

# Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Infants in the United States

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**Background:** The development and widespread use of pneumococcal conjugate vaccines (PCVs) substantially reduced the global burden of pneumococcal disease. Expanding the serotypes covered by PCVs may further reduce disease burden. A 20-valent PCV (PCV20) has been developed to add coverage for 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F and 33F) to those in the existing 13-valent PCV (PCV13). This phase 2 study evaluated the safety, tolerability and immunogenicity of PCV20 in healthy US infants.

**Methods:** In this randomized, active-controlled, double-blind study, 460 infants were randomized 1:1 to receive a 4-dose series of either PCV20 or PCV13 at 2, 4, 6 and 12 months of age. Solicited local reactions and systemic events, adverse events (AEs) and serious AEs were recorded. Immunogenicity was assessed by measuring serotype-specific IgG concentrations and opsonophagocytic activity titers at 1 month after Dose 3, before Dose 4 and 1 month after Dose 4.

**Results:** Of 460 infants, 82.8% completed the 1-month visit after Dose 4. Local reactions and systemic events were mostly mild to moderate in sever-

ity and similar between the PCV20 and PCV13 groups. Treatment-related AEs were uncommon, with no related serious AEs or deaths reported. IgG and opsonophagocytic activity responses elicited by PCV20 were robust and demonstrated a booster response after Dose 4.

**Conclusions:** Administration of PCV20 in US infants was well tolerated, with a safety profile similar to PCV13, and induced robust serotype-specific immune responses. These findings support continued development of PCV20 in the pediatric population.

**Key Words:** infant, immunogenicity and safety, 20-valent pneumococcal conjugate vaccine, *Streptococcus pneumoniae*, clinical trial

(*Pediatr Infect Dis J* 2021;40:944–951)

Pneumococcal disease (PD), caused by *Streptococcus pneumoniae*, remains a substantial global public health threat that disproportionately affects children younger than 5 years.<sup>1,2</sup> PD can manifest as noninvasive disease, such as acute otitis media (AOM), sinusitis, nonbacteremic pneumonia or invasive PD (IPD), including bacteremic pneumonia, meningitis or septicemia.<sup>3</sup> More than 95 pneumococcal serotypes have been identified, each characterized by a unique polysaccharide capsule; however, the majority of disease is caused by a limited serotype subset.<sup>4,5</sup>

Development and widespread use of pneumococcal conjugate vaccines (PCVs) in pediatric vaccination programs substantially decreased the global burden of disease, with deaths in children ≤5 years of age estimated to have decreased by >50% from 2000 to 2015.<sup>2</sup> In the United States, the 7-valent PCV (PCV7; Prevnar 7; Pfizer Inc, New York, NY), which included capsular polysaccharide conjugates from serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, was introduced in 2000 and led to a 76% reduction in IPD among children <5 years of age.<sup>1</sup> IPD caused by certain non-PCV7 serotypes increased in incidence after PCV7 introduction. The 13-valent PCV (PCV13; Prevnar 13; Pfizer Inc) was introduced in 2010 to cover PCV7 capsular polysaccharide conjugates and 6 additional serotypes (1, 3, 5, 6A, 7F and 19A). The introduction of PCV7, followed by PCV13, led to a 93% decrease in overall IPD among children <5 years of age from 1998 to 2018<sup>6</sup> and substantially affected IPD among unvaccinated populations through the herd effect.<sup>1,7,8</sup> Both vaccines have also been associated with significant reductions in AOM and pneumonia.<sup>9–11</sup>

Despite the overall decrease in PD after widespread use of PCV, there is substantial remaining invasive and non-IPD in the post-PCV era attributed to non-PCV13 serotypes,<sup>12–14</sup> highlighting the need for further expanded valent PCVs to broaden protection against PD. The global PD burden remains considerable, with an estimated 44.7 million cases of pneumococcal lower respiratory tract infections and 341,029 associated deaths occurring in children <5 years of age in 2016.<sup>15</sup> To expand serotype coverage, a 20-valent PCV (PCV20) containing PCV13 components and 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) is in development. These serotypes were targeted based on several factors, including

Accepted for publication June 20, 2021

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ClinicalTrials.gov NCT03512288.

Supported by Pfizer Inc.

S.S. has received research support from Pfizer for the current study, as well as other research support from Pfizer. N.P.K. received research support from Pfizer for the current study, as well as other research support from Pfizer, Merck, GlaxoSmithKline, Sanofi Pasteur and Protein Science (now SP). E.L., A.T., J.D., J.T., Y.P., P.C.G., K.U.J., W.C.G., D.A.S. and W.W. are employees of Pfizer Inc and may hold stock or stock options.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website ([www.pidj.com](http://www.pidj.com))

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ISSN: 0891-3668/21/4010-0944

DOI: 10.1097/INF.00000000000003277

associations with increased disease severity, invasive potential, antibiotic resistance<sup>16–20</sup> and prevalence as a cause of pediatric PD across widespread geographic areas in the post-PCV era.<sup>12,13,21</sup> A meta-analysis has highlighted that these 7 serotypes are among the most prevalent serotypes causing pediatric IPD in countries with ongoing PCV programs: 22F (estimated 5.3% of cases), 12F (4.3%), 33F (4.5%), 15B (3.7%), 10A (3.4%), 8 (2.2%) and 11A (2.0%).<sup>12</sup> Surveillance data by the Centers for Disease Control and Prevention found that in 2018, these 7 serotypes alone accounted for an estimated 37% of IPD in US children <5 years of age.<sup>22</sup>

Phase 1 and 2 studies in adults 18–64 years of age found PCV20 induces robust immune responses and has a safety profile similar to PCV13.<sup>23,24</sup> PCV20 is now being assessed in phase 3 studies in the pediatric population. The current study represents the first evaluation of PCV20 safety and immunogenicity in infants preceding and supporting the pediatric phase 3 program.

