Immunogenicity and Safety of 13-Valent Pneumococcal Conjugate Vaccine in Infants and Toddlers

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KEY WORDS

safety, immune response, pneumococcal conjugate vaccine, infants, toddlers

ABBREVIATIONS

PCV7—7-valent pneumococcal conjugate vaccine
IPD—invasive pneumococcal disease
WHO—World Health Organization
PCV13—13-valent pneumococcal conjugate vaccine
AE—adverse event
IgG—immunoglobulin G
ELISA—enzyme-linked immunosorbent assay
OPA—opsonophagocytic assay
GMC—geometric mean concentration
GMT—geometric mean titer
CI—confidence interval

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WHAT'S KNOWN ON THIS SUBJECT: To expand coverage of PCV7, a 13-valent vaccine with serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F plus 1, 3, 5, 6A, 7F, and 19A has been approved in the United States and elsewhere for routine pediatric immunization.

WHAT THIS STUDY ADDS: These study results reveal that PCV13 was as effective as PCV7 in the prevention of disease caused by the 7 common serotypes and could provide expanded protection against the 6 additional serotypes with a comparable safety profile.

abstract

BACKGROUND: 7-Valent pneumococcal conjugate vaccine (PCV7 [Prevnar, Wyeth Pharmaceuticals Inc, Philadelphia, PA], serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) is effective in preventing vaccine-serotype pneumococcal disease. 13-Valent pneumococcal conjugate vaccine (PCV13) (PCV7 serotypes plus 1, 3, 5, 6A, 7F, and 19A) was designed to provide broader pneumococcal disease coverage. We evaluated the immunogenicity and safety of PCV13 compared with PCV7.

METHODS: Infants received PCV13 or PCV7 at ages 2, 4, 6, and 12 to 15 months with routine pediatric vaccinations. Pneumococcal anticapsular polysaccharide-binding immunoglobulin G responses and functional antipneumococcal opsonophagocytic activity were assessed 1 month after dose 3, before the toddler dose, and 1 month after the toddler dose. Safety and tolerability were also assessed.

RESULTS: For the 7 common serotypes, PCV13-elicited immunoglobulin G titers were noninferior to those elicited by PCV7, although PCV13 responses were generally somewhat lower. PCV13 also elicited functional opsonophagocytic activity comparable with that elicited by PCV7. For the 6 additional serotypes in PCV13, PCV13 elicited binding and functional antibody levels notably greater than those in PCV7 recipients. After PCV13 immunization, concordance between antipolysaccharide and opsonophagocytic responses was noted for all 13 serotypes. The PCV13 toddler dose resulted in higher immune responses compared with infant-series doses. Safety and tolerability were comparable; reactogenicity was generally mild.

CONCLUSIONS: PCV13 will be as effective as PCV7 in the prevention of pneumococcal disease caused by the 7 common serotypes and could provide expanded protection against the 6 additional serotypes. The PCV13 safety profile was comparable to that of PCV7. *Pediatrics* 2010; 126:e493–e505

Approximately 14.5 million episodes of serious disease caused by *Streptococcus pneumoniae* were estimated to occur globally in children younger than 5 in 2000.[1] An estimated 1 million deaths annually are attributed to this organism in this age group worldwide.[2] In the United States, use of 7-valent pneumococcal conjugate vaccine (PCV7) has dramatically reduced the incidence of vaccine serotype-specific invasive pneumococcal disease (IPD).[3–6] In addition to direct benefits in vaccinated children, PCV7 administration has indirectly reduced IPD incidence in unvaccinated adults.[3,7]

The World Health Organization (WHO) has stated it should be a priority to include PCV7 in national immunization programs.[2] PCV7 serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F were responsible for ~80% to 90% of IPD in the United States before the introduction of PCV7.[8] Data from the Active Bacterial Core Surveillance Network revealed an overall 77% reduction in the incidence of IPD in children younger than 5, a 98% decline in vaccine-serotype IPD, and a small but significant increase in IPD because of nonvaccine serotypes, particularly type 19A.[4]

The serotypes in PCV13, which include PCV7 serotypes plus types 1, 3, 5, 6A, 7F, and 19A, are the most common serotypes that cause IPD globally, accounting for 80% to 92% of IPD in children younger than 5 worldwide.[9] Serotypes 6A and 19A are important additions, because both mediate a substantial proportion of pneumococcal disease.[4,10–12] Surveillance data have shown that PCV7 provides some protection against 6A disease, but not to the same extent as that seen against types actually contained in the vaccine.[13,14] PCV7 provides no protection against 19A disease.[2,15,16] Serotypes 1 and 5 are particularly important causes of pneumococcal disease in the developing world.[9] Finally, serotype 3 has been associated with a broad spectrum of disease, including IPD, necrotizing pneumonia, and acute otitis media.[17,18]

The current study represents the pivotal US study that compares the safety, tolerability, and immunogenicity of PCV13 with that of PCV7, administered as a 4-dose series with routine pediatric vaccinations, according to the US-recommended infant vaccination schedule. The results of another pivotal study conducted in Germany have been published elsewhere.[19]

PATIENTS AND METHODS

Study Design

This phase 3, randomized, double-blind, active-controlled, multicenter trial compared PCV7 with PCV13 given to healthy infants aged 2, 4, 6, and 12 to 15 months concomitantly with routine pediatric vaccinations. Two-month-old infants were enrolled at 1 of 38 sites and randomly assigned to receive either PCV7 or PCV13. Blood samples were obtained 1 month after the third infant dose, as well as before the toddler dose and 1 month afterward.

The study was conducted in accordance with the ethical principles that originated in the Declaration of Helsinki. The protocol was reviewed and approved by each institution's review board or delegated authority. Written informed consent was obtained from a subject's parent/guardian before study enrollment.

Eligible subjects were 2 months old (42–98 days) and healthy. Subjects were excluded if they previously were vaccinated with any study vaccines (except hepatitis B vaccine at birth); had any contraindication to vaccination; had a known or suspected immunodeficiency or suppression; had a history of *S pneumoniae* or *Haemophilus influenzae* type b disease or confirmed measles, mumps, rubella, or varicella infection; had a severe chronic disorder including significant congenital malformations; had a history of seizures; or had received blood products or γ-globulin.

Vaccines and Interventions

Each subject received 0.5 mL of either PCV13 or PCV7 at age 2, 4, 6, and 12 to 15 months. Each subject also received Pediarix (GlaxoSmithKline Biologicals, Rixensart, Belgium) and ActHIB (Sanofi Pasteur SA, Lyon, France) at the 2-, 4-, and 6-month visits, as well as ProQuad (Merck and Co, Inc, Whitehouse Station, NJ), PedvaxHIB (Merck and Co, Inc, West Point, PA), and VAQTA (Merck and Co, Inc, Whitehouse Station, NJ) at the 12- to 15-month visit.

Each vaccine was administered intramuscularly, except for ProQuad (injected subcutaneously into the arm). PCV13 and PCV7 were injected into the left thigh, and the other concomitant vaccines were injected into the right thigh.

