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Phase 3 Safety and Immunogenicity Study of a Three-dose Series of Twenty-valent Pneumococcal Conjugate Vaccine in Healthy Infants and Toddlers

Piotr Korbal, MD, PhD, Jacek Wysocki, MD, PhD,† Teresa Jackowska, MD, PhD,‡ Mary Kline, MD,§ Noor Tamimi, MD,§ Jelena Drozd, MS,§ Lanyu Lei, PhD,§ Yahong Peng, PhD,§ Peter C. Giardina, PhD,¶ William Gruber, MD,¶ Daniel Scott, MD,§ and Wendy Watson, MD§*

Background: Global pediatric immunization programs with pneumococcal conjugate vaccines (PCVs) have reduced vaccine-type pneumococcal disease, but a substantial disease burden of non-PCV serotypes remains.

Methods: This phase 3, randomized (1:1), double-blind study evaluated safety and immunogenicity of 20-valent PCV (PCV20) relative to 13-valent PCV (PCV13) in healthy infants. Participants received 2 infant doses and a toddler dose of PCV20 or PCV13, with diphtheria-tetanus-acellular pertussis combination vaccine at all doses and measles, mumps, rubella and varicella vaccines at the toddler dose. Primary pneumococcal immunogenicity objectives were to demonstrate noninferiority (NI) of PCV20 to PCV13 for immunoglobulin G geometric mean concentrations after infant and toddler doses and percentages of participants with predefined serotype-specific immunoglobulin G concentrations after infant doses. Safety endpoints included local reactions, systemic events and adverse events.

Results: Overall, 1204 participants were vaccinated (PCV20, n = 601; PCV13, n = 603). One month after the toddler dose, 19/20 serotypes met NI for immunoglobulin G geometric mean concentrations; serotype 6B narrowly missed NI [PCV20/PCV13 geometric mean ratio: 0.57 (2-sided 95% confidence interval: 0.48–0.67); NI criterion: lower 2-sided 95% confidence interval >0.5]. Sixteen/twenty serotypes met NI for ≥1 primary objective after 2 infant doses. PCV20 induced robust opsonophagocytic activity, and boosting responses were observed for all vaccine serotypes, including those missing statistical NI. The safety/tolerability profile of PCV20 was like that of PCV13.

Conclusions: PCV20 3-dose series in infants was safe and elicited robust immune responses. Based on these results and PCV13 experience, PCV20 3-dose series is expected to be protective for all 20 vaccine serotypes. NCT04546425.

Key Words: 3-dose series, 20-valent pneumococcal conjugate vaccine, immunogenicity, infants, safety

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Streptococcus pneumoniae can lead to acute otitis media, bacteremia, bacterial meningitis and pneumonia[1–3] and is a leading global cause of morbidity and mortality in <5-year-old children.[4] The first widely introduced pneumococcal conjugate vaccine (PCV) was the 7-valent PCV (PCV7; with conjugates for serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F), which was licensed in the US (2000) and Europe (2001)[5,6] and subsequently incorporated into national immunization programs globally. The 13-valent PCV (PCV13; additional conjugates for serotypes 1, 3, 5, 6A, 7F and 19A) replaced PCV7 from 2009.[5] Substantial reductions in vaccine-type pneumococcal disease have been observed globally[7–10]; however, a significant disease burden associated with non-PCV serotypes remains.[4,10–13]

A 20-valent PCV (PCV20) containing PCV13 components and conjugates for 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) is licensed in several countries for pneumococcal pneumonia and invasive pneumococcal disease (IPD) prevention among adults, for pediatric use in United States and Canada and under review in other countries.[14–16] These 7 serotypes are associated with relatively increased disease severity, invasive potential and antibiotic resistance[17–21] and are a prevalent cause of pediatric pneumococcal disease.[11,12,22,23] PCV20 induced robust immune responses and demonstrated a safety/tolerability profile similar to PCV13 in several adult and pediatric clinical trials.[24–32] This study assessed safety and immunogenicity of a 3-dose PCV20 series compared with PCV13.

METHODS

Study Design and Participants

This phase 3, randomized, double-blind study (NCT04546425) was conducted in Europe and Australia (2 participants only). A small population of Russian infants (n = 51) was added late in the study to gather country-specific safety and immunogenicity data and is not included in this analysis.

Healthy infants 42−112 days of age at time of consent and born >36 weeks of gestation were enrolled. Infants with significant neurological disorder or seizure history, known or suspected immunodeficiency or history of severe adverse reaction to a vaccine and/or severe allergic reaction to any investigational product component or

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*From the IN-VIVO, Bydgoszcz, Poland; †Poznań University of Medical Sciences, Poznań, Poland; ‡Department of Pediatrics, Center of Postgraduate Medical Education, Warsaw, Poland; §Vaccine Research and Development, Pfizer Inc, Collegeville, Pennsylvania; and ¶Vaccine Research and Development, Pfizer Inc, Pearl River, New York.

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P.K., J.W. and T.J. are involved in clinical trials for Pfizer. J.W. is also involved in clinical trials for GSK and Sanofi Pasteur and provides lectures and serves on advisory boards for Pfizer, GSK, Sanofi Pasteur, MSD and AstraZeneca. T.J. is also involved in clinical trials for MSD. All other authors are current or previous Pfizer employees and may hold stock or stock options.

