar rates and severity of prompted local reactions and systemic events were observed in both groups, most of which were mild or moderate in severity. Injection site pain was the most common local reaction, as was also observed in previous PCVs adult studies [30, 35–37]. No new safety signals were identified.

Robust bactericidal immune responses (measured via OPA, which was selected for immunogenicity assessments because it is a functional assay [38]) were observed for all 20 serotypes following vaccination with PCV20, supporting the potential for PCV20 to

expand pneumococcal serotype protection and decrease disease burden beyond that provided by PCV13. One month after PCV20 vaccination (vaccination 1), OPA GMFRs relative to baseline for the 7 serotypes unique to PCV20 ranged from 11.2 to 113.4.

The use of the group vaccinated with PCV13 and followed 1 month later with PPSV23 provided a control for all 20 serotypes in PCV20 in a contemporaneous timeframe. In the PCV13/PPSV23 group, observed OPA GMTs to the PCV13 serotypes after vaccination with PPSV23 showed a slight booster response compared with those after initial PCV13 immunization. Additionally, PCV13 did not elicit antibody titers against the 7 additional PCV20 serotypes (data not shown). These findings together support the validity of the PCV13/PPSV23 schedule as a control group for independently comparing responses induced by PCV20 against the 13 PCV13 serotypes and the 7 additional serotypes.

One limitation of this study was that it was performed in pneumococcal vaccine-naive individuals 60 through 64 years of age, potentially limiting generalizability to populations with prior pneumococcal vaccination and older age groups. Additionally, the study did not, and was not intended to, provide a statistical noninferiority comparison of immune responses to the 20 PCV20 serotypes induced by PCV20 compared with those induced by the licensed pneumococcal vaccines administered to the control group. A study designed similarly but with a much larger sample size would be needed to support such comparisons; these are generally performed in phase 3 analyses. Further studies could also assess immune response duration.

In light of the encouraging data from this study, in September 2018 the US Food and Drug Administration granted breakthrough therapy designation to PCV20 for prevention of pneumococcal disease in adults ≥18 years of age [39]. Several adult phase 3 studies of PCV20 with PCV13 and PPSV23 comparators (NCT03828617, NCT03760146, NCT03835975), including a pivotal study to evaluate noninferiority of immune responses, are currently ongoing and are expected to provide additional information on PCV20 safety and immunogenicity in this population.

CONCLUSIONS

In this phase 2, randomized study, PCV20 was well tolerated in pneumococcal vaccine-naive adults 60–64 years of age. AE and reactogenicity event profiles were consistent with those observed for PCV13 and historical PCV experience in this age group. PCV20 vaccination elicited robust OPA responses to all vaccine serotypes that were somewhat lower to those elicited by PCV13 and generally higher than those for PPSV23. These data support ongoing phase 3 clinical development in adults and demonstrate the potential for PCV20 to provide expanded protection against pneumococcal disease.

Supplementary Data

Notes

References

1. World Health Organization. Pneumococcal vaccines WHO position paper 2012. Wkly Epidemiol Rec **2012**; 87:129–44.
2. Blasi F, Mantero M, Santus P, Tarsia P. Understanding the burden of pneumococcal disease in adults. Clin Microbiol Infect **2012**; 18:7–14.
3. Drijkoningen JJ, Rohde GG. Pneumococcal infection in adults: burden of disease. Clin Microbiol Infect **2014**; 20:45–51.
4. Zhang D, Petigara T, Yang X. Clinical and economic burden of pneumococcal disease in US adults aged 19–64 years with chronic or immunocompromising diseases: an observational database study. BMC Infect Dis **2018**; 18:436.
5. Brueggemann AB, Griffiths DT, Meats E, Peto T, Crook DW, Spratt BG. Clonal relationships between invasive and carriage *Streptococcus pneumoniae* and serotype- and clone-specific differences in invasive disease potential. J Infect Dis **2003**; 187:1424–32.
6. World Health Organization. WHO vaccine-preventable diseases: monitoring system. 2019 global summary. Available at: http://apps.who.int/immunization_monitoring/globalsummary/diseases. Accessed 13 January 2020.
7. Matanock A, Lee G, Gierke R, Kobayashi M, Leidner A, Pilishvili T. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep **2019**; 68:1069–75.
8. Clutterbuck EA, Lazarus R, Yu LM, et al. Pneumococcal conjugate and plain polysaccharide vaccines have divergent effects on antigen-specific B cells. J Infect Dis **2012**; 205:1408–16.
9. Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med **2015**; 372:1114–25.
10. Frenck RW Jr, Fiquet A, Gurtman A, et al; B1851020 Study Group. Immunogenicity and safety of a second administration of 13-valent pneumococcal conjugate vaccine 5 years after initial vaccination in adults 50 years and older. Vaccine **2016**; 34:3454–62.

11. Cohen R, Cohen JF, Chalumeau M, Levy C. Impact of pneumococcal conjugate vaccines for children in high- and non-high-income countries. Expert Rev Vaccines **2017**; 16:625–40.

12. Moore MR, Link-Gelles R, Schaffner W, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. Lancet Infect Dis **2015**; 15:301–9.

13. Tomczyk S, Lynfield R, Schaffner W, et al. Prevention of antibiotic-nonsusceptible invasive pneumococcal disease with the 13-valent pneumococcal conjugate vaccine. Clin Infect Dis **2016**; 62:1119–25.

14. Vadlamudi NK, Chen A, Marra F. Impact of the 13-valent pneumococcal conjugate vaccine among adults: a systematic review and meta-analysis. Clin Infect Dis **2019**; 69:34–49.

