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A phase 3, randomized, double-blind study to evaluate the immunogenicity and safety of 3 lots of 20-valent pneumococcal conjugate vaccine in pneumococcal vaccine-naive adults 18 through 49 years of age

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ABSTRACT

Introduction: Introduction of pneumococcal conjugate vaccines (PCVs), including the 13-valent PCV (PCV13), has considerably reduced pneumococcal disease burden. However, additional serotypes not in PCV13 continue to present a substantial disease burden. The 20-valent PCV (PCV20) was developed to expand protection against pneumococcal disease beyond PCV13. As part of the phase 3 clinical development program, the current study assessed consistency of immune responses across 3 lots of PCV20 and described the safety profile of PCV20.

Methods: This phase 3, randomized, multicenter, double-blind study of pneumococcal vaccine-naive adults 18–49 years of age randomized 1710 participants in a 2:2:2:1 ratio to receive 1 of 3 lots of PCV20 or PCV13. Immunogenicity was assessed through serotype-specific opsonophagocytic activity (OPA) titers before and approximately 1 month (28–42 days) after vaccination. Reported local reactions within 10 days, systemic events within 7 days, adverse events (AEs) within 30 days, and serious AEs (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) within 6 months after vaccination were evaluated.

Results: Equivalence in immune responses (OPA geometric mean titers) for all 20 vaccine serotypes was demonstrated across the 3 PCV20 lots. Robust responses, assessed by OPA geometric mean fold rises, percentage of participants achieving ≥4-fold rises, and percentage of participants with OPA titers ≥lower limit of quantitation, were observed after PCV20. Reported rates of local reactions, systemic events, and AEs were similar between the pooled PCV20 lots and PCV13; most events were mild or moderate. Reported rates of SAEs and NDCMCs were low and similar between the PCV20 and PCV13 groups.

Conclusions: Three different lots of PCV20 demonstrated robust and consistent immunogenicity. The safety and tolerability of PCV20 was acceptable and similar to that of PCV13. (Clinicaltrials.gov: NCT03828617).

Abbreviations: AE, adverse event; CRM_{197}, cross-reactive material 197; GMFR, geometric mean fold rise; GMR, geometric mean ratio; GMT, geometric mean titer; IPD, invasive pneumococcal disease; LLOQ, lower limit of quantitation; NDCMC, newly diagnosed chronic medical condition; OPA, opsonophagocytic activity; PCV, pneumococcal conjugate vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; SAE, serious adverse event.

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1. Introduction

Infection with *Streptococcus pneumoniae* can lead to serious invasive pneumococcal disease (IPD; eg, bacteremia, meningitis, bacteremic pneumonia) and noninvasive illnesses (eg, acute otitis media, nonbacteremic pneumonia, sinusitis), and is an important cause of morbidity and mortality globally [1–3]. In 2016, pneumococcal pneumonia was the most common cause of lower respiratory tract infections across 195 countries and was responsible for 1.2 million deaths [4]. Of these, approximately 490,000 deaths were in adults >70 years of age [4].

A limited subset of the more than 95 known pneumococcal serotypes (characterized by their distinct polysaccharide capsules) account for the majority of disease [1,3,5]. Two types of vaccines that target multiple serotypes are used to protect against pneumococcal disease [3]. The 23-valent pneumococcal polysaccharide vaccine (PPSV23) elicits a T-cell-independent immune response that does not induce long-lasting immunity and results in attenuated responses upon subsequent pneumococcal vaccination [6,7]. Additionally, there is a lack of consensus regarding the effectiveness of PPSV23 against non-bacteremic pneumonia due to contradictory findings [7]. Conversely, pneumococcal conjugate vaccines (PCVs), such as the 13-valent PCV (PCV13), elicit a T cell–dependent immune response and are associated with robust and long-lasting protection; a booster response may be observed upon subsequent vaccine exposure [6–9]. PCV13 provides protection against bacteremic and non-bacteremic pneumonia in adults, with demonstrated vaccine efficacy and real-world effectiveness [10,11]. Introduction of PCVs has helped to decrease pneumococcal disease burden globally [12–15]. For example, in the United States, overall IPD rates among adults ≥65 years of age decreased by 60% from 1998 to 2018 [16]. Despite this reduction, serotypes not included in PCV13 continue to cause disease [17–20].

Seven serotypes not in PCV13 (ie, 8, 10A, 11A, 12F, 15B, 22F, and 33F) cause invasive and noninvasive disease in adults [21–23]. These serotypes were estimated to cause 9900 cases of IPD, 44,000 cases of inpatient and 52,000 cases of outpatient pneumonia, and 4300 deaths in US adults in 2017 [21]. Further, these 7 serotypes accounted for approximately 30% of IPD cases in adults ≥60 years of age in Germany in 2017–2018 [22] and 50% and 39% of IPD cases in adults 18–64 and ≥65 years of age, respectively, in Spain in 2019 [23]. These serotypes also have other important characteristics, such as antibiotic resistance, association with meningitis and/or higher mortality rates, invasive potential, and association with outbreaks, that contribute to disease burden [17,18,24–29].