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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Address for correspondence: Mary Kline, MD, Vaccine Research and Development, Pfizer Inc, 500 Arcola Rd, Collegeville, PA 19426. E-mail: Mary.Kline@pfizer.com.

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any diphtheria toxoid-containing vaccine were excluded. Text, Supplemental Digital Content 1, http://links.lww.com/INF/F457 includes key eligibility criteria and additional methodology.

Participants were randomized 1:1 to receive PCV20 or PCV13: dose 1 at enrollment, dose 2 approximately 8 weeks later and dose 3 (toddler dose) at 11–12 months of age (Figure, Supplemental Digital Content 2, http://links.lww.com/INF/F458). Diphtheria-tetanus-acellular pertussis-hepB-polio-*Haemophilus influenzae* type b combination vaccine (Infanrix Hexa, GSK Vaccines GmbH, Marburg, Germany) was administered with each dose. Measles, mumps, rubella (MMRVaxPro, Merck Sharp & Dohme, West Point, PA) and varicella vaccines (Varilrix, GlaxoSmithKline, Brentford, United Kingdom) were administered with dose 3, except where local guidelines made this impractical. Rotavirus and influenza vaccine administration was permitted during the study according to local guidelines.

Assessments and Objectives

Immune responses for serotype-specific immunoglobulin G (IgG) concentrations were measured using a Luminex immunoassay[33] on sera collected 1 month after dose 2 and before and 1 month after dose 3. IgG concentrations were also measured at certain sites if parents/guardians consented to optional blood draws before doses 1 and 2 for exploratory purposes. Opsonophagocytic activity (OPA) titers were measured by Pfizer OPA assay[34,35] in randomly selected subsets after dose 2 and before and after dose 3. Immune responses to specified concomitant vaccine antigens were measured in randomly selected subsets.

Primary immunogenicity objectives were to demonstrate noninferiority (NI) of PCV20 to PCV13 for IgG geometric mean concentrations (GMCs) 1 month after doses 2 and 3 and percentages of participants with predefined serotype-specific IgG concentrations 1 month after dose 2. For the 13 matched serotypes, the PCV20 group was compared with the corresponding serotypes in the PCV13 group. For the 7 additional serotypes, the PCV20 group was compared with the lowest result among the 13 serotypes in the PCV13 group (excluding serotype 3 because of its atypical immunogenicity). Predefined IgG concentrations were ≥0.35 μg/mL, except for serotypes 5 (≥0.23 μg/mL), 6B (≥0.10 μg/mL) and 19A (≥0.12 μg/mL), based on the Luminex assay bridging to the World Health Organization (WHO) pneumococcal enzyme-linked immunosorbent assay.[36]

Secondary immunogenicity endpoints included differences in percentages of participants with predefined IgG concentrations between the PCV20 and PCV13 groups 1 month after dose 3, description of OPA geometric mean titers (GMTs) and geometric mean fold rises in IgG concentrations. Percentages of participants with OPA titers greater than lower limit of quantitation (LLOQ) were an exploratory endpoint.

A primary objective for concomitant immunogenicity was to demonstrate NI (PCV20 to PCV13) of immune responses to protocol-specified concomitant vaccine antigens 1 month after dose 3; these results will be published separately.

Safety objectives were to describe percentages of participants with local reactions (redness, swelling, injection site pain) and systemic events (fever, drowsiness, decreased appetite, irritability) within 7 days after each dose, adverse events (AEs), serious AEs (SAEs) and newly diagnosed chronic medical conditions (NDCMCs). AEs were collected from dose 1 to 1 month after dose 2 and from dose 3 to 1 month after dose 3 (see visit windows: Figure, Supplemental Digital Content 2, http://links.lww.com/INF/F458). SAEs and NDCMCs were collected throughout the study.

Statistical Analyses

Immunogenicity analyses were based on evaluable immunogenicity sets of eligible participants who were within the dose 1 and dose 3 protocol-defined age windows, received 2 or 3 doses of vaccine as randomized, had ≥1 valid immunogenicity result from blood collected within a prespecified window 1 month after dose 2 or 3 and had no other major protocol deviations.

IgG GMCs, GMC ratios and geometric mean fold rises were calculated by exponentiating the mean logarithm of IgG concentrations, concentration differences and fold rises in IgG concentrations, respectively, with associated confidence intervals (CIs) calculated based on Student *t* distributions.

NI of PCV20 to PCV13 for IgG GMCs was declared for a serotype if the lower bound of the 2-sided 95% CI for the IgG geometric mean ratio of the PCV20 group to the PCV13 control was >0.5 (2-fold NI margin). For percentages of participants with predefined IgG concentrations, NI of PCV20 to PCV13 was declared if the lower bound of the 2-sided 95% CI for the difference (PCV20 group − PCV13 group) in percentages, computed using the Miettinen and Nurminen method, was above −10% (10% NI margin). Descriptive summary statistics were provided for safety endpoints in the safety population (participants receiving ≥1 study vaccine dose with safety follow-up after any dose).