As with PCV7, each PCV13 polysaccharide is covalently conjugated to a common carrier protein, cross-reactive material 197, a nontoxic variant of diphtheria toxin. PCV13 contains 2.2 μg of each polysaccharide, except for 4.4 μg of type 6B, with 0.125 mg per dose of aluminum as aluminum phosphate. The presentations of PCV13 and PCV7 were identical.

Study Objectives

Our objectives were to compare immune responses of PVC13 with those of PCV7, 1 month after both the infant series and the toddler dose, when coadministered with concomitant vaccines. As an exploratory measure, the functional opsonophagocytic capacity of the elicited antibodies was assessed in a randomly selected subset of 100 subjects per group.

The safety of PCV13 was evaluated by incidence rates of local reactions, sys-

temic events, and adverse events (AEs). Immune responses to specific concomitant antigens also were determined. These results will be published separately.

Randomization

Eligible subjects were randomly assigned (1:1) to receive PCV13 or PCV7 on the basis of a randomization schedule with a block size of 4 performed through the sponsor's Clinical Operations Randomization Environment system accessible via Internet and telephone 24 hours/day. Participants, study staff, and those who assessed outcomes were blinded to the group assignment.

Analysis Population

Immunogenicity was analyzed only in the evaluable infants who adhered to protocol requirements, had valid and determinate assay results, and had no major protocol violations. The all-available infant immunogenicity population included all subjects who had at least 1 valid and determinate assay result; results were similar to those for the evaluable immunogenicity population (data not shown). The safety population included all subjects who received ≥1 dose of PCV.

Antipneumococcal Immunogenicity Assessments

Serotype-specific immunoglobulin G (IgG) was measured using standard pneumococcal anticapsular polysaccharide enzyme-linked immunosorbent assay (ELISA).[20–23] Functional antibacterial opsonophagocytic activity was measured by opsonophagocytic assay (OPA). The OPA used in this study[24] is a modification of the method of Romero-Steiner et al.[25] Unlike IgG ELISA, OPA has no agreed-on reference sera. Therefore, although antibody concentration values measured by ELISA can be compared across serotypes, OPA titer values cannot be similarly compared. Nonetheless, OPA titers within individual serotypes can be compared.

Statistical Analysis

The study was designed by using the intersection-union procedure described by Wellek[26] (Supplemental Text 1).

End points included immunologic comparisons of pneumococcal responses elicited by PCV13 relative to PCV7 1 month after both the infant series and the toddler dose. Responders after the infant series were defined as the proportion of subjects for whom there was an anticapsular polysaccharide IgG concentration of ≥0.35 μg/mL, a reference concentration for assessment of vaccine efficacy against IPD defined by the WHO.[27,28] Postinfant series and posttoddler dose analyses included comparison of antipolysaccharide IgG geometric mean concentrations (GMCs), comparison of functional antibacterial OPA titer of ≥1:8 as defined by the WHO,[26,27] and a comparison of functional antibacterial OPA geometric mean titers (GMTs).

Within each vaccine group and for each serotype, GMCs (IgG) or GMTs (OPA) and corresponding 2-sided 95% confidence intervals (CIs) were calculated by using logarithmically transformed values and the Student's *t* test distribution for CIs.

After the infant series, the difference in proportion of antipolysaccharide IgG responders elicited by PCV13 relative to PCV7 (PCV13–PCV7) was calculated for each serotype. The exact, unconditional, 2-sided 95% CIs on the difference in proportion of responders were computed using the noninferiority procedure of Chan and Zhang.[29] For the serotypes in common to the 2 vaccines, noninferiority was declared if the lowest limit of the 2-sided 95% CI for the difference in proportion of responders in the 2 groups was more than −0.10.

For the comparison of IgG GMCs elicited by PCV13 relative to PCV7, the GMC ratio (PCV13/PCV7) for each pneumococcal serotype was calculated. Noninferiority of PCV13 relative to PCV7 for the common serotypes was declared if the lower limit of the 2-sided 95% CI for the GMC ratio was >0.5 (twofold criterion). Fold-rises in antibody concentrations from pretoddler dose to posttoddler dose were reported by geometric means and CIs, also computed using the logarithmically transformed assay results.

Sample-size estimation was based on the anticipated proportion of responders in each vaccine group. Data from 2 previous PCV clinical studies (studies 6096A1-003[30] and D140-P001 [unpublished data]) were used to estimate proportion of responders and GMCs for each pneumococcal serotype. The study was powered to show the noninferiority of PCV13 relative to PCV7. After the infant series, it was estimated that 250 evaluable subjects per group provided 91% power to declare noninferiority for each pneumococcal serotype when using a noninferiority criterion of −0.10 and a 2-sided, type I error of 0.05.

Safety Assessments

Local pneumococcal vaccine injection site reactions (tenderness, redness, and swelling), systemic events (rectal temperature, decreased appetite, irritability, increased sleep, and decreased sleep), presences of hives, and use of antipyretic medication to prevent or treat symptoms were monitored by parents or legal guardians and recorded using an e-diary that solicited specific signs and symptoms for 7 days after each vaccination. Tenderness was recorded as none, present, or interfered with limb movement. Redness and swelling were measured