The 20-valent PCV (PCV20) has been developed to expand protection of a conjugate vaccine beyond that of PCV13 and is licensed for use in adults in the United States [30]. The vaccine contains the components of PCV13, (including the polysaccharide conjugates of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and 7 additional conjugates for serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F. Phase 1 and phase 2 studies of PCV20 in adults 18–49 and 60–64 years of age, respectively, found that PCV20 elicited robust immune responses to all 20 vaccine serotypes and had a safety profile consistent with that of PCV13, which supported phase 3 development [31,32].

As part of a phase 3 vaccine clinical development program, the US Food and Drug Administration generally expects demonstration of a clinical assessment of manufacturing consistency by comparing immunogenicity across 3 vaccine lots, particularly for complex combination vaccines such as multivalent PCVs [33]. This phase 3 study evaluated the immune responses across 3 different lots of PCV20 to demonstrate lot-to-lot consistency and also described the safety profile of PCV20.

2. Material and methods

2.1. Study design and participants

This was a phase 3, randomized, double-blind study conducted at 21 US sites from February 2019 to October 2019 (ClinicalTrials.gov: NCT03828617).

Men and women 18–49 years of age with no prior pneumococcal vaccination (pneumococcal vaccine-naive), including those with pre-existing stable disease (ie, not requiring significant change in therapy in the previous 6 weeks or hospitalization for worsening disease within 12 weeks before receipt of the vaccine), were eligible for inclusion. Adults 18–49 years of age were selected for this study as they were unlikely to have received a prior pneumococcal vaccination and were expected to represent a relatively homogeneous population in terms of immune response, facilitating interpretation of the immunologic data for this complex multivalent vaccine. To be eligible for participation, a woman could not be pregnant or breastfeeding. Key exclusion criteria included planned pneumococcal vaccination; serious chronic disorder or other acute or chronic medical or psychiatric condition that, in the investigator's opinion, excluded participation; history of microbiologically proven invasive disease caused by *S pneumoniae* obtained from review of medical history with the participant and review of medical records (if available); current or planned treatment with immunosuppressive therapy; or known or suspected immunodeficiency or other immunosuppressive condition.

Participants were randomly assigned to 1 of 4 groups in a 2:2:2:1 ratio to receive a single 0.5-mL dose of 1 of 3 manufacturing scale lots of PCV20 (PCV20 Lot 1 [Pfizer; lot #18-001439], PCV20 Lot 2 [Pfizer; lot #18-002741], PCV20 Lot 3 [Pfizer; lot #18-002653]) or PCV13 (Pfizer; lot #17-004639) administered intramuscularly in the deltoid muscle. Each 0.5 mL dose of PCV20 contains 2.2 μg of each saccharide individually conjugated to CRM_{197} for serotypes 1, 3, 4, 5, 6A, 7F, 8, 9 V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F, and 4.4 μg of 6B. Each 0.5 mL dose of PCV13 contains 2.2 μg of each saccharide individually conjugated to CRM_{197} for serotypes 1, 3, 4, 5, 6A, 7F, 9 V, 14, 18C, 19A, 19F, and 23F, and 4.4 μg of 6B. Both PCV20 and PCV13 contain 0.125 mg aluminum as aluminum phosphate per 0.5 mL dose. The PCV13 group was included as a safety control; immunogenicity assessments of this group were included to maintain blinding and for descriptive purposes. Blood was drawn for immunogenicity assessments before vaccination and approximately 1 month (28–42 days) after vaccination.

Participants were allocated to vaccine groups by site personnel through the use of an interactive web-based response technology system. Randomization was site-based. Site personnel taking part in any study activities were blinded to investigational product assignments during the study. Vaccination was administered in a double-blind fashion as the appearance of PCV20 and PCV13 were identical.

The study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation Good Clinical Practice Guidelines. The institutional review board and/or independent ethics committee for each participating study site approved the study. All participants provided written informed consent before any study-specific activity was performed.

2.2. Objectives and endpoints

The primary immunogenicity objective was to demonstrate that the immune responses, assessed by serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs)

1 month after PCV20, were equivalent across the 3 lots. The secondary immunogenicity objective was to describe other immune responses to PCV20, assessed by geometric mean fold rises (GMFRs) and percentages of participants with ≥4-fold rise in OPA titers from baseline to 1 month after vaccination, and percentage of participants with OPA titers ≥the lower limit of quantitation (LLOQ) 1 month after vaccination, for each of the 20 vaccine serotypes.