RESULTS

Participants

From September 9, 2020 to April 22, 2022, 1207 participants were randomized; 97.9% (n = 1182) received all 3 study vaccine doses. Participant disposition was similar between PCV20 and PCV13 groups (Figure, Supplemental Digital Content 3, http://links.lww.com/INF/F459). Demographic characteristics were generally similar in both groups (Table, Supplemental Digital Content 4, http://links.lww.com/INF/F460). Most participants were White (97.8%) and non-Hispanic/non-Latino (96.6%); median (range) age was 68 (43–112) days at dose 1 and 371 (335–468) days at dose 3.

Immunogenicity

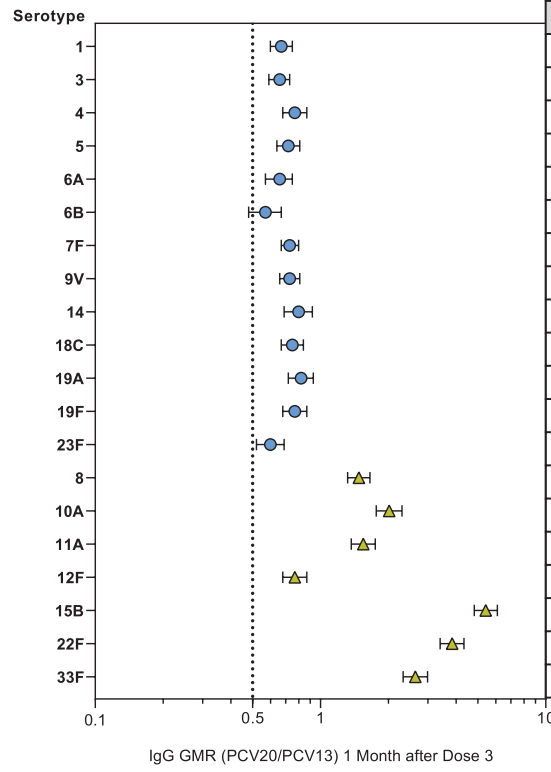
One month after dose 3, 19/20 vaccine serotypes met the statistical NI criterion for the primary immunogenicity objective comparing IgG GMCs after PCV20 with those after PCV13 (Fig. 1A). Serotype 6B missed the criterion by a small margin [PCV20/PCV13 geometric mean ratio: 0.57; 95% CI: 0.48−0.67 (2-fold NI criterion: lower bound of CI >0.5)].

One month after dose 2, 16/20 vaccine serotypes met NI criteria for ≥1 of 2 primary immunogenicity objectives at this time point (Figs. 1B and 2). Of the matched serotypes, 6A, 6B, 9V and 23F missed NI criteria for both objectives 1 month after dose 2. Two of the 7 additional serotypes (10A, 12F) missed the statistical NI criterion only for the primary objective of percentage of participants with predefined IgG concentrations after dose 2 compared with the lowest result among the 13 matched serotypes in the PCV13 group. Responses to the 7 additional serotypes in the PCV20 group were substantially higher compared with corresponding serotypes in the PCV13 group after doses 2 and 3 (Fig. 1).

For the 13 matched serotypes, reverse cumulative distribution curves for IgG concentration were generally similar between vaccine groups after doses 2 and 3, and well-differentiated and substantially higher for PCV20 than PCV13 for the additional 7 serotypes (Figure, Supplemental Digital Content 5, http://links.lww.com/INF/F461).

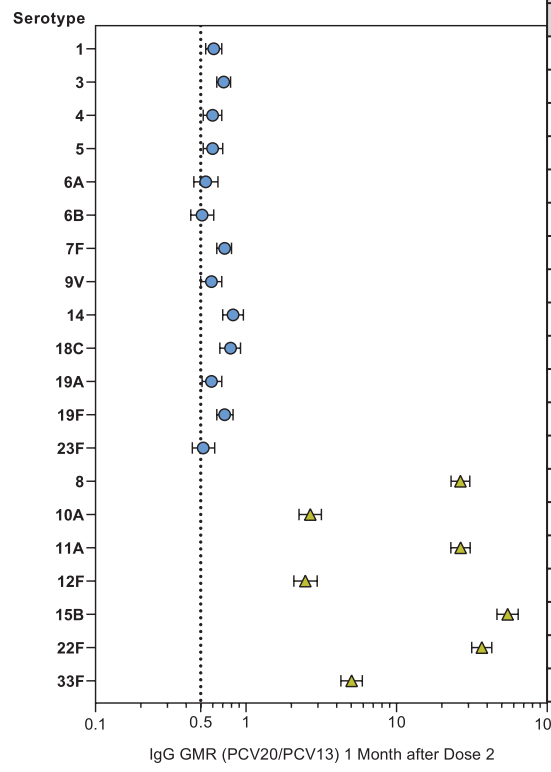
Secondary and exploratory objectives provided additional support for serotypes missing statistical NI criteria for primary objectives. One month after dose 3, ≥96.4% of participants had IgG concentrations greater than predefined levels to all serotypes except serotype 3 (82.6%; Figure, Supplemental Digital Content 6, http://links.lww.com/INF/F462). The PCV20 group had substantial