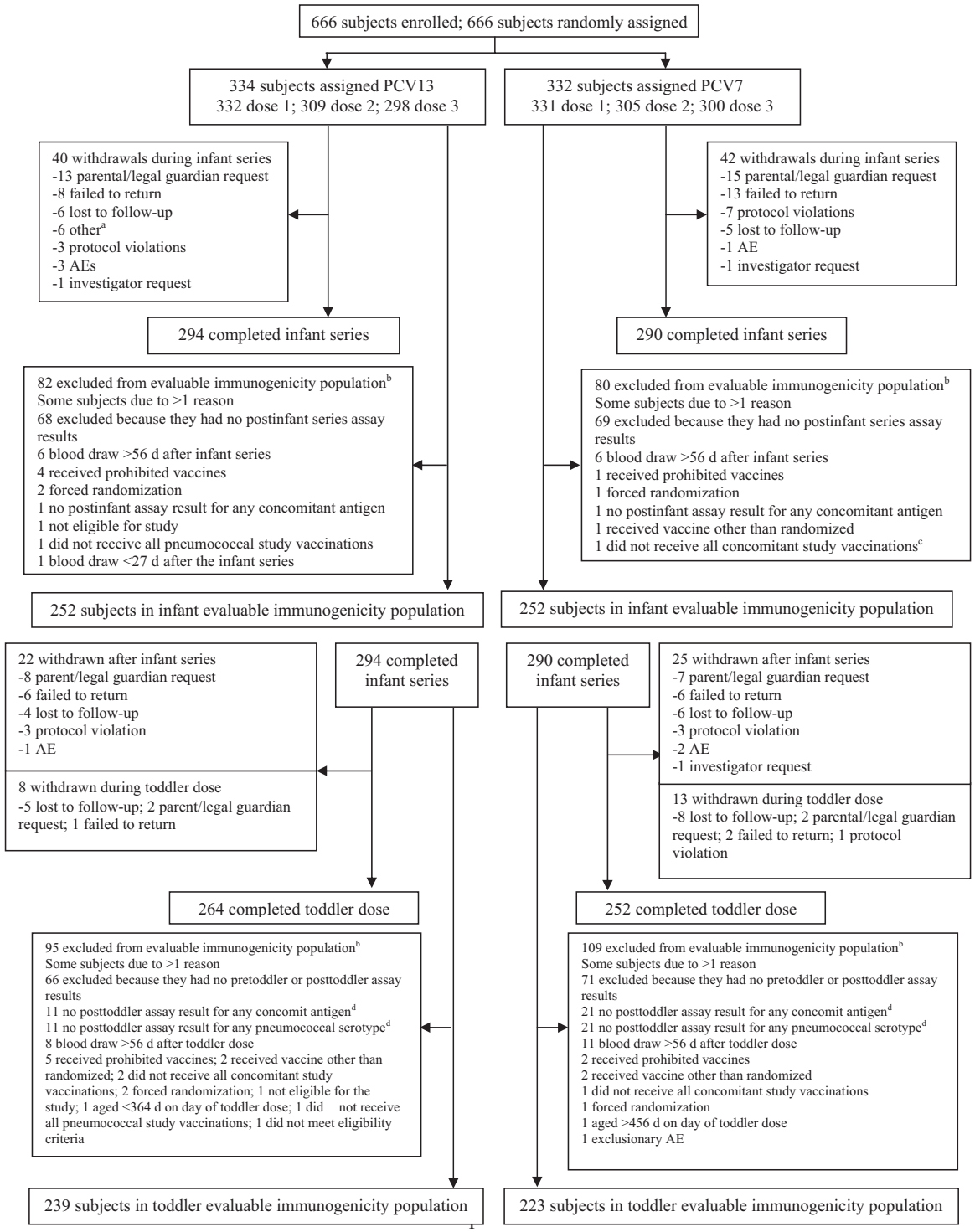

FIGURE 1

Subject disposition. [a]Other reasons were that subjects lost Kaiser coverage (4 subjects), the child was removed from the home and put in protective custody (1 subject), and the subject's parent/legal guardian never provided consent and the child was randomly assigned in error (1 subject). [b]Subjects may have been excluded for >1 reason. [c]Subject was not counted among the subjects who received Pediarix at dose 2 because of an error. [d]Subjects with no posttoddler assay results for any serotype/concomitant vaccine antigen are not included in this category and are classified as "No data received for these subjects."

with a caliper, reported in the diary as caliper units (1 unit = 0.5 cm), and then categorized as absent, mild (0.5–2.0 cm), moderate (2.5–7.0 cm), or severe (>7.0 cm). Temperature was measured each evening and whenever the child felt feverish; the highest temperature was recorded each day. Severity of fever was categorized as ab-

sent (<38.0°C), mild (≥38.0°C to ≤39.0°C), moderate (>39.0°C to ≤40.0°C), or severe (>40°C). Unsolicited AEs were recorded until 6 months after the last vaccination.

RESULTS

Baseline Characteristics and Disposition of Subjects

A total of 666 subjects were enrolled, consented to participate, and were randomly assigned (see Fig 1) from September 18 to December 14, 2006. The 6-month follow-up was completed on June 2, 2008. The evaluable immunogenicity populations consisted of 504 infants (PCV13: 252; PCV7: 252) and 462 toddlers (PCV13: 239; PCV7: 223).

Demographic characteristics are presented in Table 1. There were no statistically significant differences in baseline characteristics between groups. The safety population included 663 subjects (PCV13: 332; PCV7: 331). Characteristics were similar to those in the evaluable immunogenicity populations.

Immune Responses to the Common Serotypes After the Infant Series

Comparison of immune responses to the 7 common serotypes is shown in Table 2. With regard to the antipolysaccharide responder proportion at 0.35 μg/mL (see "Patients and Methods"), noninferiority was achieved for 5 of the 7 serotypes. The exceptions were serotypes 6B and 9V, for which the values at the lower limit of the 95% CI did not meet noninferiority criteria (−10.9 and −12.4, respectively). The antipolysaccharide GMC noninferiority criterion for each of the common serotypes was met for all 7 serotypes, although the GMCs in the PCV13 group were somewhat lower than those in the PCV7 group.

The proportions of subjects with a serotype-specific OPA antibody titer of ≥1:8 were 90.4% or higher in the PCV13 group and 92.6% or higher in the PCV7 group. PCV13 and PCV7 also elicited comparable functional antibody responses, as noted by comparison of OPA GMTs. For all 7 serotypes and for both vaccines, functional antibody responses were concordant with antipolysaccharide responses (Fig 2).

Immune Responses to the Additional Serotypes After the Infant Series

Immune responses against the 6 additional serotypes are shown in Table 3. For all, PCV13 generally gave rise to anticapsular polysaccharide-binding IgG levels that were notably greater than those induced by PCV7, both in terms of proportion of responders as well as by GMC comparison. In addition, PCV13 elicited notably greater functional antibody activity against the additional serotypes.

OPA responses after PCV7 for the additional serotypes did not correlate with serotype-specific binding IgG concentrations, with the exception of serotype 6A (Fig 2). By contrast, OPA titers after PCV13 correlated with IgG concentrations for all serotypes. For serotype 6A, OPA response was 10-fold greater in the PCV13 group compared with PCV7.

For type 7F, data in Table 3 and Fig 2 show that PCV7 recipients achieved high concentrations of 7F OPA activity despite known ineffectiveness of PCV7 against serotype 7 disease.[27,28] A second OPA titer cutoff of 1:2048 was selected, therefore, as indicative of a type 7F OPA response on the basis of the 95th percentile of observed responses in PCV7 recipients. The proportion of responders above this level was 90.4% (95% CI: 82.6–95.5) in PCV13 recipients and 13.5% (95% CI: 7.2–22.4) in PCV7 recipients.