The primary safety objective was to describe the safety profile in the PCV20 recipients (participants pooled across the 3 lots). Endpoints included the percentage of participants with prompted local reactions (ie, redness, swelling, pain at the injection site) within 10 days, systemic events (ie, fever [≥38.0 °C], headache, fatigue, muscle pain, joint pain) within 7 days, adverse events (AEs) within 1 month, and serious AEs (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) within 6 months after vaccination.

3. Statistical analyses

3.1. Population size

The sample size was determined using a 2-fold equivalence margin for each between-lot comparison of OPA titers with a total of 60 comparisons from 3 lots and 20 serotypes. The true maximum difference in serotype-specific OPA titers in natural log scale between any 2 lots was assumed to be 0.2 in the power calculation, corresponding to an assumption that the true geometric mean ratio (GMR) of any lot to another lot is between 0.82 and 1.22. Power for each pairwise comparison was calculated using SAS version 9.4 (SAS Institute, Cary, NC, USA). For each serotype, the probabilities of meeting the equivalence criterion for the 3 pairwise comparisons were multiplied. The resulting 20 serotype-specific probabilities were then multiplied to estimate the power for declaring overall equivalence of the 3 lots. The study sought to enroll 1610 participants (460 in each of the 3 PCV20 lot groups and 230 in the PCV13 group) to provide an overall power of 89.8% to demonstrate equivalence in immune response to the 3 PCV20 lots.

3.2. Immunogenicity

The evaluable immunogenicity population was used for the lot-to-lot consistency analysis of immunogenicity endpoints and included any participant who received 1 of the 3 lots of PCV20 as randomized, had ≥1 OPA titer for any serotype from a blood sample collected within a prespecified window 1 month after vaccination, and had no other major protocol deviations. OPA titers were quantified as previously described [34,35]. For analysis of the primary immunogenicity endpoint, hypothesis testing was performed to assess equivalence of the immune responses induced by 3 lots of PCV20. A linear regression model was used to calculate the serotype-specific OPA GMRs and 2-sided CIs for each pair of lot comparisons (PCV20 Lot 1/PCV20 Lot 2, PCV20 Lot 1/PCV20 Lot 3, PCV20 Lot 2/PCV20 Lot 3), with terms for PCV20 lot, sex, smoking status, age at vaccination in years, and baseline log-transformed OPA titers. Equivalence among the 3 lots for a given serotype was declared if the pairwise model-based 2-sided 95% CIs for each GMR was contained in the prespecified interval (0.5, 2.0). Overall lot consistency was declared if equivalence was demonstrated for all 20 vaccine serotypes.

Descriptive summaries were calculated for each of the 3 PCV20 lots and PCV13 (immune responses to PCV13 were included for completeness) for analysis of the secondary immunogenicity endpoints. Fold rises in serotype-specific OPA titers were calculated as the ratio of the titer at 1 month after vaccination to the titer before vaccination. Serotype-specific OPA GMTs and GMFRs from before to 1 month after vaccination were calculated by exponentiating the mean logarithm of the titers or fold rises. The associated 2-sided 95% CIs were obtained by constructing CIs with reference to the *t* distribution for the logarithm scale of the titers or fold rises and exponentiating the confidence limits. The percentage of participants with a ≥4-fold rise in OPA titers from before to 1 month after vaccination and the percentage of participants with OPA titers ≥LLOQ was provided; associated 2-sided 95% CIs were obtained using the Clopper-Pearson method.

An exploratory post hoc analysis evaluated noninferiority of PCV20 to PCV13 1 month after vaccination for each of the 13 matched serotypes. Serotype-specific GMTs and GMRs (ratio of GMTs of pooled PCV20 to PCV13) and corresponding 2-sided 95% CIs for the pooled PCV20 lots and PCV13 were calculated by exponentiating the least squares means and corresponding CIs based on an analysis of log-transformed OPA titers using a regression model with terms for vaccine group, sex, smoking status, age at vaccination in years, and baseline log-transformed OPA titers. Noninferiority was declared if the lower bound of the 2-sided 95% CI was > 0.5, the criteria used in the PCV13 program and PCV20 pivotal study [36,37].

3.3. Safety

The safety population was used for analysis of safety endpoints and included all PCV20 recipients (ie, pooled PCV20 group) or PCV13 recipients with safety follow-up after vaccination. Descriptive statistics were provided for each safety endpoint in the pooled PCV20 and PCV13 groups, which included percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs.

4. Results

4.1. Participants

We randomized a total of 1710 participants and vaccinated 1708 (99.9%) participants across the 4 study groups (Fig. 1). Overall, 1673 (97.8%) participants completed the visit 1 month after vaccination and 1635 (95.6%) completed the study. Of the 75 (4.4%) participants who withdrew from the study, the most common reason for withdrawal was lost to follow-up. The study population included representation from women (65.3%), Black or African American race (18.5%), and Hispanic/Latino ethnicity (11.2%). Demographic characteristics were similar across vaccine groups; the mean age at vaccination was 35.3 years (**Supplemental** Table 1).