A



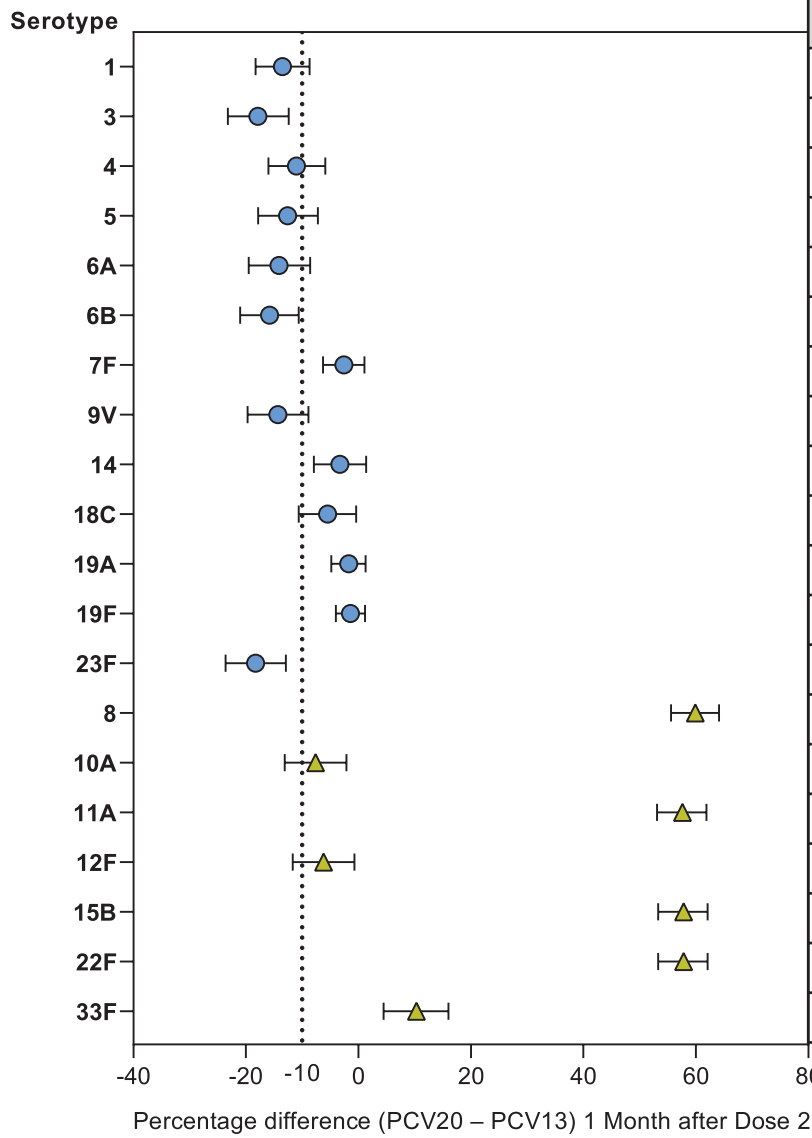
	PCV20		PCV13	
	N	GMC	N	GMC
1	494	1.71	502	2.53
3	494	0.72	502	1.09
4	494	4.11	502	5.36
5	494	1.74	502	2.41†
6A	494	7.75	501	11.82
6B	494	2.64	501	4.63
7F	494	3.61	502	4.93
9V	494	3.68	502	5.04
14	493	4.52	501	5.66
18C	494	2.71	502	3.61
19A	494	4.51	502	5.49
19F	494	6.19	502	8.08
23F	494	2.64	502	4.40
8	495	3.57	501	0.03*
10A	495	4.86	502	0.01*
11A	495	3.74	502	0.02*
12F	495	1.86	502	0.01*
15B	495	13.09	502	0.02*
22F	495	9.27	502	0.00*
33F	495	6.37	501	0.01*

B



	PCV20		PCV13	
	N	GMC	N	GMC
1	566	0.57	562	0.93
3	566	0.41	562	0.58
4	566	0.55	562	0.92
5	566	0.34	562	0.56
6A	566	0.45	562	0.84
6B	564	0.03	561	0.06†
7F	566	1.02	562	1.41
9V	566	0.45	562	0.77
14	565	1.05	562	1.28
18C	566	0.69	562	0.87
19A	566	0.67	562	1.13
19F	566	2.21	562	3.06
23F	566	0.13	562	0.25
8	567	1.62	561	0.02*
10A	567	0.16	562	0.02*
11A	567	1.62	562	0.02*
12F	567	0.15	562	0.01*
15B	566	3.33	562	0.04*
22F	567	2.25	562	0.01*
33F	566	0.31	562	0.03*

FIGURE 1. IgG GMRs (PCV20/PCV13) and 2-sided 95% CIs 1 month after dose 3 (A) and 1 month after dose 2 (B). Assay results below LLOQ were set to 0.5 × LLOQ. For the PCV13 serotypes (circles), the compared results are from the corresponding serotype in the PCV13 group. †For the 7 additional serotypes (triangles), in (A), the compared results are from serotype 5 (the PCV13 serotype with the lowest GMC, not including serotype 3) in the PCV13 group, and in (B), the compared results are from serotype 6B (the PCV13 serotype with the lowest GMC) in the PCV13 group. *In the tables, actual values are shown for the PCV13 group for the 7 additional serotypes. Results are for the dose 3 and dose 2 evaluable immunogenicity populations for (A) and (B), respectively. GMR indicates geometric mean ratio. full color online