## METHODS

### Study Design and Participants

This was a phase 2, multicenter, randomized, active-controlled, double-blind study with a 2-arm parallel design conducted in the United States from April 2018 to February 2020 (NCT03512288). Participants were randomized 1:1 to receive PCV20 or PCV13 at 2, 4, 6 and 12 months of age (Doses 1, 2, 3 and 4, respectively). A diphtheria, tetanus, acellular pertussis, hepatitis B and inactivated poliovirus combination vaccines [Pediarix (DTaP-HepB-IPV); GlaxoSmithKline, Brentford, United Kingdom] were administered concomitantly with the first 3 doses of PCV20 or PCV13. Other permitted vaccines included *Haemophilus influenzae* type B and rotavirus vaccines with the first 3 doses and the measles, mumps and rubella vaccine with Dose 4. Influenza vaccine could also be given with study vaccine in age-eligible participants during influenza season.

Eligible infants were healthy, born at >36 weeks gestation, 42–98 days of age at consent, expected to be available for the study duration and had a legal representative willing and able to comply with study procedures, including telephone contact. Key exclusion criteria included previous receipt of a pneumococcal vaccine; contraindication to vaccination with PCV13, diphtheria, tetanus or pertussis vaccines; history of IPD; neurologic disorder, history of seizure or other medical/psychiatric condition and known or suspected immunodeficiency or receipt of immunosuppressive therapy.

For each vaccination, participants received a single 0.5-mL intramuscular dose of PCV20 or PCV13 into the left anterolateral thigh. The PCV20 dose included capsular polysaccharides of all 20 pneumococcal serotypes (2.2 µg of each, except 4.4 µg of 6B) each individually conjugated to CRM<sub>197</sub>. The PCV13 supply was representative of licensed PCV13.

The study was conducted in accordance with legal and regulatory requirements, the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Conference on Harmonization Guideline for Good Clinical Practice and the Declaration of Helsinki. The study was approved by the institutional review board and/or independent ethics committee for each participating site. Written informed consent was required from each participant’s legal representative before participation in study procedures.

### Study Objectives and Endpoints

The primary objective was to describe PCV20 safety in study participants. Endpoints included percentages of participants experiencing prompted local reactions and systemic events within 7 days after each dose, adverse events (AEs) from Dose 1 to 1 month

after Dose 3 and from Dose 4 to 1 month after Dose 4 and serious AEs (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) from Dose 1 to 6 months after Dose 4. An electronic diary (filled out by each participant’s legal representative) was used to record the occurrence of local reactions (ie, redness, swelling, pain at the injection site) and systemic events (ie, fever, irritability, drowsiness, decreased appetite) occurring ≤7 days after each dose.

The secondary objective was to describe PCV20 immunogenicity in participants, as measured by pneumococcal serotype-specific IgG concentrations 1 month after Doses 3 and 4. The exploratory objectives were to further describe the immunogenicity of PCV20 in healthy infants and to describe the immune responses to concomitantly administered diphtheria and pertussis vaccine antigens. Exploratory endpoints included IgG concentrations before Dose 4, pneumococcal serotype-specific opsonophagocytic activity (OPA) titers 1 month after Dose 3 and before and 1 month after Dose 4 and diphtheria toxoid and pertussis antibody levels 1 month after Dose 3. Blood samples for immunogenicity assessments were collected 1 month after Dose 3, before Dose 4 (ie, at the 12-month visit) and 1 month after Dose 4. Immunogenicity measurements included serotype-specific IgG concentrations, determined using a Luminex-based multiplex direct immunoassay (dLIA) based on those previously described,<sup>25,26</sup> and OPA titers. To assess immune responses to diphtheria or pertussis antigens, concentrations of antibodies against diphtheria toxoid, pertussis toxoid, pertactin and filamentous hemagglutinin were determined in a randomly selected subset of participants 1 month after Dose 3.

### Analyses

The study planned to enroll approximately 460 participants; this study size was not based on formal statistical hypothesis testing for safety or immunogenicity endpoints. However, the planned sample size was based on previous clinical experience in similar phase studies in infants and the probability of observing at least 1

**TABLE 1. Demographic Characteristics of All Randomized Participants**

Characteristic	PCV20 (N* = 232)		PCV13 (N* = 228)	
	n†	%	n†	%
Sex				
Male	120	51.7	113	49.6
Female	112	48.3	115	50.4
Race‡				
White	161	69.4	171	75
Black	35	15.1	29	12.7
Asian	9	3.9	5	2.2
American Indian or Alaska Native	4	1.7	3	1.3
Native Hawaiian or other Pacific Islander	1	0.4	3	1.3
Multiracial	22	9.5	15	6.6
Not reported	0	0.0	2	0.9
Ethnicity				
Hispanic/Latino	41	17.7	40	17.5
Non-Hispanic/non-Latino	191	82.3	188	82.5
Age at Dose 1, d§				
Mean (SD)	64.5 (8.1)		64.5 (6.7)	
Median	64		64	
Minimum, maximum	44, 95		45, 89	

\*N = number of participants in the specified group.

†n = number of participants in the specified category.

‡Participants whose race is not in the listed categories are included in the “not reported” category.

§For participants randomized but not vaccinated, age is calculated using enrollment date instead of the date of Dose 1.