4.2. Immunogenicity

4.2.1. Primary immunogenicity endpoint: lot equivalence

The OPA GMT pairwise comparisons (GMRs) between the 3 lots of PCV20 at 1 month after vaccination for each of the 20 vaccine serotypes demonstrated equivalence, with the 95% CI of the OPA GMRs all within the prespecified 2-fold equivalence interval (0.5, 2.0) for each serotype across all 3 lots (Fig. 2).

4.2.2. Secondary immunogenicity endpoints

The OPA GMTs 1 month after PCV20 administration and OPA GMFRs from baseline to 1 month after vaccination for the 20 serotypes were generally similar across the 3 lots (Fig. 3). OPA GMFRs for the 20 vaccine serotypes ranged from 4.6 to 175.7 across the 3 PCV20 lots. The percentage of participants achieving a ≥4-fold rise in OPA titers from baseline to 1 month after vaccination for the 20

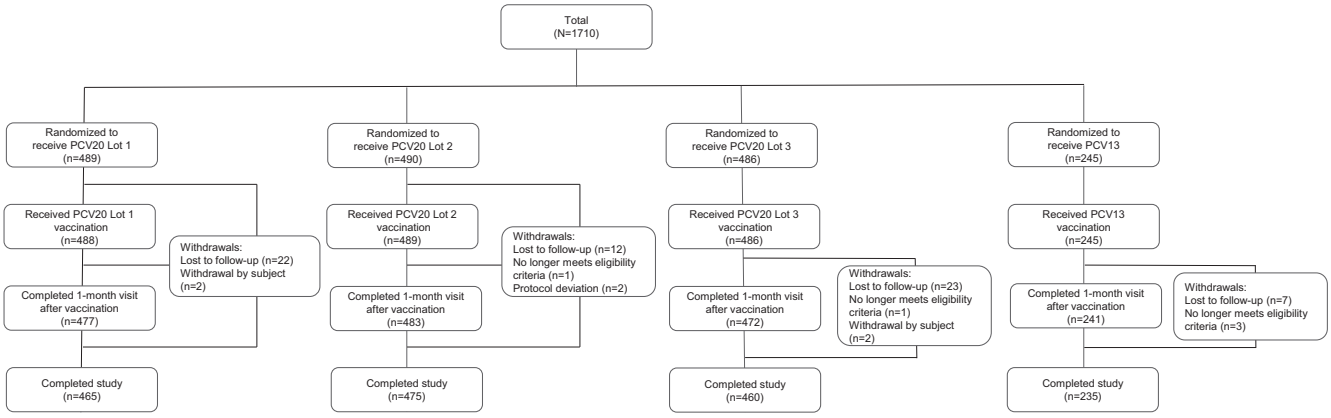


Fig. 1. Participant disposition. PCV13 = 13-valent pneumococcal conjugate vaccine; PCV20 = 20-valent pneumococcal conjugate vaccine. Two randomized participants were not vaccinated; 1 participant randomized to receive PCV20 Lot 2 was unable to provide the required blood sample, and 1 participant randomized to receive PCV20 Lot 1 had concerns about the side effects.

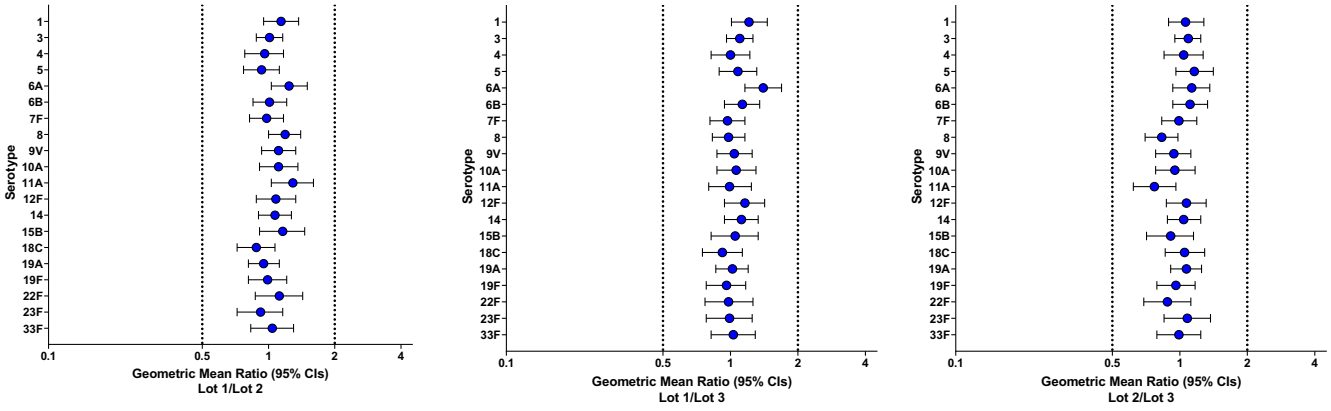


Fig. 2. Lot consistency: Model-based OPA GMRs with 95% CIs 1 month after vaccination for the 20 vaccine serotypes. GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity. Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

serotypes was generally similar across the 3 PCV20 lots and ranged from 42.2% to 94.5% across all 3 lots (Fig. 4). The percentage of participants with OPA titers ≥LLOQ at 1 month after vaccination for the 20 serotypes was generally similar across the 3 PCV20 lots and ranged from 80.3% to 100% across all 3 lots (**Supplemental** Fig. 1).