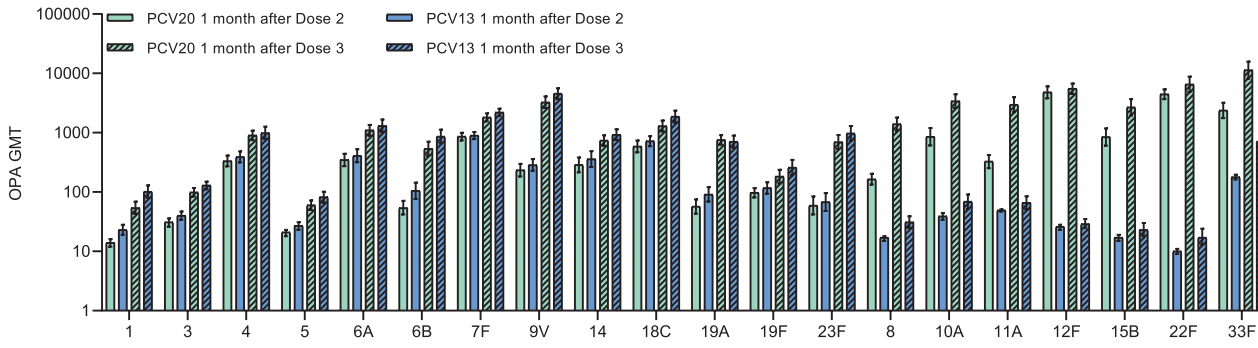


PCV20		PCV13	
N	%	N	%
566	70.7	562	84.2
566	58.0	562	75.8
566	68.6	562	79.5
566	63.4	562	76.0
566	59.5	562	73.7
564	20.7	561	36.5†
566	87.6	562	90.2
566	60.2	562	74.6
565	78.6	562	81.9
566	71.0	562	76.5
566	92.2	562	94.0
566	94.3	562	95.7
566	23.5	562	41.8
567	96.5	561	2.9*
567	28.9	562	2.7*
567	94.2	562	2.0*
567	30.3	562	0.2*
566	94.3	562	8.5*
567	94.4	562	2.0*
566	46.8	562	2.7*

FIGURE 2. Differences (PCV20 – PCV13) with 2-sided 95% CIs in percentages of participants with predefined pneumococcal IgG levels 1 month after dose 2. The predefined pneumococcal IgG level for all serotypes is ≥0.35 µg/mL, except for the following: 5 (≥0.23 µg/mL), 6B (≥0.10 µg/mL) and 19A (≥0.12 µg/mL). For the PCV13 serotypes (circles), the compared results are from the corresponding serotype in the PCV13 group. †For the 7 additional serotypes (triangles), the compared results are from serotype 6B (the PCV13 serotype with the lowest percentage) in the PCV13 group. *In the table, actual values are shown for the PCV13 group for the 7 additional serotypes. Results are for the dose 2 evaluable immunogenicity population. full color online

increases in IgG concentrations of all 20 serotypes from before to 1 month after dose 3 (Figure, Supplemental Digital Content 7, http://links.lww.com/INF/F463). Boosting of IgG levels in the PCV20 group was also observed for all serotypes between 1 month after dose 2 and 1 month after dose 3. IgG GMC patterns from before doses 1 and 2 to 1 month after dose 3 varied between serotypes but were similar for the 13 matched serotypes in both groups (Figure, Supplemental Digital Content 8, http://links.lww.com/INF/F464).

For most of the 13 matched serotypes, OPA GMTs 1 month after dose 2 and dose 3 were generally similar in both groups (Fig. 3). Boosting of OPA titers was observed from 1 month after dose 2 to 1 month after dose 3 of PCV20; this was particularly notable for the serotypes missing statistical NI criteria 1 month after dose 2 (6A, 6B, 9V, 23F). Robust OPA responses were elicited to all 7 additional serotypes, including 10A and 12F, which missed a primary objective statistical NI criterion. As expected, observed OPA GMTs were substantially higher in the PCV20 group than the PCV13 group 1 month after doses 2 and 3 for the 7 additional serotypes. Substantial OPA titer increases were observed from before to 1 month after dose 3 for all 20 vaccine serotypes (Figure, Supplemental Digital Content 9, http://links.lww.com/INF/F465).