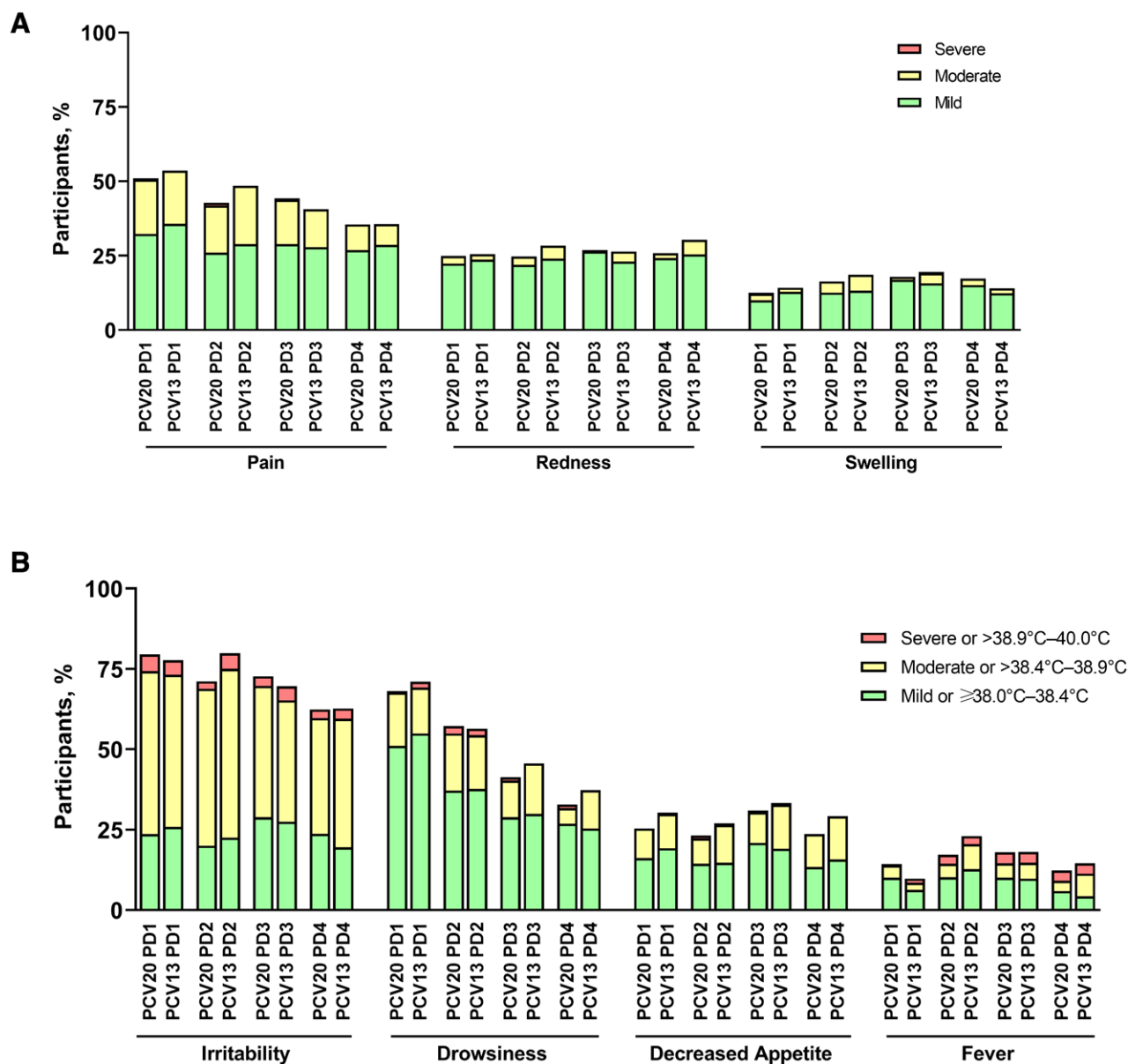
AE, local reaction or systemic event. All statistical analyses were descriptive.

Safety analyses included results from all participants who received  $\geq 1$  dose of PCV20 or PCV13 and had safety follow-up. For all safety endpoints, percentages of participants with the indicated endpoint were reported along with associated 95% CIs calculated by the Clopper–Pearson method.

The evaluable immunogenicity population was the primary population for immunogenicity analyses at each time point, which included eligible participants who were 42–98 days of age at Dose

1, received the randomized vaccine for all 3 doses (all 4 doses for Dose 4 results), had  $\geq 1$  valid IgG concentration from blood collected 27–56 days after Dose 3 (after Dose 4 for Dose 4 results) and had no other major protocol deviations as determined by the clinician. The evaluable immunogenicity population for Dose 4 results also required that participants received Dose 4 at 365–386 days of age.

Pneumococcal serotype-specific IgG geometric mean concentrations (GMCs) at each time point were evaluated along with associated 95% CIs, which were calculated by taking the mean



**FIGURE 1.** Percentages of participants with reported (A) local reactions and (B) systemic events after each dose. For Dose 1, PCV20,  $n = 229$ ; PCV13,  $n = 224$ . For Dose 2, PCV20,  $n = 215$ ; PCV13,  $n = 204$ . For Dose 3, PCV20,  $n = 201$ ; PCV13,  $n = 204$ . For Dose 4, PCV20,  $n = 186$ ; for PCV13,  $n = 185$ .  $n$  values refer to the number of participants with any electronic diary data reported after the specified dose. Severity was graded by the parents/legal guardians as instructed by the investigator staff (mild: Grade 1, moderate: Grade 2, severe: Grade 3). For redness and swelling, grading was based on size (mild,  $>0$  to  $2.0$  cm; moderate,  $>2.0$  to  $7.0$  cm; severe,  $>7$  cm) or description of the affected area. For pain and all systemic events, grading was based on degree to which the event interfered with activity. Fever was reported as a range of temperatures (mild,  $\geq 38.0$ – $38.4^{\circ}\text{C}$ ; moderate,  $>38.4$ – $38.9^{\circ}\text{C}$ ; severe,  $>38.9$ – $40.0^{\circ}\text{C}$ ).

and 95% CIs of log-transformed concentrations using a Student *t* distribution and exponentiating the results. Percentages of participants achieving prespecified IgG concentrations after Dose 3 were also evaluated along with 95% CIs calculated using the Clopper–Pearson method; these prespecified concentrations were defined based on serotype-specific threshold values previously determined by bridging analyses between the validated 13-plex dLIA and the World Health Organization reference enzyme-linked immunosorbent assay.<sup>26</sup> Geometric mean fold rises were summarized in a manner similar to GMCs. For evaluation of OPA titers, participants were randomly divided into 3 subsets, so that approximately 40–60 participants from each group could be evaluated in 20 individual OPA assays specific for each serotype. OPA geometric mean titers (GMTs) were summarized in a manner similar to IgG GMCs.