The GMFRs from baseline to 1 month after vaccination for the 13 vaccine serotypes included in PCV13 ranged from 5.6 to 146.5, the percentage of participants with ≥4-fold rises ranged from 62.7 to 95.1%, and the percentage of participants with OPA titers ≥LLOQ ranged from 86.6 to 99.6% at 1 month after PCV13 (Figs. 3 and 4 and **Supplemental** Fig. 1). As expected, there was no response in PCV13 recipients to the 7 additional serotypes included in PCV20 but not in PCV13.

At 1 month after vaccination, noninferiority criteria were met for all 13 matched serotypes between the pooled PCV20 lots and PCV13 (lower bound of the 2-sided 95% CI for the GMR > 0.5; **Supplemental Table 2**).

4.3. Safety

4.3.1. Local reactions

Local reactions within 10 days after vaccination were mostly mild or moderate and similar between the pooled PCV20 and PCV13 groups (Fig. 5). Pain at the injection site was the most frequent local reaction, reported by 78.7% of PCV20 and 75.7% of PCV13 recipients (difference 3.0, 95% CI: −2.4, 9.1). Median onset for local reactions ranged from day of to 1 day after vaccination in both the PCV20 and PCV13 groups and reactions resolved with a median duration of 1–2 days.

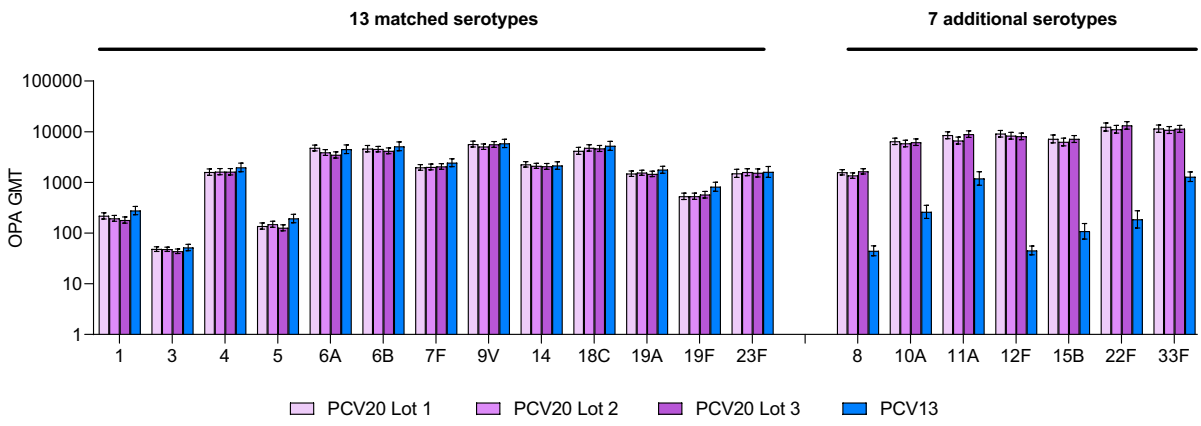
4.3.2. Systemic events

Systemic events within 7 days after vaccination were similar between the pooled PCV20 and PCV13 groups and were mostly mild or moderate (Fig. 5). Muscle pain was the most frequent systemic event, reported by 62.1% of PCV20 and 60.5% of PCV13 recipients. Fever was uncommon, reported by 1.2% of PCV20 and 0.8% of PCV13 recipients, and was typically low grade (38.0 °C–38.4 °C). Median onset of systemic events generally ranged from day of to 1 day after vaccination, and resolved within a median of 1–2.5 days in the PCV20 and PCV13 groups.