15. Pilishvili T, Lexau C, Farley MM, et al; Active Bacterial Core Surveillance/Emerging Infections Program Network. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis **2010**; 201:32–41.

16. Hausdorff WP, Hanage WP. Interim results of an ecological experiment–conjugate vaccination against the pneumococcus and serotype replacement. Hum Vaccin Immunother **2016**; 12:358–74.

17. Metcalf BJ, Gertz RE Jr., Gladstone RA, et al. Strain features and distributions in pneumococci from children with invasive disease before and after 13-valent conjugate vaccine implementation in the USA. Clin Microbiol Infect **2016**; 22:60.e9–60.e29.

18. Wantuch PL, Avci FY. Invasive pneumococcal disease in relation to vaccine type serotypes. Hum Vaccin Immunother **2019**; 15:874–5.

19. Isturiz RE, Ramirez J, Self WH, et al. Pneumococcal epidemiology among US adults hospitalized for community-acquired pneumonia. Vaccine **2019**; 37:3352–61.

20. Balsells E, Guillot L, Nair H, Kyaw MH. Serotype distribution of *Streptococcus pneumoniae* causing invasive disease in children in the post-PCV era: a systematic review and meta-analysis. PLoS One **2017**; 12:e0177113.

21. Cui YA, Patel H, O'Neil WM, Li S, Saddier P. Pneumococcal serotype distribution: a snapshot of recent data in pediatric and adult populations around the world. Hum Vaccin Immunother **2017**; 13:1–13.

22. Wroe PC, Lee GM, Finkelstein JA, et al. Pneumococcal carriage and antibiotic resistance in young children before 13-valent conjugate vaccine. Pediatr Infect Dis J **2012**; 31:249–54.

23. Yahiaoui RY, Bootsma HJ, den Heijer CDJ, et al. Distribution of serotypes and patterns of antimicrobial resistance among commensal *Streptococcus pneumoniae* in nine European countries. BMC Infect Dis **2018**; 18:440.

24. Harboe ZB, Thomsen RW, Riis A, et al. Pneumococcal serotypes and mortality following invasive pneumococcal disease: a population-based cohort study. PLoS Med **2009**; 6:e1000081.

25. Pneumovax® 23 (pneumococcal vaccine polyvalent). Whitehouse Station, NJ: Full Prescribing Information, Merck & Co., Inc., **2015**.

26. Thompson A, Lamberth E, Severs J, et al. Phase 1 trial of a 20-valent pneumococcal conjugate vaccine in healthy adults. Vaccine **2019**; 37:6201–7.

27. Cooper D, Yu X, Sidhu M, Nahm MH, Fernsten P, Jansen KU. The 13-valent pneumococcal conjugate vaccine (PCV13) elicits cross-functional opsonophagocytic killing responses in humans to *Streptococcus pneumoniae* serotypes 6C and 7A. Vaccine **2011**; 29:7207–11.

28. CDC. Pneumococcal disease. Available at: https://www.cdc.gov/pneumococcal/surveillance.html#surveillance. Accessed 4 December 2019.

29. Musher DM, Manof SB, Liss C, et al. Safety and antibody response, including antibody persistence for 5 years, after primary vaccination or revaccination with pneumococcal polysaccharide vaccine in middle-aged and older adults. J Infect Dis **2010**; 201:516–24.

30. Jackson LA, Gurtman A, Rice K, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in adults 70 years of age and older previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Vaccine **2013**; 31:3585–93.

31. Jackson LA, Gurtman A, van Cleeff M, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine compared to a 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naive adults. Vaccine **2013**; 31:3577–84.

32. Greenberg RN, Gurtman A, Frenck RW, et al. Sequential administration of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naïve adults 60–64 years of age. Vaccine **2014**; 32:2364–74.

33. Shiramoto M, Hanada R, Juergens C, et al. Immunogenicity and safety of the 13-valent pneumococcal conjugate vaccine compared to the 23-valent pneumococcal polysaccharide vaccine in elderly Japanese adults. Hum Vaccin Immunother **2015**; 11:2198–206.

34. Juergens C, de Villiers PJ, Moodley K, et al. Safety and immunogenicity of 13-valent pneumococcal conjugate vaccine formulations with and without aluminum phosphate and comparison of the formulation of choice with 23-valent pneumococcal polysaccharide vaccine in elderly adults: a randomized open-label trial. Hum Vaccin Immunother **2014**; 10:1343–53.

35. Durando P, Rosselli R, Cremonesi I, et al. Safety and tolerability of 13-valent pneumococcal conjugate vaccine in the elderly. Hum Vaccin Immunother **2015**; 11:172–7.

36. Jackson LA, Gurtman A, van Cleeff M, et al. 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. Vaccine **2013**; 31:3594–602.

37. Jackson LA, Neuzil KM, Whitney CG, et al. Safety of varying dosages of 7-valent pneumococcal protein conjugate vaccine in seniors previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Vaccine **2005**; 23:3697–703.

38. Song JY, Moseley MA, Burton RL, Nahm MH. Pneumococcal vaccine and opsonic pneumococcal antibody. J Infect Chemother **2013**; 19:412–25.

39. Pfizer Inc. Pfizer granted FDA breakthrough therapy designation for 20-valent pneumococcal conjugate vaccine for the prevention of invasive disease and pneumonia in adults aged 18 years and older. Available at: https://www.pfizer.com/news/press-release/press-release-detail/pfizer_granted_fda_breakthrough_therapy_designation_for_20_valent_pneumococcal_conjugate_vaccine_for_the_prevention_of_invasive_disease_and_pneumonia_in_adults_aged_18_years_and_older. Accessed 15 May 2019.