## RESULTS

### Study Population

A total of 460 infants were included in the study, with 232 randomized to PCV20 and 228 to PCV13 (Supplemental Digital Content 1, <http://links.lww.com/INF/E489>). Of these participants, 89.3% (411/460) and 82.8% (381/460) completed the 1-month visit after Doses 3 and 4, respectively; 85.9% (395/460) completed through the 6-month follow-up. Demographic characteristics of participants were similar in both groups (Table 1), with a racial distribution generally representative of the United States. The most common nonstudy vaccines included *Haemophilus influenzae* type B and rotavirus (with Doses 1, 2 and 3) and measles, mumps and rubella (with Dose 4).

### Safety

Reported rates of local reactions were similar between PCV20 and PCV13 groups after each dose (Fig. 1A), with a slight decrease in frequency and severity after subsequent doses. Local reactions lasted a median of 1.0–2.0 days after each dose and were largely mild or moderate; severe reactions were reported in  $\leq 0.9\%$  ( $n = 0-2$ ) of participants per group after each dose.

Similar percentages of participants across groups reported systemic events (Fig. 1B). Most systemic events were mild or moderate; severe systemic events occurred in  $\leq 4.9\%$  of participants after each dose. Fever  $>38.9^\circ\text{C}$  occurred in  $\leq 3.5\%$  of participants

after each dose, and no fevers  $>40.0^\circ\text{C}$  were reported. Individual systemic events lasted a median of 1.0–2.0 days.

The percentage of PCV20 and PCV13 recipients with AEs were generally similar, with most belonging to the infection and infestation system organ class (Table 2). Related AEs were uncommon, occurring in 7 PCV20 and 6 PCV13 recipients. Only 4 immediate AEs were reported in 3 subjects, all after infant doses in the PCV20 group (injection site hypersensitivity after Doses 2 and 3 in the same subject, contact dermatitis after Dose 1 in another subject and redness after Dose 3 in the third subject). Of note, injection site hypersensitivity was characterized by a red, flat rash that resolved on the same day. SAEs were reported in 5.2% of PCV20 and 2.2% of PCV13 recipients (Table 2). SAEs of respiratory syncytial virus infection or bronchiolitis were reported in 4 participants, all requiring hospitalization. No other SAEs were reported more than once (Supplemental Digital Content 2, <http://links.lww.com/INF/E489>). NDCMCs were reported in 5.2% and 3.5% of PCV20 and PCV13 recipients, respectively. No SAEs or NDCMCs were considered vaccine related. One participant was withdrawn from the study because of an unrelated SAE of failure to thrive. No deaths occurred during the study.

### Immunogenicity

#### Serotype-Specific IgG Concentrations

One month after Dose 3, IgG GMCs for the 13 matched serotypes were generally similar after PCV20 or PCV13, albeit modestly numerically lower in the PCV20 group (Table 3). Percentages of participants with prespecified IgG concentrations for the 13 serotypes were similar and numerically within  $<5\%$  across serotypes between the groups, except for serotype 3 (PCV20, 65.1%; PCV13, 75.4%) (Table 3). Of note, the empirical IgG reverse cumulative distribution curves (RCDCs) for the 13 matched serotypes 1 month after Dose 3, including serotype 3, showed similar distributions between the PCV20 and PCV13 groups (Supplemental Digital Content 3, <http://links.lww.com/INF/E489>). For the 7 additional PCV20 serotypes, IgG GMCs 1 month after Dose 3 were 0.86–5.86  $\mu\text{g}/\text{mL}$  in the PCV20 group and, as expected, were low ( $\leq 0.05 \mu\text{g}/\text{mL}$ ) in the PCV13 group (Table 4). High percentages of PCV20 recipients achieved prespecified IgG concentrations to the 7 serotypes; percentages were low ( $\leq 4.3\%$ ) in the PCV13 group (Table 4). RCDCs for the 7 additional serotypes 1 month after Dose 3 are shown in Supplemental Digital Content 4 (<http://links.lww.com/INF/E489>).

**TABLE 2.** Summary of AEs; Safety Population

Type of AE	PCV20			PCV13		
	n*	%	95% CI†	n*	%	95% CI†
Time Period						
Relationship to Treatment						
Any AE						
Dose 1 to 1 month after Dose 3‡	141	61.0	54.4–67.4	128	56.4	49.7–62.9
Related‡	5	2.2	0.7–5.0	3	1.3	0.3–3.8
Dose 4 to 1 month after Dose 4§	36	18.3	13.1–24.4	49	25.3	19.3–32.0
Related§	2	1.0	0.1–3.6	3	1.5	0.3–4.5
Immediate AE¶,**	4	1.9	0.0–3.4	0	0.0	0.0–1.8
SAE						
Dose 1 through 6 months after Dose 4‡	12	5.2	2.7–8.9	5	2.2	0.7–5.1
NDCMC						
Dose 1 through 6 months after Dose 4‡	12	5.2	2.7–8.9	8	3.5	1.5–6.8

\*n = number of participants reporting  $\geq 1$  occurrence of the specified event.