4.3.3. Adverse events

The percentage of participants reporting any AE was similar between the pooled PCV20 and PCV13 recipients (Table 1), with events in the infections and infestations category being reported most frequently. Few AEs were considered by the investigator to be related to study vaccine and the percentage was similar between the PCV20 (0.3%) and PCV13 (0.8%) groups. Reported percentages of severe AEs were low and similar between the PCV20 (0.5%) and PCV13 (0.8%) groups. Two severe AEs were considered by the investigator to be related to the study vaccine: a PCV20 Lot 1 recipient reported migraine, and a PCV13 recipient reported musculoskeletal and neck pain. The percentage of participants

A



B

GMFRs From Baseline to 1 Month After Vaccination																				
Serotype		13 matched serotypes													7 additional serotypes					
		1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F	8	10A	11A	12F	15B	22F	33F
PCV20 Lot 1	GMFR	20.2	5.0	77.6	8.7	157.2	72.5	18.3	25.4	18.2	80.4	35.9	14.0	99.5	38.3	20.8	6.9	175.5	112.5	83.8	8.3
	95% CI	17.6, 23.1	4.4, 5.5	63.8, 94.4	7.5, 10.0	132.6, 186.3	59.9, 87.8	15.5, 21.7	21.1, 30.7	14.8, 22.3	63.9, 101.2	29.9, 43.2	12.0, 16.5	80.4, 123.1	31.3, 46.8	16.6, 26.1	5.4, 8.9	141.3, 217.9	83.8, 150.9	59.2, 118.6	6.7, 10.4
PCV20 Lot 2	GMFR	17.8	5.0	94.7	9.4	119.6	75.4	19.5	23.3	16.3	95.0	39.1	14.7	125.1	38.8	19.0	5.0	174.6	84.2	63.3	8.6
	95% CI	15.6, 20.3	4.5, 5.5	79.4, 112.9	8.2, 10.7	100.5, 142.3	62.9, 90.4	16.5, 23.0	19.4, 27.9	13.2, 20.0	76.6, 117.7	32.4, 47.1	12.6, 17.2	102.4, 152.7	32.1, 46.9	15.2, 23.7	3.9, 6.4	140.8, 216.7	64.5, 110.0	46.8, 85.7	7.0, 10.6
PV20 Lot 3	GMFR	17.3	4.6	81.0	8.0	128.4	70.5	19.0	21.6	18.1	79.9	41.8	15.4	120.9	46.1	20.2	5.3	175.7	91.7	77.8	7.4
	95% CI	15.0, 19.8	4.1, 5.1	67.0, 97.8	6.9, 9.1	107.6, 153.1	58.1, 85.6	16.1, 22.5	17.7, 26.4	14.6, 22.3	63.8, 100.0	34.9, 50.2	13.1, 18.0	97.9, 149.5	37.9, 56.0	15.9, 25.6	4.2, 6.7	141.6, 218.1	69.4, 121.3	56.8, 106.6	6.0, 9.1
PCV13	GMFR	26.6	5.6	105.3	12.6	146.5	77.6	27.4	23.4	20.7	92.8	40.6	22.5	133.2	1.3	1.0	1.0	1.1	1.5	1.1	1.1
	95% CI	21.9, 32.4	4.8, 6.6	80.9, 137.1	10.4, 15.2	115.5, 185.8	58.7, 102.6	21.7, 34.6	17.9, 30.7	15.2, 28.1	69.2, 124.5	31.3, 52.5	18.1, 27.8	100.4, 176.7	1.1, 1.5	0.9, 1.2	0.8, 1.3	0.9, 1.2	1.2, 1.9	0.9, 1.4	0.9, 1.2

Fig. 3. Pneumococcal OPA (A) GMTs 1 month after vaccination and (B) GMFRs from baseline to 1 month after vaccination for the PCV20 serotypes. 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. Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis. The PCV13 group was included in the study as a safety control; immunogenicity assessments of this group were included to maintain blinding and for descriptive purposes.

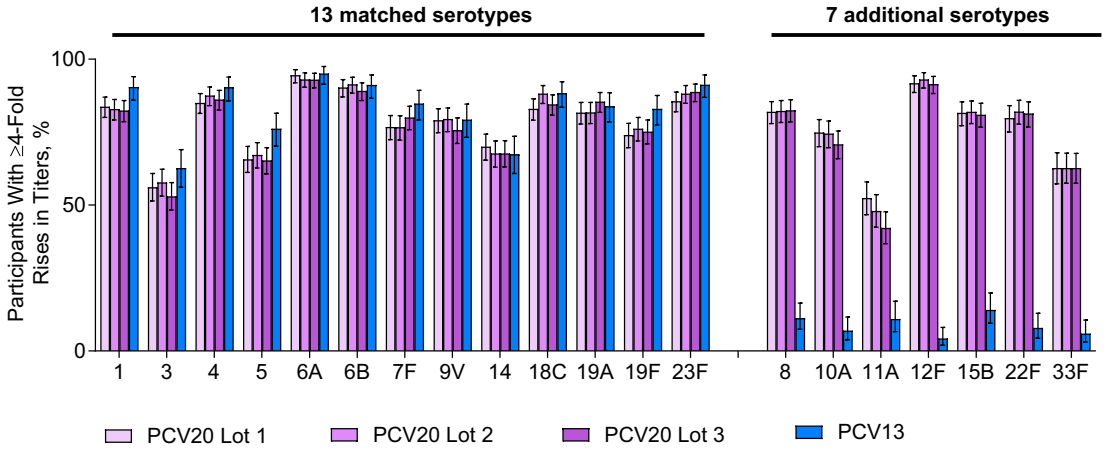


Fig. 4. Percentage of participants with a ≥4-fold rise in OPA titers from baseline to 1 month after vaccination for the PCV20 serotypes. LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV20 = 20-valent pneumococcal conjugate vaccine. Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis. The PCV13 group was included in the study as a safety control; immunogenicity assessments of this group were included to maintain blinding and for descriptive purposes.