TABLE 1 Demographic Characteristics: Evaluable Infant and Toddler Immunogenicity Populations

Population	Evaluable Infant Immunogenicity			Evaluable Toddler Immunogenicity		
	PCV13 (*N* = 252)	PCV7 (*N* = 252)	Total (*N* = 504)	PCV13 (*N* = 239)	PCV7 (*N* = 223)	Total (*N* = 462)
Gender, *n* (%)						
Male	129 (51.2)	146 (57.9)	275 (54.6)	124 (52)	134 (60)	258 (56)
Female	123 (48.8)	106 (42.1)	229 (45.4)	115 (48)	89 (40)	204 (44)
Race, *n* (%)						
White	175 (69.4)	179 (71.0)	354 (70.2)	173 (72)	163 (73)	336 (73)
Black	52 (20.6)	46 (18.3)	98 (19.4)	45 (19)	33 (15)	78 (17)
Other	19 (7.5)	21 (8.3)	40 (7.9)	15 (6)	20 (9)	35 (8)
Asian	6 (2.4)	5 (2.0)	11 (2.2)	6 (3)	6 (3)	12 (3)
Native Hawaiian or other Pacific Islander	0 (0)	1 (0.4)	1 (0.2)	0 (0)	1 (0.4)	1 (0.2)
Ethnicity, *n* (%)						
Non-Hispanic and non-Latino	212 (84.1)	206 (81.7)	418 (82.9)	204 (85)	188 (84)	392 (85)
Hispanic or Latino	40 (15.9)	46 (18.3)	86 (17.1)	35 (15)	35 (16)	70 (15)
Weight at enrollment						
n	252	252	504	—	—	—
Mean (SD), lb	11.5 (1.6)	11.7 (1.6)	11.6 (1.6)	—	—	—
Age at toddler dose, mo						
n	—	—	—	239	223	462
Mean (SD)	—	—	—	12.4 (0.4)	12.4 (0.4)	12.4 (0.4)

TABLE 2 Immune Responses to the 7 Common Serotypes After the Infant Vaccination Series

Immune Measurement	4	6B	9V	14	18C	19F	23F
% of responders according to antipolysaccharide IgG (95% CI)[a]							
PCV13	94.4 (90.9 to 96.9)[b]	87.3 (82.5 to 91.1)	90.5 (86.2 to 93.8)	97.6 (94.9 to 99.1)	96.8 (93.8 to 98.6)	98.0 (95.4 to 99.4)	90.5 (86.2 to 93.8)
PCV7	98.0 (95.4 to 99.4)	92.8 (88.9 to 95.7)	98.4 (96.0 to 99.6)	97.2 (94.4 to 98.9)	98.4 (96.0 to 99.6)	97.6 (94.9 to 99.1)	94.0 (90.4 to 96.6)
Difference[c]	−3.6 (−7.3 to −0.1)[d]	−5.5 (−10.9 to −0.1)	−7.9 (−12.4 to −4.0)	0.4 (−2.7 to 3.5)	−1.6 (−4.7 to 1.2)	0.4 (−2.4 to 3.4)	−3.6 (−8.5 to 1.2)
Antipolysaccharide IgG GMC (95% CI), μg/mL[e]							
PCV13	1.31 (1.19 to 1.45)[f]	2.10 (1.77 to 2.49)	0.98 (0.89 to 1.08)	4.74 (4.18 to 5.39)	1.37 (1.24 to 1.52)	1.85 (1.69 to 2.04)	1.33 (1.17 to 1.51)
PCV7	1.93 (1.75 to 2.13)	3.14 (2.64 to 3.74)	1.40 (1.27 to 1.55)	5.67 (5.02 to 6.40)	1.79 (1.63 to 1.96)	2.24 (2.01 to 2.50)	1.90 (1.68 to 2.15)
Ratio[g]	0.68 (0.59 to 0.78)[h]	0.67 (0.52 to 0.85)	0.70 (0.61 to 0.80)	0.84 (0.70 to 1.00)	0.77 (0.67 to 0.88)	0.83 (0.72 to 0.96)	0.70 (0.59 to 0.84)
OPA titer, % ≥1:8 (95% CI)[i]							
PCV13	97.8 (92.4 to 99.7)[j]	98.9 (94.2 to 100)	100 (96.1 to 100)	100 (96.2 to 100)	100 (96.2 to 100)	90.4 (82.6 to 95.5)	98.9 (94.2 to 100)
PCV7	98.9 (94.1 to 100)	100 (96.2 to 100)	98.9 (94.2 to 100)	100 (96.2 to 100)	100 (96.2 to 100)	92.6 (85.3 to 97.0)	98.9 (94.2 to 100)
OPA GMT (95% CI)[i]							
PCV13	359 (276 to 468)[k]	1055 (817 to 1361)	4035 (2933 to 5553)	1240 (935 to 1646)	276 (210 to 361)	54 (40 to 74)	791 (605 to 1034)
PCV7	536 (421 to 681)	1514 (1207 to 1899)	3259 (2288 to 4641)	1481 (1133 to 1934)	376 (292 to 484)	45 (34 to 60)	924 (709 to 1204)

[a] The proportion of subjects with antipolysaccharide IgG concentrations of ≥0.35 μg/mL (see text).
[b] Exact 2-sided CI is based on the observed proportion of subjects.
[c] Difference in proportions, PCV13–PCV7, expressed as a percentage.
[d] Exact 2-sided CI for the difference in proportions, PCV13–PCV7, is expressed as a percentage. Noninferiority was met if the lower limit of the 2-sided CI was greater than −10.0.
[e] GMCs were calculated by using all subjects with available data for the specified blood draw.
[f] CIs are back-transformations of a CI based on the Student's *t* test distribution for the mean logarithm of the concentrations.
[g] Ratio of GMCs: PCV13/PCV7.
[h] Exact 2-sided 95% CI of ratios. Noninferiority was met if the lower limit of the 2-sided CI was >0.5.
[i] Number of subjects with a determinate antibody titer for the specified serotype ranged from 89 to 94.
[j] Exact 2-sided CI is based on the observed proportion of subjects.
[k] CIs are back-transformations of a CI based on the Student's *t* distribution for the mean logarithm of the titers.

Immune Responses Before and After the Toddler Dose

For all vaccine serotypes in the respective vaccines, antipolysaccharide IgG GMCs before the toddler dose had decreased substantially (Table 4). The toddler dose elicited a marked increase in antibody levels. IgG GMCs to the 7 common serotypes elicited by PCV13 after the toddler dose were noninferior to those in PCV7 recipients for all serotypes. For the 6 additional serotypes, GMCs induced by PCV13 were notably higher than those induced by PCV7.

OPA responses after the toddler dose were also higher than after the infant series. For the 7 common serotypes, proportions of subjects who achieved an OPA antibody titer of ⩾1:8 were similar across groups, and OPA GMTs were comparable (Table 5). For the 6 additional serotypes, OPA responder rates and OPA GMTs were uniformly higher in PCV13 recipients (Table 5).

Postinfant and Posttoddler Population Immune Responses

Reverse cumulative distributions curves in Fig 3 present the proportion of responders 1 month after the infant series and toddler dose at different antibody concentrations and provide comparisons of the full spectrum of immune response distribution. For the common serotypes, responses elicited by PCV13 were slightly lower than those elicited by PCV7, but in all cases, responses were well above levels considered effective. Population responses after the toddler dose were substantially greater than those after the infant series.