GMFRs from 1 month after Dose 2 to 1 month after Dose 3																			
Serotype	**1**	**3**	**4**	**5**	**6A**	**6B**	**7F**	**9V**	**14**	**18C**	**19A**	**19F**	**23F**	**8**	**10A**	**11A**	**12F**	**15B**	**22F**	**33F**
PCV20	4.0	3.2	2.8	2.9	3.0	8.8	2.2	14.5	2.5	2.2	13.2	1.9	11.2	7.1	4.0	9.8	1.2	2.9	1.4	4.8
PCV13	4.7	3.3	2.6	3.1	3.6	9.6	2.5	16.1	2.7	2.7	7.9	2.4	15.2	-	-	-	-	-	-	-

FIGURE 3. OPA GMTs (2-sided 95% CIs) 1 month after dose 2 and 1 month after dose 3. Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis. OPA titers were determined on serum from randomly selected subsets of participants assuring equal representation of both vaccine groups. The number of participants with valid OPA titers for specified serotypes ranged from 96–118 after dose 2 to 72–109 after dose 3. GMFRs are not presented for PCV13 for the 7 additional serotypes not included in PCV13. Results are for the dose 2 and dose 3 evaluable immunogenicity populations. GMFR indicates geometric mean fold rise. full color online

In the PCV20 group, percentages of participants with OPA titers ≥LLOQ for the 13 matched serotypes ranged from 76.0% (serotype 1) to 100.0% (4, 7F, 18C, 19A) 1 month after dose 3 and from 26.5% (serotype 1) to 98.2% (7F) 1 month after dose 2 (Figure, Supplemental Digital Content 10, http://links.lww.com/INF/F466).

Safety and Tolerability

Local reactions and systemic events occurred at similar frequencies in both vaccine groups and were mostly mild to moderate (Fig. 4). The most frequent local reactions were injection site pain (doses 1 and 3) and redness (dose 2). The most frequent systemic events were irritability and drowsiness. Similar percentages of participants in both groups experienced fever after dose 1 (PCV20: 8.9%; PCV13: 8.5%), dose 2 (14.9%; 14.0%) and dose 3 (24.3%; 23.7%). Fever ≥38.9 °C was reported by ≤3.6% of participants in either group at any time point; fever >40.0 °C was reported in 2 participants (0.3%) in the PCV20 group after dose 3. At all doses, solicited reactions and events had a median onset 1−2 days after vaccination, with median 1−3 day duration.

From dose 1 to 1 month after dose 2, AEs occurred in 13.8% (PCV20) and 14.4% (PCV13) of participants; from dose 3 to 1 month after dose 3, rates were 15.5% and 16.5%, respectively (Table 1). AEs were generally consistent with illnesses and medical conditions expected in the age population; the most frequent were upper respiratory tract infection, nasopharyngitis and conjunctivitis. SAE rates at any time after dose 1 were low and similar in PCV20 (5.7%) and PCV13 (6.6%) groups. SAEs of seizure or seizure-like events were reported for 1 and 2 participants randomized to PCV20 (>8 months after last dose) and PCV13 (n = 1, day 19 after dose 1; n = 1, >8 months after dose 3), respectively, and were not considered vaccine related. A single SAE of inflammation 7 days after dose 1 of PCV20 was considered by the investigator to be potentially related to PCV20 (left leg administration) or concomitant diphtheria-tetanus-acellular pertussis combination vaccine (right leg administration); the participant was hospitalized with fever and had elevated laboratory inflammatory markers. Right groin pain and swelling, diagnosed as hernia, were present. No participants died during the study. Following dose 1, NDCMCs occurred in ≤0.7% of participants in either group, all before 1 month after dose 2; the majority involved new atopic dermatitis diagnoses.

DISCUSSION

In this phase 3 study, PCV20 elicited robust immune responses to all 20 serotypes with a similar safety profile to PCV13.

IgG responses to PCV20 serotypes were robust and like PCV13 responses after the 3-dose series although statistical NI criteria for both primary objectives after dose 2 were missed for matched serotypes 6A, 6B, 9V and 23F and narrowly missed for serotype 6B after dose 3. IgG concentration distributions for the 13 matched serotypes were similar to those after PCV13, and responses to the 7 additional serotypes were substantially greater with PCV20 than with PCV13. Other supportive data showed a high percentage of participants with predefined IgG concentrations after dose 3, robust OPA responses after doses 2 and 3 that were like PCV13 for the matched serotypes and substantially higher for the 7 additional serotypes and boosting after dose 3 showing PCV20-primed memory responses after 2 infant doses for all vaccine serotypes. The totality of evidence suggests that PCV20 is expected to help protect children against pneumococcal disease caused by vaccine serotypes, including those that missed NI.

Based on experience with PCV13 showing substantial effectiveness despite missing NI for serotypes in the pivotal comparisons to PCV7, the totality of immunogenicity data, including confirmation of functionality of immune response and evidence of memory, is a better predictor of impact than simply assessing individual IgG endpoints after vaccination.[37,38] In key US and German PCV13 trials, IgG responses were generally lower for PCV13 than PCV7 for the 7 matched serotypes, 2 of which missed a coprimary NI objective.[37,39] Supportive data (OPA responses, boosting, IgG concentration distributions) were robust for all matched serotypes.[37,39] Israeli