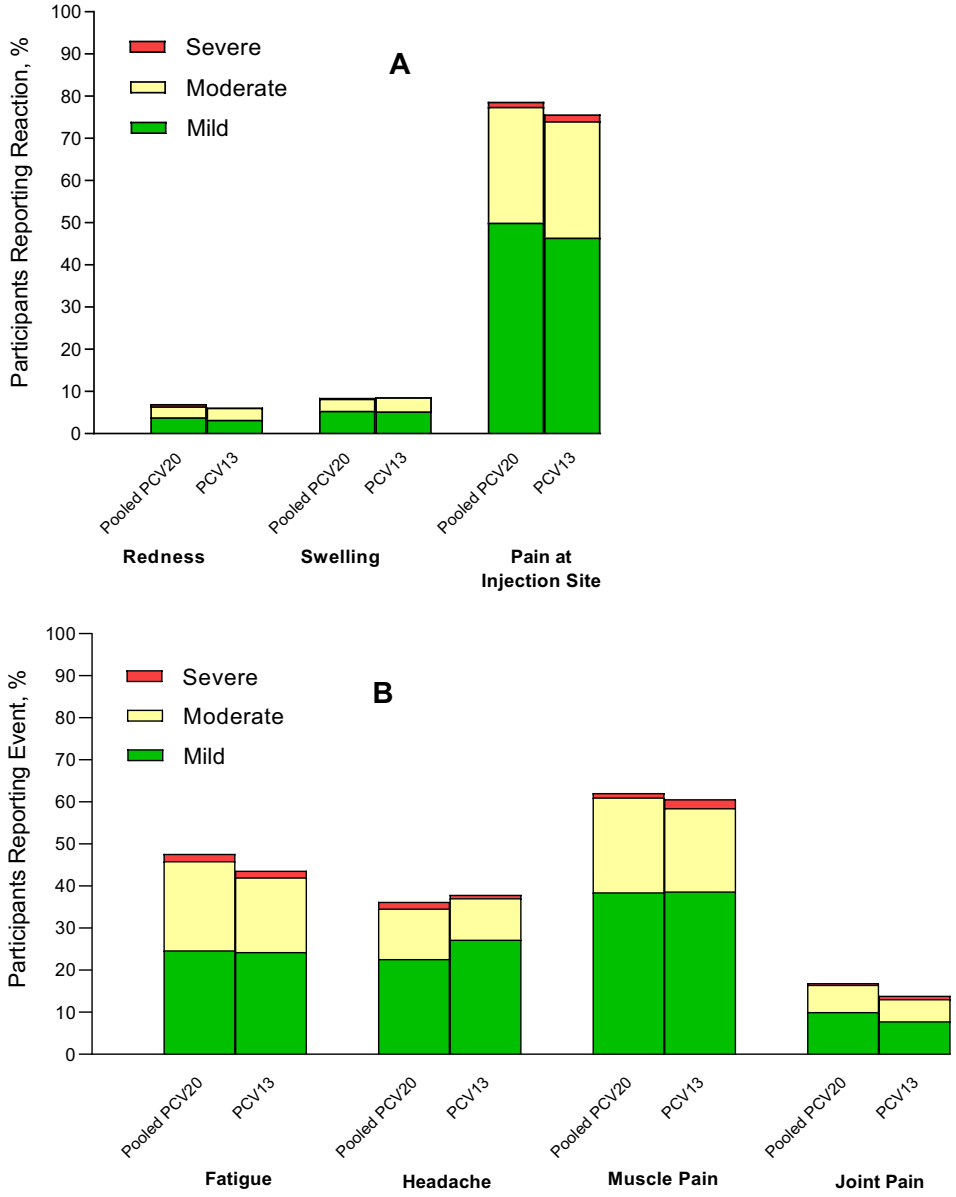


Fig. 5. Prompted reactogenicity events including (A) local reactions within 10 days of vaccination and (B) systemic events within 7 days of vaccination. PCV13 = 13-valent pneumococcal conjugate vaccine; PCV20 = 20-valent pneumococcal conjugate vaccine. Safety data were compared between the pooled PCV20 and PCV13 groups. Fever is not included in this figure but was reported by 1.2% of pooled PCV20 recipients and 0.8% of PCV13 recipients. The grading scale for prompted events was based on the US Food and Drug Administration Center for Biologics Evaluation and Research guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventative vaccine clinical trials. Local reactions and systemic events were categorized as mild, moderate, or severe (Grade 1–3); investigator confirmation was required for classification as Grade 4.