Safety and Tolerability

Local reactions (Table 6) and systemic events (Table 7) were mainly mild and comparable between groups. There were no statistical differences in incidence of solicited injection site local

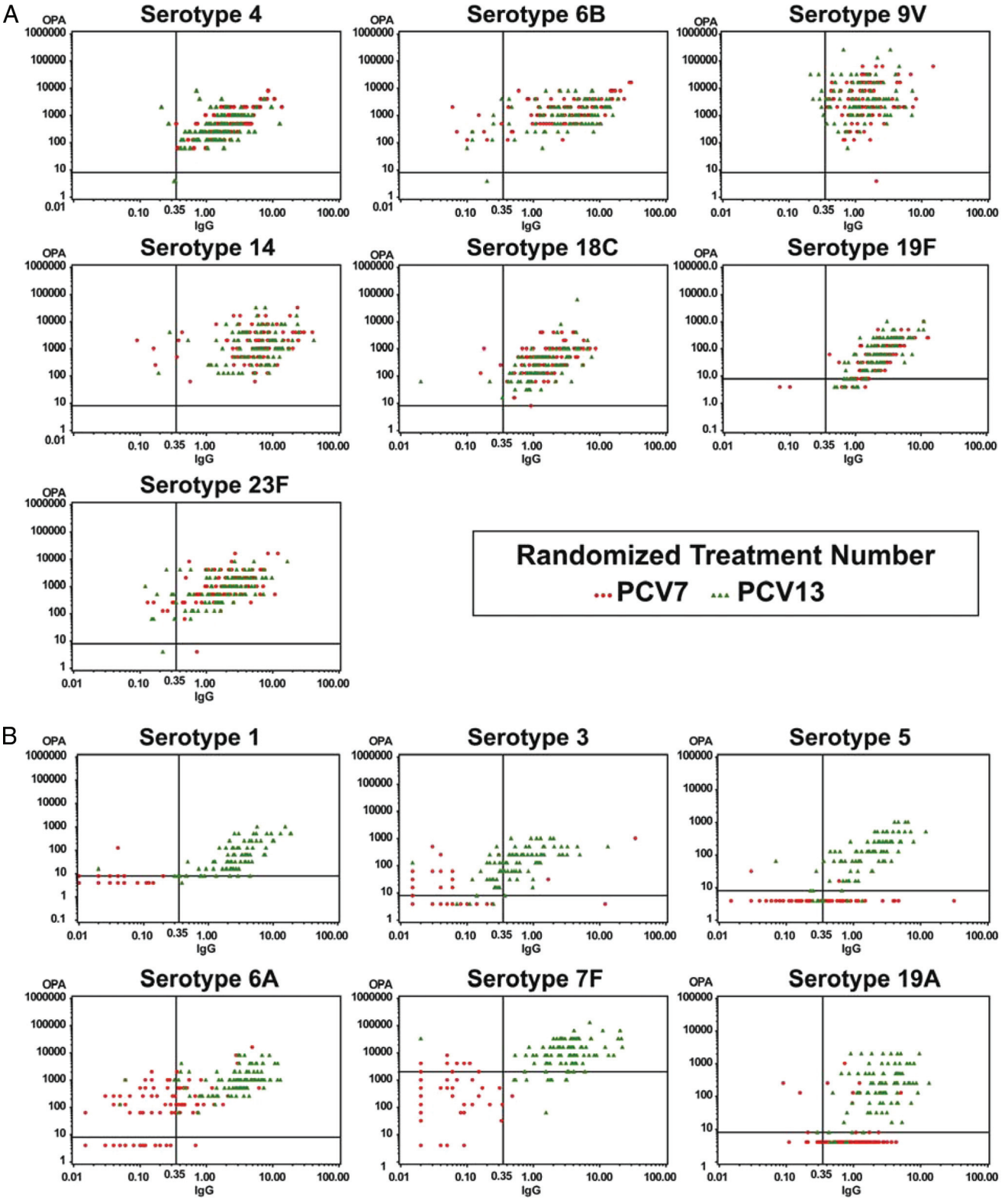

FIGURE 2

Concordance analysis between antipolysaccharide-binding IgG and functional OPA responses. A, Common serotypes; B, additional serotypes. Shown are postinfant series data from samples with IgG concentrations (x-axis) and OPA titers (y-axis). PCV7 or PCV13 recipient data are represented. Vertical lines denote IgG reference concentrations; horizontal lines denote OPA responder titer.

TABLE 3 Immune Responses to the 6 Additional Serotypes After the Infant Vaccination Series

Immune Measurement	1	3	5	6A	7F	19A
% responders according to antipolysaccharide IgG (95% CI)[a]						
PCV13	95.6 (92.3–97.8)[b]	63.5 (57.1–69.4)	89.7 (85.2–93.1)	96.0 (92.8–98.1)	98.4 (96.0–99.6)	98.4 (96.0–99.6)
PCV7	1.6 (0.4–4.1)	4.6 (2.3–8.0)	31.0 (24.6–37.9)	42.5 (36.2–49.0)	2.8 (1.1–5.7)	86.6 (81.6–90.6)
Antipolysaccharide IgG GMC (95% CI), μg/mL[c]						
PCV13	2.03 (1.78–2.32)[d]	0.49 (0.43–0.55)	1.33 (1.18–1.50)	2.19 (1.93–2.48)	2.57 (2.28–2.89)	2.07 (1.87–2.30)
PCV7	0.02 (0.02–0.03)	0.04 (0.03–0.04)	0.20 (0.16–0.24)	0.25 (0.21–0.29)	0.04 (0.03–0.04)	0.89 (0.79–0.99)
OPA titer, % $\geq$1:8 (95% CI)[e]						
PCV13	98.9 (94.1–100)[f]	96.8 (91.0–99.3)	92.3 (84.8–96.9)	100 (96.2–100)	100[g] (96.2–100)	91.4 (83.8–96.2)
PCV7	9.8 (4.6–17.8)	21.3 (13.5–30.9)	2.2 (0.3–7.6)	77.7 (67.9–85.6)	76.4[g] (66.2–84.8)	16.3 (9.4–25.5)
OPA GMT (95% CI)[e]						
PCV13	52 (39–69)[h]	121 (92–158)	91 (67–123)	980 (783–1226)	9494 (7339–12 281)	152 (105–220)
PCV7	4 (4–5)	7 (5–9)	4 (4–4)	100 (66–152)	128 (80–206)	7 (5–8)

[a] Proportion of subjects with antipolysaccharide IgG concentrations of $\geq$0.35 μg/mL (see text).
[b] Exact 2-sided CI is based on the observed proportion of subjects.
[c] GMCs were calculated by using all subjects with available data for the specified blood draw.
[d] CIs are back-transformations of a CI based on the Student's *t* test distribution for the mean logarithm of the concentrations.
[e] Number of subjects with a determinate antibody titer for the specified serotype ranged from 89 to 94.
[f] Exact 2-sided CI is based on the observed proportion of subjects.
[g] 7F responder rate at $\geq$1:2048 is 90.4% (95% CI: 82.6–95.5) in PCV13 recipients and 13.5% (95% CI: 7.2–22.4) in PCV7 recipients.
[h] CIs are back-transformations of a CI based on the Student's *t* distribution for the mean logarithm of the titers.