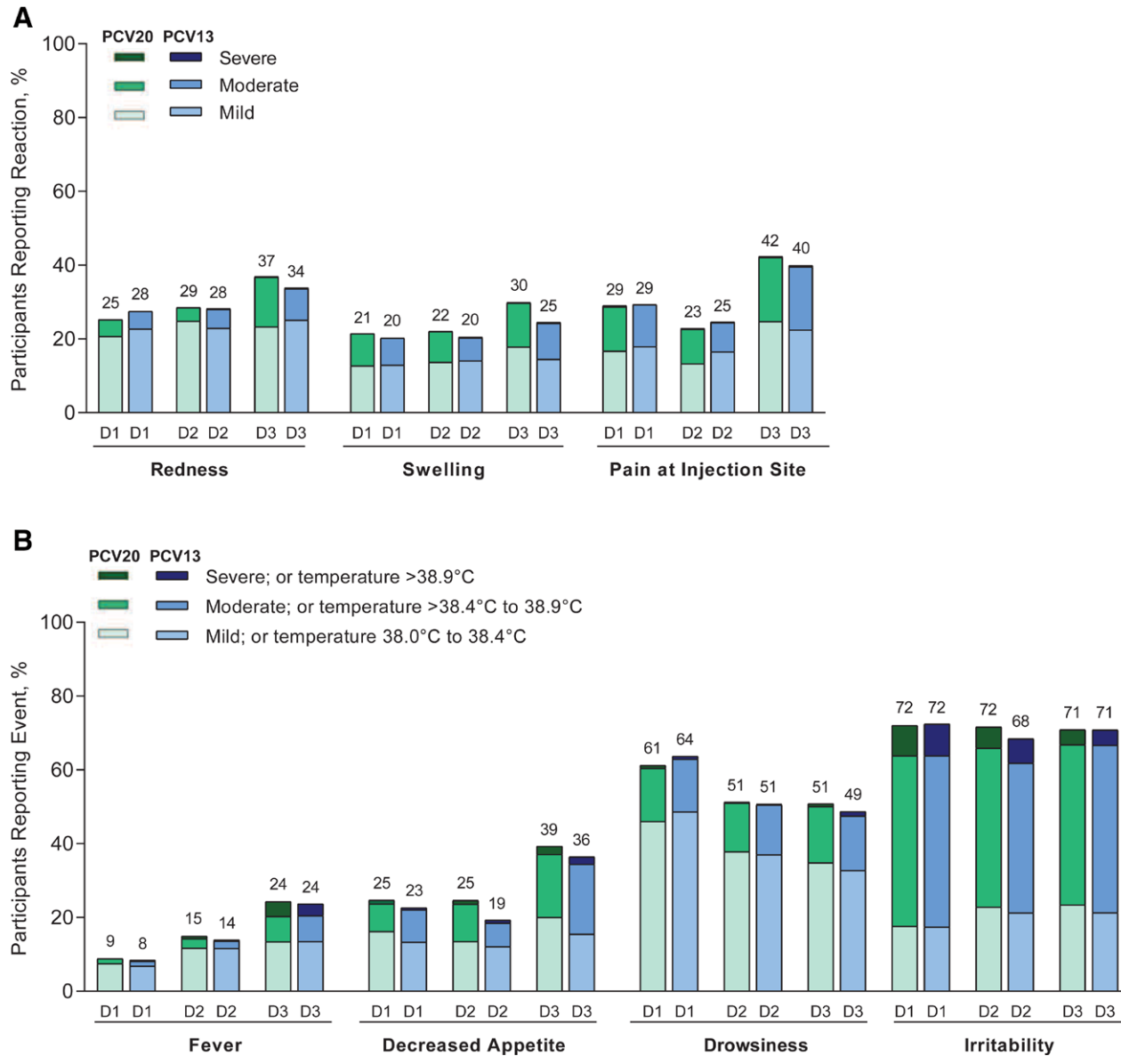


FIGURE 4. Percentages of participants with reported (A) local reactions and (B) systemic events after each dose. For redness and swelling, mild: >0.0–2.0 cm; moderate: >2.0–7.0 cm; severe: >7.0 cm. For pain at the injection site, mild: hurts if gently touched; moderate: hurts if gently touched with crying; severe: causes limitation of limb movement. For decreased appetite, mild: decreased interest in eating; moderate: decreased oral intake; severe: refusal to feed. For drowsiness, mild: increased or prolonged sleeping bouts; moderate: slightly subdued, interfering with daily activity; severe: disabling, not interested in usual daily activity. For irritability, mild: easily consolable; moderate: requiring increased attention; severe: inconsolable, crying cannot be comforted. The number of participants included in each group was 580–603 depending on the group and time point. Values above bars are the percentages of participants reporting an event of any severity rounded to whole numbers. Results are for the safety population. Fever >40.0 °C was reported in 2 participants (0.3%) in the PCV20 group after dose 3. D indicates dose. full color online

and UK IPD surveillance data further demonstrated that PCV13 achieved near elimination of matched PCV7 serotypes over its decade of use.[40,41] Notably, a 3-dose series was recommended in Israel and UK at PCV13 introduction.[42,43]

Assessment of various immune responses for PCVs is important because the mechanism of protection of PCVs against pneumococcal disease is multifactorial, and no minimum circulating IgG level predicting protection is established. The 0.35 µg/mL predefined IgG concentration threshold measured by WHO pneumococcal enzyme-linked immunosorbent assay (or equivalent level in a bridged assay) used as 1 endpoint for comparison of PCVs is derived from a meta-analysis of 3 efficacy trials: 2 PCV7 trials (4-dose regimens) and 1 investigational PCV9 trial (3 infant doses).[44] The threshold was generated by pooling IgG concentrations across all vaccine serotypes after the third infant dose and correlating it to observed vaccine efficacy, but is suboptimal for