Table 1
Summary of adverse events.

Time point AE type	Pooled PCV20 (N = 1463[a]) n[b](%)	PCV13 (N = 245[a]) n[b](%)
Through 1 month after vaccination		
Any AE	100 (6.8)	13 (5.3)
Related	5 (0.3)	2 (0.8)
Severe	7 (0.5)	2 (0.8)
Through 6 months after vaccination		
SAE	10 (0.7)	0
NDCMC	15 (1.0)	5 (2.0)

AE = adverse event; NDCMC = newly diagnosed chronic medical condition; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV20 = 20-valent pneumococcal conjugate vaccine; SAE = serious adverse event.

[a] N = number of participants in the specified group.

[b] n = number of participants reporting at least 1 occurrence of the event specified.

reporting SAEs and NDCMCs were low and similar between the PCV20 (0.7% and 1.0%, respectively) and PCV13 (0% and 2.0%, respectively) groups. The investigators considered the SAEs and NDCMCs to be unrelated to study vaccine and consistent with medical diagnoses that occur in the age group of the study population. No safety-related withdrawals or deaths occurred during the study.

5. Discussion

This phase 3 study of the immunogenicity and safety of 3 lots of PCV20 in adults 18–49 years of age without prior pneumococcal vaccination demonstrated that the 3 lots of PCV20 met the criteria for lot consistency based on a 2-fold equivalence margin comparing OPA GMTs between each pair of PCV20 lots for each serotype. The 3 lots of PCV20 elicited similar and robust immune responses

at 1 month after vaccination against the 20 vaccine serotypes, as indicated by OPA GMFRs and the percentages of participants achieving a ≥4-fold rise and OPA titers ≥LLOQ. In addition, noninferiority of OPA GMRs for the pooled PCV20 lots compared to PCV13 at 1 month after vaccination was shown for all 13 PCV13 serotypes.

Demonstrating lot-to-lot consistency in a clinical study is considered necessary in most cases to satisfy the vaccine licensure requirements of the US Food and Drug Administration [33]. Therefore, demonstration of clinical lot consistency was an important component of the PCV20 clinical program. Pneumococcal conjugate vaccines are complex multivalent biologics, containing capsular polysaccharides of pneumococcal serotypes, each of which needs to be purified, separately activated, individually conjugated to an immunogenic protein, then formulated with excipients into the final drug product [38]. Achieving lot consistency with a complex multivalent biologic containing 20 independent conjugated polysaccharides is not trivial: 1 dose of PCV20 involves >600 raw materials, >900 manufacturing steps, and >1200 quality tests.

In the current study, pooled PCV20 safety and tolerability data were comparable to that observed following PCV13. Reports of local reactions and systemic events were generally mild or moderate and similar between the PCV20 pooled recipients and the PCV13 recipients; rates of AEs were similar between groups. The safety and tolerability findings from this phase 3 study are consistent with the results of other phase 2 [32] and phase 3 PCV20 studies in adults (NCT03835975 and NCT03760146).

Strengths of this study include the large sample size and good retention of study participants (95.6% of participants completed the study). This study was not designed to compare safety endpoints across the 3 PCV20 lots and, therefore, individual lot data were not reported in the safety results. However, subgroup analyses (data not shown) showed similar trends across the 3 lots of PCV20. Limitations of the noninferiority analysis include that the analysis was not prespecified and the randomization (6:1) was originally designed to measure lot consistency rather than noninferiority of PCV20 compared with PCV13. Additionally, adults 18–49 years of age are not the population that will use PCV20 most often. However, noninferiority has also been demonstrated in adults ≥60 years of age in a specifically designed trial [37], thus our results further support the similar performance of PCV20 compared to PCV13.

6. Conclusions

In this study, PCV20 in pneumococcal vaccine-naive adults 18–49 years of age elicited a consistent and robust immune response to all 20 vaccine serotypes across 3 manufacturing scale lots. The safety and tolerability of PCV20 was acceptable and similar to PCV13. These data, in conjunction with results from the other clinical studies in adults, support that PCV20 has the potential to expand protection and should be as effective as PCV13 against vaccine-type pneumococcal disease in adults.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: PP, KY, NC, XX, IS, DS, KJ, WG, and WW are employees of Pfizer and may hold stock or stock options. NK received research support from Pfizer for this study and research support from Pfizer, GSK, Merck, Sanofi Pasteur and Protein Science (now Sanofi Pasteur) for unrelated studies.

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Data sharing statement

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Author contributions

All authors attest they meet the ICMJE criteria for authorship. PP, NC, XX, IS, DS, KJ, WG, and WW contributed to study conception and design. XX contributed to statistical analysis. All authors participated in data analysis and/or interpretation and drafting the manuscript and/or revising it critically for intellectual content. All authors approved the final manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.07.004.

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