TABLE 4 Pneumococcal Antipolysaccharide IgG GMCs (μg/mL) Before and After the Toddler Dose

	Before Toddler Dose		After Toddler Dose		Ratio[c] (95% CI[d])
	PCV13, GMC[a] (95% CI[b])	PCV7, GMC[a] (95% CI[b])	PCV13, GMC[a] (95% CI[b])	PCV7, GMC[a] (95% CI[b])	
Common serotypes					
4	0.35 (0.31–0.39)	0.51 (0.45–0.57)	3.73 (3.28–4.24)	5.49 (4.91–6.13)	0.68 (0.57–0.80)
6B	0.78 (0.69–0.89)	1.01 (0.88–1.15)	11.53 (9.99–13.30)	15.63 (13.80–17.69)	0.74 (0.61–0.89)
9V	0.39 (0.35–0.43)	0.53 (0.48–0.59)	2.62 (2.34–2.94)	3.63 (3.25–4.05)	0.72 (0.62–0.85)
14	1.89 (1.64–2.17)	2.49 (2.17–2.85)	9.11 (7.95–10.45)	12.72 (11.22–14.41)	0.72 (0.60–0.86)
18C	0.34 (0.30–0.37)	0.45 (0.41–0.50)	3.20 (2.82–3.64)	4.70 (4.18–5.28)	0.68 (0.57–0.81)
19F	0.73 (0.65–0.82)	0.65 (0.57–0.74)	6.60 (5.85–7.44)	5.60 (4.87–6.43)	1.18 (0.98–1.41)
23F	0.38 (0.33–0.44)	0.48 (0.42–0.55)	5.07 (4.41–5.83)	7.84 (6.91–8.90)	0.65 (0.54–0.78)
Additional serotypes					
1	0.64 (0.57–0.72)	0.03 (0.02–0.03)	5.06 (4.43–5.80)	0.03 (0.03–0.03)	86.48 (72.95–102.52)
3	0.15 (0.13–0.17)	0.05 (0.04–0.06)	0.94 (0.83–1.05)	0.07 (0.05–0.08)	13.88 (11.42–16.87)
5	0.77 (0.69–0.86)	0.44 (0.37–0.51)	3.72 (3.31–4.18)	0.55 (0.47–0.64)	6.76 (5.44–8.41)
6A	0.83 (0.75–0.92)	0.30 (0.26–0.35)	8.20 (7.30–9.20)	1.87 (1.60–2.19)	8.78 (7.15–10.78)
7F	0.83 (0.75–0.93)	0.04 (0.04–0.05)	5.67 (5.01–6.42)	0.05 (0.04–0.05)	69.30 (58.40–82.24)
19A	0.92 (0.81–1.05)	0.70 (0.61–0.80)	8.55 (7.64–9.56)	3.54 (3.15–3.98)	2.34 (2.01–2.72)

[a] GMCs were calculated by using all subjects with available data for the specified blood draw.
[b] CIs are back-transformations of a CI based on the Student's *t* distribution for the mean logarithm of the concentrations.
[c] Ratio of GMCs; PCV13/PCV7.
[d] CIs for the ratio are back-transformations of a CI based on the Student's *t* distribution for the mean difference of the logarithms of the measures (PCV13–PCV7 reference). Noninferiority was met if the lower limit of the 2-sided CI was >0.5.

reactions within 7 days after any infant-series dose. In most instances, the highest percentages of subjects experiencing local reactions occurred on day 1 or 2 (data not shown).

In general, there were no statistical differences in incidence of "any" systemic event after any dose between groups. For specific reactions, the only statistical difference was in the incidence of moderate fever after dose 1 (2.8% vs 0.0% for PCV13 and PCV7, respectively; $P = .026$). Most cases of fever were mild in severity in each group. Severe fever was reported in only 2 subjects, both in the PCV7 group. There were no differences between groups in the use of antipyretic medications to prevent or treat symptoms after any dose. There were a total of 12 reported cases of hives within 7 days of the infant series (10 for PCV13 and 2 for PCV7). Only 1 case after dose 3 (in the PCV7 group) was confirmed. The other cases were not confirmed. After the toddler dose, 3 subjects in each group reported hives within 7 days

TABLE 5 Opsonophagocytic Activity Responses to the 7 Common Serotypes After the Toddler Dose

Immune Measurement	OPA Titer % ≥1:8[a]		OPA GMT[a]	
	PCV13, OPA (95% CI)	PCV7, OPA (95% CI)	PCV13, OPA (95% CI)	PCV7, OPA (95% CI)
Common serotypes				
4	98.9 (93.8–100)[b]	98.9 (94.1–100)	1180 (847–1643)[c]	1492 (1114–1999)
6B	98.9 (94.1–100)	100 (96.2–100)	3100 (2337–4111)	4066 (3243–5098)
9V	98.9 (94.0–100)	100 (96.2–100)	11 856 (8810–15 955)	18 032 (14 125–23 021)
14	100 (96.1–100)	100 (96.2–100)	2002 (1453–2760)	2366 (1871–2992)
18C	98.9 (94.0–100)	100 (96.2–100)	993 (754–1308)	1722 (1327–2236)
19F	96.7 (90.8–99.3)	94.8 (88.3–98.3)	200 (144–276)	167 (121–230)
23F	98.9 (94.0–100)	100 (96.1–100)	2723 (1961–3782)	4982 (3886–6387)
Additional serotypes				
1	98.9 (93.9–100)	12.0 (6.1–20.4)	164 (114–237)	5 (4–6)
3	97.8 (92.3–99.7)	43.8 (33.6–54.3)	380 (300–482)	12 (9–16)
5	98.9 (94.0–100)	5.2 (1.7–11.7)	300 (229–393)	5 (4–6)
6A	98.9 (94.1–100)	94.8 (88.3–98.3)	2242 (1707–2945)	539 (375–774)
7F	100[d] (96.0–100)	80.4[d] (70.9–88.0)	11 629 (9054–14 938)	268 (164–436)
19A	97.8 (92.3–99.7)	53.2 (42.6–63.6)	1024 (774–1355)	268 (164–436)

Opsonophagocytic activity responses before the toddler dose were not measured.

[a] Number of subjects with a determinate antibody titer for the specified serotype ranged from 88 to 96.

[b] Exact 2-sided CI is based on the observed proportion of subjects.

[c] CIs are back-transformations of a CI based on the Student's *t* distribution for the mean logarithm of the titers.

[d] 7F responder rate at ≥1:2048 is 93.4% (95% CI: 86.2–97.5) in PCV13 recipients and 23.9% (95% CI: 15.6–33.9) in PCV7 recipients.

of vaccination; none were clinically confirmed.

AEs reported reflected anticipated childhood illnesses (data not shown). One serious AE in each group was judged by the investigator to be related to study vaccine after the infant series: pyrexia with febrile convulsion (PCV13 group) and nephroblastoma (PCV7 group) diagnosed 3 months after dose 3 (thought to be related by the site investigator but not by the study medical monitor). No related serious AEs were reported after the toddler dose.