†Exact 95% CIs were calculated using the Clopper–Pearson method.

‡PCV20, n = 231; PCV13, n = 227, these values were used as denominators for the percentage calculations.

§PCV20, n = 197; PCV13, n = 194, these values were used as denominators for the percentage calculations.

¶Occurring within 30 minutes of vaccination. No immediate AEs were reported after Dose 4.

\*\*PCV20, n = 210; PCV13, n = 206, these values were used as denominators for the percentage calculations.

**TABLE 3. Immune Responses to 13 Matched Serotypes as Measured by Pneumococcal Serotype-Specific IgG GMCs, IgG GMFRs and OPA GMTs, Evaluable Immunogenicity Population**

Immune Measurement	Serotype													
	Group	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
Participants achieving prespecified IgG concentrations* 1 month after Dose 3, % (95% CI)†	PCV20	87.8	65.1	87.8	87.8	93.7	86.8	98.9	89.4	94.2	92.6	98.4	98.4	79.9
	(n† = 189)	(82.3-92.1)	(57.8-71.9)	(82.3-92.1)	(82.3-92.1)	(89.2-96.7)	(81.1-91.3)	(96.2-99.9)	(84.1-93.4)	(89.8-97.1)	(87.9-95.9)	(95.4-99.7)	(95.4-99.7)	(73.5-85.4)
	PCV13	87.7	75.4	91.4	89.8	92.5	90.4	97.9	89.3	95.7	95.2	97.9	96.8	81.8
(n† = 187)	(82.1-92.0)	(68.6-81.4)	(86.5-95.0)	(84.6-93.8)	(87.8-95.8)	(85.2-94.2)	(94.6-99.4)	(84.0-93.3)	(91.7-98.1)	(91.1-97.8)	(94.6-99.4)	(93.1-98.8)	(93.1-98.8)	(75.5-87.1)
IgG GMCs 1 month after Dose 3, % (95% CI)‡	PCV20	0.92	0.43	1.36	0.93	2.28	0.63	2.15	1.22	3.15	1.59	0.85	1.98	0.94
	(n† = 189)	(0.81-1.05)	(0.38-0.48)	(1.16-1.61)	(0.79-1.11)	(1.94-2.67)	(0.49-0.80)	(1.92-2.40)	(1.05-1.42)	(2.69-3.70)	(1.37-1.84)	(0.74-0.96)	(1.76-2.22)	(0.78-1.14)
	PCV13	1.16	0.56	1.64	1.13	2.57	0.99	2.59	1.45	3.6	2.05	1.02	2.28	1.26
(n† = 187)	(1.00-1.33)	(0.49-0.64)	(1.39-1.93)	(0.96-1.34)	(2.16-3.05)	(0.77-1.27)	(2.28-2.93)	(1.24-1.70)	(3.07-4.21)	(1.76-2.38)	(0.89-1.17)	(1.99-2.61)	(1.03-1.55)	
IgG GMCs before Dose 4, % (95% CI)§	PCV20	0.28	0.10	0.45	0.29	0.70	0.26	0.85	0.40	1.15	0.36	0.19	0.53	0.25
	(n† = 163)	(0.25-0.31)	(0.08-0.11)	(0.39-0.52)	(0.25-0.34)	(0.61-0.80)	(0.22-0.32)	(0.76-0.94)	(0.35-0.46)	(0.94-1.41)	(0.32-0.41)	(0.16-0.22)	(0.47-0.60)	(0.21-0.30)
	PCV13	0.37	0.14	0.62	0.43	0.93	0.43	1.11	0.54	1.85	0.51	0.24	0.65	0.42
(n† = 161)	(0.32-0.42)	(0.11-0.16)	(0.54-0.71)	(0.37-0.50)	(0.80-1.08)	(0.35-0.52)	(0.98-1.25)	(0.47-0.62)	(1.56-2.19)	(0.44-0.58)	(0.20-0.28)	(0.57-0.74)	(0.35-0.51)	
IgG GMCs 1 month after Dose 4, % (95% CI)¶	PCV20	2.65	1.15	7.16	3.41	13.77	6.37	6.14	5.52	8.61	5.58	5.71	7.79	6.06
	(n† = 168)	(2.33-3.02)	(0.97-1.35)	(6.22-8.24)	(2.95-3.93)	(12.16-15.59)	(5.42-7.50)	(5.51-6.83)	(4.82-6.31)	(7.32-10.12)	(4.89-6.36)	(4.91-6.64)	(6.73-9.01)	(5.16-7.12)