TABLE 1. Summary of AEs (Safety Population)

Time point AE type	PCV20	PCV13
From dose 1 to 1 month after dose 2	(N = 601*)	(N = 603*)
Any AE	83 (13.8)	87 (14.4)
Related	2 (0.3)	4 (0.7)
Severe	4 (0.7)	2 (0.3)
NDCMC	4 (0.7)	4 (0.7)
Serious AE	14 (2.3)	14 (2.3)
From dose 3 to 1 month after dose 3	(N = 588†)	(N = 594†)
Any AE	91 (15.5)	98 (16.5)
Related	1 (0.2)	1 (0.2)
Severe	5 (0.9)	4 (0.7)
NDCMC	0	0
Serious AE	3 (0.5)	7 (1.2)
Throughout study (after dose 1)	(N = 601*)	(N = 603*)
NDCMC	6 (1.0)	6 (1.0)
Serious AE	34 (5.7)	40 (6.6)

Adverse events were categorized according to MedDRA terms (v25.0).

*Number of participants in the specified group; denominator used in the percentage calculations for AEs reported from dose 1 through 1 month after dose 2 or throughout study.

†Number of participants who received dose 3 in the specified group; denominator used in the percentage calculations for AEs reported from dose 3 through 1 month after dose 3.

inferring individual or serotype-specific protection and was not developed to infer protection after 2 infant doses.

Recognizing these limitations, WHO guidance proposes a totality of data approach; that is, for coprimary endpoints after infant doses, "meeting one of the two sets of criteria should be considered adequate for approval."[45] If IgG responses fail to meet both sets of criteria, WHO recommends accounting for serotype-associated disease burden, available effectiveness data and secondary immunogenicity analyses.[45,46]

Immune responses for several serotypes, particularly 6B and 23F, may be lower after 2 PCV7, PCV10 or PCV13 doses than after a third infant dose.[47–49] This has also been observed with PCV15.[50,51] Additionally, based on immunogenicity findings in a UK study assessing a 3-dose series, percentages of participants with predefined IgG concentrations were also substantially lower for serotype 6B and IgG GMC for serotype 14 after 2 infant PCV13 doses than after 2 PCV7 doses, but OPA responses after 2 infant doses were robust.[49] In a Spanish study, percentages of participants with predefined IgG concentrations were substantially lower for serotypes 6B and 23F after PCV13 versus PCV7, but boosting after the toddler dose was supportive of a robust response.[49] Subsequent introduction of the 3-dose PCV13 series in Europe has been associated with continued impact on disease for the original PCV7 serotypes, including 6B, 14 and 23F, suggesting results after 2 infant doses would have underestimated effectiveness.[52] A 4-dose PCV20 series (3 infant doses plus a toddler dose) was investigated in a phase 3, double-blind study.[30] IgG GMCs were lower for some serotypes after 2 infant doses in this study compared with 3 infant doses; however, functional antibodies were induced after the infant series for all serotypes, and IgG GMCs were largely similar for both regimens after the toddler dose, supporting effectiveness of both schedules.[30] To reduce the likelihood of rejecting a potentially effective PCV in a 3-dose series, particularly a higher valent PCV, it is crucial to consider supportive immunogenicity data for serotypes missing statistical NI criteria, consistent with WHO guidance. This is important considering that the 7 additional PCV20 serotypes are associated with severe/invasive disease and antibiotic resistance[17–21] and are estimated to cause 21%–42% of IPD in young children in Europe.[11,52–56]

In our trial, PCV20 and PCV13 responses to serotype 3 were similar, with PCV20 meeting 2 of 3 primary objectives. PCV13 demonstrated effectiveness of direct vaccination of 65% against serotype 3 IPD in European children <5 years old from 2011 to 2018 and significant reductions in serotype 3 otitis media in Israeli children <2 years old from 2004 to 2013.[9,57] We anticipate that PCV20 will provide similar direct protection as PCV13 against serotype 3 to vaccinated children.

In this study, no unexpected safety concerns were identified. Solicited reactions and events were mostly mild to moderate and transient. Fever after the toddler dose in both vaccine groups may be attributable to concomitant vaccines given with PCV and did not result in complications such as hospitalizations or febrile seizure. Percentages of participants reporting AEs, SAEs and NDCMCs were similar between groups.

Study strengths include the number of immunogenicity endpoints studied and investigation of IgG concentrations and OPA titers. Evaluation of antibody levels before doses 1 and 2 provided insight into baseline and early vaccine responses. Limitations include the impracticability of powering such a study to meet all statistical NI criteria of PCV20 to PCV13 given the large number of regulatory agency-requested NI comparisons in the primary objectives. In addition, some serotypes, such as serotype 6B, have inherently lower IgG responses after 2 infant doses. OPA titers were only measured in a subset of participants because of limited blood volume collected in infants and the number of serotypes needed to test; however, the sample size was adequate to show that PCV20 generated robust functional responses to all 20 serotypes.

In conclusion, an infant 3-dose PCV20 regimen elicited robust immune responses expected to be protective against all 20 vaccine serotypes with a similar safety profile to PCV13.

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