DISCUSSION

For the 7 common serotypes, antipolysaccharide IgG responses of ≥0.35 μg/mL were found to be noninferior between the 2 vaccines for 5 of the serotypes. Serotypes 6B and 9V did not meet this noninferiority criterion because they were slightly outside the −10% CI. When comparing GMCs, PCV13 met noninferiority for all the common serotypes including 6B and 9V, although the actual titers were lower than those after PCV7 (Table 2). These GMC responses can be seen graphically in the reverse cumulative distributions curves in Fig 3; the curves for PCV13 and PCV7 were similar in shape for each of the common serotypes, with the PCV13 curves being slightly shifted to the left. In addition, PCV13 elicited functional OPA responses similar to PCV7 for each common serotype. Collectively, these data support that PCV13 is immunogenic against the 7 common serotypes, including 6B and 9V.

For the additional 6 serotypes, PCV13 elicited higher concentrations of antipolysaccharide IgGs and notably higher titers of OPA antibodies (Table 3) compared with PCV7. For serotypes 5 and 19A, PCV7 seemed to elicit some IgG antibodies, but these antibodies have no antibacterial functional activity. This lack of OPA activity is likely the reason for the known lack of PCV7 effectiveness against serotype 19A disease.[14,15,31,32] By contrast, PCV13 elicited substantial antitype 19A OPA activity, which suggests that it would provide protection against type 19A disease.

PCV7 is known to provide some cross-protection against serotype 6A-mediated IPD. This was reflected by the antitype 6A binding and functional antibodies elicited by PCV7. Nonetheless, PCV13 elicited a substantially higher level of functional antibody relative to the antipolysaccharide-binding IgG response, which suggests that PCV13 would be more effective than PCV7 in providing direct protection against type 6A-mediated pneumococcal disease.

Although serotype 3 exhibited the lowest IgG responses of the 6 additional serotypes, the functional antibody response for serotype 3 in the PCV13 group exceeded the response in the PCV7 group by 18-fold after the infant series and 32-fold after the toddler dose; accordingly, PCV13 will likely provide added protection against serotype 3 disease.

For the 7 serotypes in Prevnar, an OPA titer of 1:8 after the infant series was shown to correlate with protective levels of anticapsular binding antibody.[28] In the current study, a cutoff of 1:8 was also used to analyze the OPA activity for the 6 additional serotypes. For serotype 6A, there was a high percentage of responders in both the PCV13 (100%)

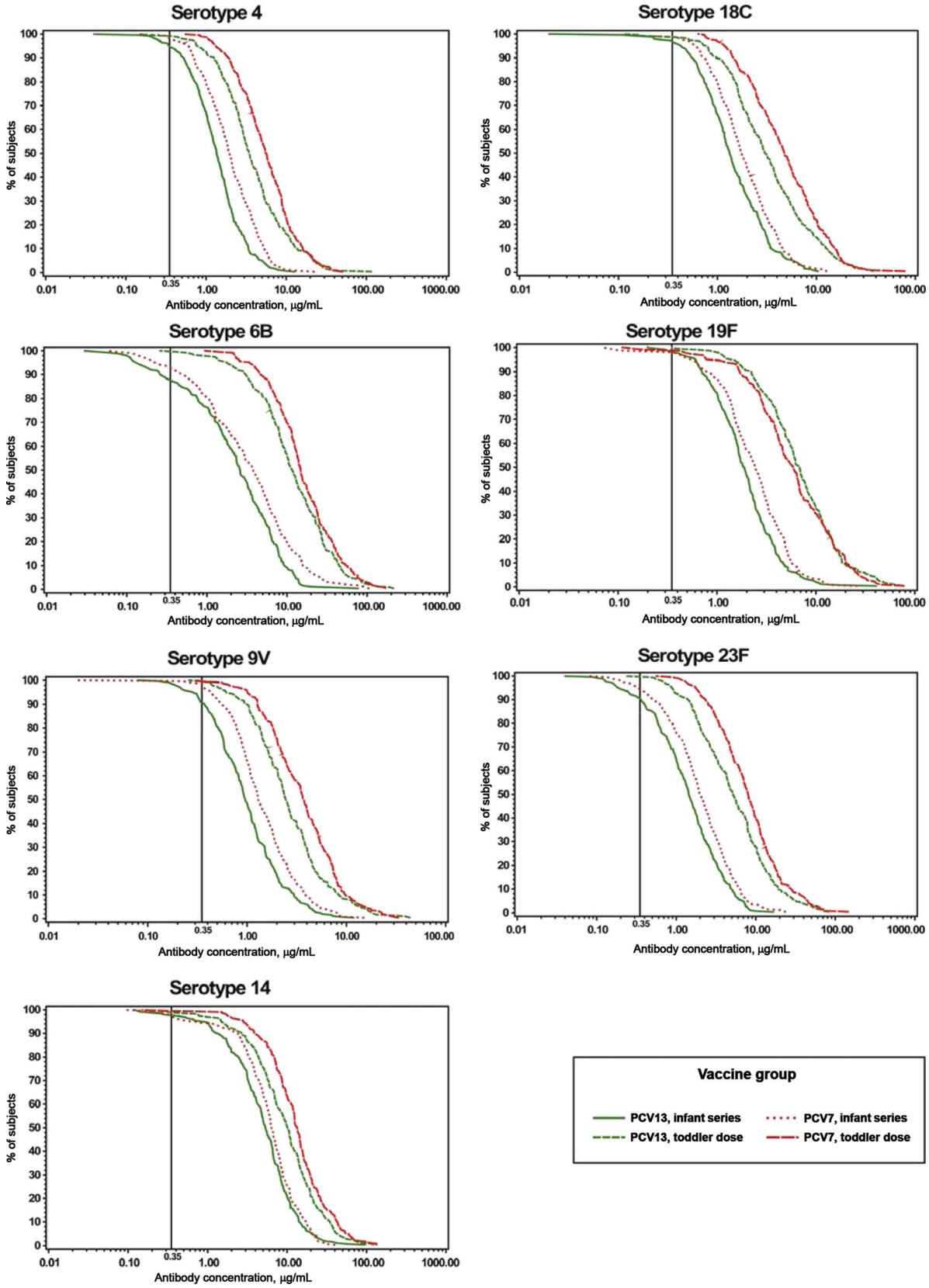

FIGURE 3

Reverse cumulative distribution curves of the antipolysaccharide IgG responses 1 month after the infant and toddler vaccinations for each of the 7 common serotypes. The vertical lines denote the IgG reference concentration of 0.35 μg/mL (see text).