	PCV13	3.63	1.49	9.45	4.95	18.83	9.73	9.32	7.78	11.04	8.46	7.05	9.30	9.81
(n† = 166)	(3.20-4.11)	(1.28-1.74)	(8.16-10.95)	(4.29-5.71)	(16.39-21.63)	(8.13-11.65)	(8.26-10.52)	(6.77-8.95)	(9.44-12.90)	(7.25-9.88)	(6.04-8.24)	(7.99-10.83)	(8.10-11.88)	
IgG GMFRs from 1 month after Dose 3 to 1 month after Dose 4, % (95% CI)‡	PCV20	3.09	2.95	5.87	3.98	6.72	11.04	3.01	4.98	3.17	3.85	7.67	4.43	7.38
	(n† = 157)	(2.67-3.58)	(2.47-3.51)	(4.86-7.11)	(3.35-4.73)	(5.69-7.95)	(8.77-13.89)	(2.66-3.42)	(4.20-5.91)	(2.58-3.89)	(3.26-4.54)	(6.41-9.18)	(3.73-5.25)	(6.14-8.87)
	PCV13	3.10	2.67	5.44	4.09	7.10	9.22	3.46	5.16	3.06	3.99	6.65	4.09	7.52
(n† = 159)	(2.73-3.53)	(2.27-3.13)	(4.64-6.38)	(3.48-4.80)	(5.95-8.46)	(7.53-11.29)	(3.08-3.89)	(4.43-6.01)	(2.53-3.69)	(2.53-3.69)	(3.50-4.53)	(3.54-4.73)	(6.31-8.95)	
IgG GMFRs from before Dose 4 to 1 month after Dose 4, % (95% CI)§	PCV20	9.39	11.85	15.82	11.36	19.63	23.94	7.26	13.44	7.38	15.13	30.40	14.31	24.06
	(n† = 163)	(8.17-10.79)	(10.07-13.96)	(13.53-18.49)	(10.00-12.90)	(17.18-22.43)	(20.68-27.70)	(6.51-8.10)	(11.75-15.38)	(6.01-9.06)	(13.34-17.15)	(25.81-35.81)	(12.02-17.05)	(20.68-27.99)
	PCV13	9.70	10.88	15.38	11.69	20.60	22.91	8.34	14.57	5.91	16.57	29.95	14.13	23.22
(n† = 161)	(8.41-11.19)	(9.20-12.88)	(13.10-18.06)	(10.08-13.57)	(17.65-24.04)	(19.56-26.83)	(7.38-9.43)	(12.47-17.03)	(5.06-6.91)	(14.47-18.97)	(25.05-35.82)	(11.95-16.71)	(19.62-27.48)	
OPA GMTs 1 month after Dose 3, % (95% CI)¶	PCV20	16.3	50.2	424.5	32.4	817.0	432.6	1480.4	522.4	606.9	1218.6	105.3	90.9	234.1
	(n† = 47-53)	(12.8-20.8)	(39.0-64.6)	(296.2-608.2)	(25.1-41.7)	(590.3-1130.7)	(287.0-652.2)	(1155.5-1896.6)	(359.1-759.8)	(400.9-918.7)	(948.2-1566.2)	(73.2-151.4)	(66.2-124.8)	(158.0-346.7)
	PCV13	31.3	61.8	390.3	45.2	866.8	668.8	1390.7	601.4	456.9	1491.7	157.2	121.2	268.2
(n† = 53-57)	(22.8-43.0)	(50.1-76.2)	(239.5-636.0)	(35.9-57.0)	(690.3-1088.6)	(474.8-942.2)	(1040.6-1858.4)	(400.6-902.7)	(310.0-673.4)	(1070.7-2078.2)	(105.1-235.3)	(91.3-160.9)	(157.0-458.3)	
OPA GMTs 1 month after Dose 4, % (95% CI)¶	PCV20	50.4	93.0	490.3	78.7	1671.4	1354.9	2590.7	1280.2	933.8	2016.2	651.3	500.5	693.1
	(n† = 42-49)	(35.4-71.9)	(73.1-118.4)	(310.6-774.0)	(59.3-104.5)	(1181.4-2364.5)	(987.1-1859.8)	(2143.2-3131.7)	(981.6-1669.7)	(715.8-1218.1)	(1596.5-2546.1)	(519.9-816.0)	(337.2-743.0)	(519.9-923.8)
	PCV13	92.9	109.3	662.5	112.8	2155.8	1808.1	3280.7	2030.0	1127.9	2703.3	874.8	751.0	1253.9
(n† = 48-51)	(65.9-131.1)	(92.4-129.2)	(415.3-1056.9)	(85.6-148.6)	(1716.2-2708.1)	(1269.4-2575.4)	(2576.5-4177.5)	(1469.6-2804.3)	(831.5-1530.0)	(1980.4-3690.0)	(650.6-1176.4)	(546.6-1032.0)	(894.6-1757.6)	

\*Prespecified concentrations were  $\geq 0.23$   $\mu\text{g/mL}$  for serotype 5,  $\geq 0.10$   $\mu\text{g/mL}$  for serotype 6B,  $\geq 0.12$   $\mu\text{g/mL}$  for serotype 19A and  $\geq 0.35$   $\mu\text{g/mL}$  for all other serotypes.

†Number of participants with valid and determinate assay results for the given serotype at the specified time point(s).

‡Two-sided CIs were calculated based on the Clopper-Pearson method.

§Two-sided CIs were calculated based on the Student *t* distribution.

¶GMFR indicates geometric mean fold rise; LLOQ, lower limit of quantitation.

Assay results below the LLOQ were set to  $0.5 \times$  LLOQ in the analyses. For GMFRs, the analysis included data from participants with serology results available from both time points.

**TABLE 4. Immune Responses to 7 Additional Serotypes in PCV20 as Measured by Pneumococcal Serotype-Specific IgG GMCs, IgG GMFRs and OPA GMTs; Evaluable Immunogenicity Population**

Immune Measurement	Group	Serotype						
		8	10A	11A	12F	15B	22F	33F
Participants achieving prespecified IgG concentration* 1 month after Dose 3, % (95% CI)†	PCV20 (n† = 189) PCV13 (n† = 187)	99.5 (97.1–100.0) 3.7 (1.5–7.6)	87.8 (82.3–92.1) 1.1 (0.1–3.8)	97.4 (93.9–99.1) 1.6 (0.3–4.6)	82.5 (76.4–87.7) 0.5 (0.0–2.9)	98.9 (96.2–99.9) 4.3 (1.9–8.3)	98.9 (96.2–99.9) 1.1 (0.1–3.8)	92.1 (87.2–95.5) 1.6 (0.3–4.6)
IgG GMCs 1 month after Dose 3, % (95% CI)†	PCV20 (n† = 189)	2.09 (1.90–2.30)	1.67 (1.35–2.08)	1.94 (1.70–2.21)	0.86 (0.72–1.01)	5.86 (5.11–6.72)	4.62 (3.99–5.35)	2.21 (1.87–2.61)
IgG GMCs 1 month after Dose 3, % (95% CI)‡	PCV13 (n† = 187)	0.04 (0.03–0.04)	0.03 (0.03–0.03)	0.01 (0.01–0.01)	0.02 (0.02–0.02)	0.04 (0.04–0.05)	0.01 (0.01–0.01)	0.05 (0.04–0.05)
IgG GMCs before Dose 4, % (95% CI)‡	PCV20 (n† = 163)	0.41 (0.37–0.46)	1.11 (0.95–1.31)	0.49 (0.42–0.58)	0.20 (0.17–0.22)	2.07 (1.78–2.41)	1.70 (1.47–1.97)	0.84 (0.74–0.94)
IgG GMCs 1 month after Dose 4, % (95% CI)‡	PCV13 (n† = 161)	0.04 (0.04–0.05)	0.03 (0.03–0.04)	0.01 (0.01–0.02)	0.02 (0.02–0.03)	0.03 (0.03–0.04)	0.01 (0.01–0.01)	0.04 (0.04–0.05)
IgG GMCs from 1 month after Dose 3 to 1 month after Dose 4, % (95% CI)§	PCV20 (n† = 168)	3.12 (2.78–3.49)	9.93 (8.58–11.50)	5.70 (4.96–6.54)	1.92 (1.68–2.20)	18.45 (16.43–20.72)	14.68 (12.62–17.08)	4.70 (4.20–5.27)
IgG GMFRs from 1 month after Dose 3 to 1 month after Dose 4, % (95% CI)§	PCV13 (n† = 166)	0.05 (0.04–0.06)	0.03 (0.03–0.04)	0.01 (0.01–0.02)	0.02 (0.02–0.03)	0.04 (0.04–0.05)	0.01 (0.01–0.01)	0.05 (0.04–0.05)
IgG GMFRs from 1 month after Dose 3 to 1 month after Dose 4, % (95% CI)§	PCV20 (n† = 157)	1.55 (1.35–1.78)	6.50 (5.21–8.12)	3.16 (2.71–3.67)	2.51 (2.10–3.01)	3.49 (3.00–4.05)	3.42 (2.96–3.95)	2.30 (1.91–2.77)
IgG GMFRs from before Dose 4 to 1 month after Dose 4, % (95% CI)§	PCV13 (n† = 159)	1.29 (1.08–1.55)	1.11 (0.98–1.26)	1.34 (1.04–1.73)	1.22 (1.11–1.36)	1.12 (0.95–1.31)	1.12 (0.90–1.39)	0.97 (0.84–1.13)
IgG GMFRs from before Dose 4 to 1 month after Dose 4, % (95% CI)§	PCV20 (n† = 163)	7.38 (6.48–8.41)	8.86 (7.65–10.27)	11.58 (9.79–13.69)	9.70 (8.59–10.95)	8.81 (7.52–10.32)	8.61 (7.47–9.93)	5.59 (4.98–6.28)
OPA GMTs 1 month after Dose 3, % (95% CI)§	PCV13 (n† = 161)	1.22 (1.09–1.36)	1.03 (0.96–1.11)	1.20 (1.05–1.36)	1.02 (0.96–1.09)	1.30 (1.18–1.44)	1.23 (1.09–1.38)	1.03 (0.96–1.10)
OPA GMTs 1 month after Dose 3, % (95% CI)§	PCV20 (n† = 53–61)	475.5 (346.6–652.2)	1846.7 (1347.6–2530.5)	423.9 (287.0–626.3)	6084.9 (4578.8–8086.4)	1085.8 (702.9–1677.4)	6304.0 (4430.3–8970.1)	7266.5 (4855.4–10,875.1)
OPA GMTs 1 month after Dose 4, % (95% CI)§	PCV13 (n† = 52–59)	17.3 (15.2–19.8)	36.8 (31.6–42.8)	19.9 (14.6–27.2)	26.5 (22.7–30.9)	22.8 (17.4–29.9)	11.1 (8.6–14.1)	60.7 (39.5–93.3)
OPA GMTs 1 month after Dose 4, % (95% CI)§	PCV20 (n† = 56–59)	1721.7 (1298.7–2282.6)	2697.7 (2082.3–3494.8)	5307.7 (4007.3–7030.2)	8518.9 (6030.5–12,034.1)	3087.9 (2304.5–4137.6)	9339.2 (6575.3–13,265.0)	8244.6 (5797.7–11,724.2)
	PCV13 (n† = 37–50)	35.2 (23.2–53.3)	63.1 (43.2–92.3)	76.7 (33.6–175.2)	27.8 (22.6–34.1)	28.2 (19.1–41.7)	16.5 (11.0–24.9)	135.6 (77.7–236.5)

\*Prespecified concentration was  $\geq 0.35$  µg/mL for all of the 7 additional PCV20 serotypes.

†Number of participants with valid and determinate assay results for the given serotype at the specified time point(s).

‡Two-sided CIs were calculated based on the Clopper–Pearson method.

§Two-sided CIs were calculated based on the Student *t* distribution.

GMFR indicates geometric mean fold rise; LLOQ, lower limit of quantification.

Assay results below the LLOQ were set to 0.5 × LLOQ in the analyses. For GMFRs, the analysis included data from participants with serology results available from both time points.

One month after Dose 4 of PCV20 or PCV13, IgG GMCs for the 13 matched serotypes were generally similar across groups (Table 3). The IgG GMCs were numerically lower in the PCV20 group, but robust boosting was observed at 1 month after Dose 4, compared with 1 month after Dose 3 and before Dose 4. For the 7 additional serotypes, IgG GMCs 1 month after Dose 4 ranged from 1.92 to 18.45  $\mu\text{g}/\text{mL}$  in the PCV20 group and remained low ( $\leq 0.05$   $\mu\text{g}/\text{mL}$ ) in the PCV13 group (Table 4). A boosting of IgG GMCs 1 month after Dose 4 for the 7 additional PCV20 serotypes was observed only in the PCV20 group (Table 4).

### Serotype-Specific OPA Titers

OPA titers were determined in a subset of participants for each serotype to confirm functional activity of PCV20-elicited immune responses. One month after Dose 3 and 1 month after Dose 4, OPA GMTs for the 13 matched serotypes were largely similar across groups (Table 3) (Supplemental Digital Content 5A, <http://links.lww.com/INF/E489>). Boosting of OPA GMTs for the 13 matched serotypes was observed after Dose 4. For the 7 additional serotypes, GMTs were high in the PCV20 group after Dose 3 and generally increased further after Dose 4 but remained low in the PCV13 group relative to the PCV20 group (Table 4) (Supplemental Digital Content 5B, <http://links.lww.com/INF/E489>).

### Immune Responses to Concomitant Vaccines

At 1 month after Dose 3, 100% and 96.9% of participants in the PCV20 and PCV13 groups, respectively, achieved prespecified antibody concentrations for diphtheria ( $\geq 0.1$   $\mu\text{IU}/\text{mL}$ ). GMCs of antibodies to the pertussis antigens (pertussis toxoid, filamentous hemagglutinin, pertactin) ranged from 70.64 to 109.28  $\mu\text{g}/\text{mL}$  in the PCV20 group and 67.12 to 102.48  $\mu\text{g}/\text{mL}$  in the PCV13 group.

## DISCUSSION

In this phase 2 study, the investigational PCV20 was safe and well tolerated when administered to healthy infants at 2, 4, 6 and 12 months of age. Serotype-specific immune responses elicited by PCV20 were robust, functional and demonstrated a strong booster response.

The safety and tolerability profile of PCV20 was consistent with that of PCV13. Local reactions and systemic events were mostly mild or moderate and transient and did not increase in frequency with subsequent doses. AEs were reported at similar frequencies across groups and reflected common medical events or conditions for this age group. Most reported AEs considered related to vaccination overlapped with solicited local reactions and systemic events; there were no SAEs or NDCMCs related to vaccination.

Robust immune responses to all 20 vaccine serotypes were induced after 3 infant doses of PCV20, as measured by serotype-specific IgG GMCs and percentages of participants with prespecified IgG concentrations 1 month after Dose 3. Of note, although prespecified IgG concentrations for serotype 3 were modestly lower in the PCV20 group, RDCs indicate performance of PCV20 is likely similar to that of PCV13. Dose 4, administered at 12 months of age, induced strong boosting responses to all serotypes. Functional immune responses as measured by OPA showed similar patterns to IgG responses. Immune responses to diphtheria and pertussis antigens coadministered with PCV20 or PCV13 were similar between groups.

Widespread PCV7 and PCV13 use has markedly reduced the global burden of PD.<sup>2</sup> However, nonvaccine serotypes continue to be associated with the large remaining disease burden,<sup>12,13,21</sup> necessitating development of higher valent PCVs to provide protection against these serotypes. Recent estimates indicate that the

additional serotypes in PCV20 are responsible for substantial disease burden in US children  $< 5$  years of age.<sup>27</sup> Based on CDC Active Bacterial Core surveillance, theoretical coverage of IPD during 2017 in children  $< 5$  years of age was 25.0% by PCV13, whereas PCV20 could theoretically cover 58.1% of cases.<sup>27</sup> Extrapolating from these data, the current annual burden of disease (ie, IPD, pneumonia and AOM) because of the 7 additional serotypes is estimated to be 700,000 cases and 69 deaths in US children  $< 5$  years of age, representing \$445 million in direct costs.<sup>27</sup> Use of PCVs in pediatric vaccination programs also has the potential to provide a level of herd protection<sup>7</sup> for unvaccinated populations and may have some indirect impact on the estimated 9900 cases of IPD, 97,000 cases of pneumonia and 4300 deaths and associated costs, because of the 7 additional serotypes in US adults ( $\geq 18$  years of age) annually.<sup>28</sup> Therefore, the potential benefits of PCV20 are considerable.

This study was strengthened by its randomized design and inclusion of an active comparator control group. The racial distribution was generally similar between groups and generally reflective of the US population, and there were roughly equal percentages of male and female participants in both groups. The study size was not based on formal statistical hypothesis testing for safety or immunogenicity endpoints. This study was not designed to provide statistical noninferiority comparisons between the PCV20 and PCV13 groups. A similarly designed study with a much larger sample size to support these comparisons is typically conducted in phase 3.

Findings of this study supported the breakthrough therapy designation granted for the PCV20 pediatric indication by the US Food and Drug Administration in 2020<sup>29</sup> in recognition of its potential to be a substantial improvement over currently available therapies for prevention of serious disease. The phase 3 program will further evaluate the safety and immunogenicity of PCV20 in infant and other pediatric populations.

In conclusion, safety and tolerability of a 4-dose series of PCV20 were similar to those of the licensed and widely used PCV13. PCV20 elicited robust IgG responses against all 20 vaccine serotypes and demonstrated functional immune responses as measured by OPA, whereas immune responses directed against the 7 non-PCV13 serotypes remained low among PCV13 recipients. These findings suggest that PCV20 may expand protection against PD and support further clinical development of the vaccine for the pediatric population.

## ACKNOWLEDGMENTS

The authors thank Lindsey Kirkland, PhD, and Philippa Jack, PhD, of ICON plc (North Wales, PA) who provided editorial/medical writing support that was funded by Pfizer Inc.

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