TABLE 6 Subjects Reporting Local Reactions Within 7 Days

Local Reaction	Dose 1		Dose 2		Dose 3		Toddler Dose	
	PCV13, % (n^a/N^b)	PCV7, % (n/N)	PCV13, % (n/N)	PCV7, % (n/N)	PCV13, % (n/N)	PCV7, % (n/N)	PCV13, % (n/N)	PCV7, % (n/N)
Tenderness								
Any	72.7 (192/264)	72.2 (195/270)	77.0 (154/200)	75.9 (164/216)	78.7 (140/178)	80.9 (140/173)	81.2 (121/149)	84.4 (124/147)
Significant[c]	13.7 (25/182)	9.2 (18/195)	10.6 (13/123)	11.5 (15/131)	8.8 (8/91)	9.3 (8/86)	15.4 (10/65)	12.2 (6/49)
Swelling								
Any	27.4 (55/201)	23.6 (51/216)	31.2 (44/141)	29.5 (43/146)	37.9 (44/116)	36.9 (38/103)	44.0 (40/91)	50.7 (37/73)
Mild[d]	23.1 (46/199)	21.2 (45/212)	29.8 (42/141)	26.1 (37/142)	35.4 (40/113)	36.9 (38/103)	43.3 (39/90)	46.5 (33/71)
Moderate[d]	6.8 (12/176)	5.2 (10/193)	5.1 (6/118)	7.1 (9/126)	6.6 (6/91)	6.1 (5/82)	14.7 (10/68)	14.3 (7/49)
Severe[d]	0.0 (0/173)	0.0 (0/187)	0.0 (0/116)	0.0 (0/120)	0.0 (0/87)	0.0 (0/79)	0.0 (0/59)	0.0 (0/44)
Redness								
Any	35.6 (72/202)	32.3 (72/223)	45.2 (70/155)	37.8 (62/164)	48.9 (64/131)	50.0 (59/118)	54.4 (56/103)	65.5 (57/87)
Mild[d]	34.5 (69/200)	31.4 (69/220)	44.5 (69/155)	37.0 (60/162)	47.7 (61/128)	48.7 (57/117)	53.9 (55/102)	63.5 (54/85)
Moderate[d]	4.5 (8/177)	2.6 (5/191)	1.7 (2/117)	3.2 (4/124)	5.5 (5/91)	5.0 (4/80)	8.1 (5/62)	14.0 (7/50)
Severe[d]	0.0 (0/173)	0.0 (0/186)	0.0 (0/116)	0.0 (0/120)	0.0 (0/87)	0.0 (0/79)	0.0 (0/59)	0.0 (0/44)

No differences were statistically significant; $P < .05$ (Fisher's exact test, 2-sided).

[a] Number of subjects who reported the specific characteristic.

[b] Number of subjects who reported "yes" for at least 1 day or "no" for all days.

[c] Present and interfered with limb movement.

[d] Mild, 0.5–2.0 cm; moderate, 2.5–7.0 cm; and severe, >7.0 cm.

TABLE 7 Subjects Reporting Systemic Events and Antipyretic Medication Use Within 7 Days

Systemic Reaction	Dose 1		Dose 2		Dose 3		Toddler Dose	
	PCV13, % (n^a/N^b)	PCV7, % (n/N)	PCV13, % (n/N)	PCV7, % (n/N)	PCV13, % (n/N)	PCV7, % (n/N)	PCV13, % (n/N)	PCV7, % (n/N)
Fever								
≥38°C but ≤39°C	24.0 (47/196)	21.2 (43/203)	43.2 (63/146)	40.4 (61/151)	39.8 (49/123)	37.7 (40/106)	53.5 (53/99)	51.3 (39/76)
>39°C but ≤40°C	2.8 (5/177)	0.0 (0/187)[c]	2.5 (3/118)	4.9 (6/123)	8.5 (8/94)	2.5 (2/81)	6.6 (4/61)	12.5 (6/48)
>40°C	0.0 (0/174)	0.0 (0/187)	0.0 (0/116)	0.8 (1/121)	0.0 (0/87)	1.3 (1/80)	1.7 (1/60)	0.0 (0/45)
Decreased appetite	54.8 (125/228)	45.4 (108/238)	59.9 (106/177)	52.3 (91/174)	59.2 (87/147)	59.6 (81/136)	65.5 (76/116)	73.6 (81/110)
Irritability	89.6 (259/289)	85.9 (249/290)	89.8 (212/236)	91.5 (216/236)	88.4 (191/216)	92.2 (201/218)	92.0 (183/199)	93.1 (163/175)
Increased sleep	79.5 (213/268)	78.5 (212/270)	79.3 (161/203)	73.5 (147/200)	71.3 (117/164)	69.8 (104/149)	70.4 (81/115)	74.3 (81/109)
Decreased sleep	45.7 (101/221)	47.9 (113/236)	49.1 (83/169)	55.8 (96/172)	60.4 (93/154)	63.4 (85/134)	58.4 (66/113)	64.2 (61/95)
Hives	1.7 (3/178)	1.1 (2/188)	2.5 (3/118)	0.0 (0/120)	4.5 (4[c]/89)	0.0 (0[d]/79)	4.8 (3/62)	6.4 (3/47)
Use of antipyretic medication to prevent symptoms	75.0 (204/272)	74.8 (205/274)	86.7 (202/233)	83.5 (193/231)	81.2 (164/202)	84.1 (159/189)	88.4 (145/164)	90.7 (147/162)
Use of antipyretic medication to treat symptoms	78.6 (202/257)	71.8 (191/266)	82.4 (182/221)	81.9 (181/221)	82.3 (167/203)	85.6 (160/187)	84.0 (136/162)	87.7 (121/138)

[a] Number of subjects who reported the specific characteristic.

[b] Number of subjects who reported "yes" for at least 1 day or "no" for all days.

[c] Statistically significant difference; $P < .05$ (Fisher's exact test, 2-sided).

[d] One report of hives was recorded in error on the e-diary of a subject in the PCV13 group; the case was actually in a subject in the PCV7 group.

and PCV7 (77%) groups, which was expected on the basis of cross-reactivity of antigens within serogroup 6 and correlates with the protection that Prevnar has shown against 6A disease. The higher GMT to 6A in PCV13 recipients suggests there would be an added benefit from the inclusion of 6A in the vaccine. For serotypes 1, 3, 5, and 19A, serotypes that are not in Prevnar and where there is no cross-protection from the inclusion of serotype 19A, a cutoff of 1:8 discriminates well between PCV7 recipients who are not protected against these serotypes and PCV13 recipients in whom protection against disease caused by these serotypes is anticipated. However, for serotype 7F, a high percentage of PCV13 (100%) and PCV7 (76%) recipients had titers of ≥1:8, despite the fact that Prevnar does not provide protection against 7F strains. The 2 groups can easily be differentiated by the OPA GMT, which was ~100-fold greater in PCV13 recipients, and by using a cutoff of ≥1:2048 based on the 95th percentile of observed responses in PCV7 recipients. Postlicensure effectiveness studies will provide the data needed to assess the appropriateness of this cutoff.

It was suggested in a recent study that the use of an antipyretic medication led to a reduction in immunogenicity with a 10-valent PCV.[33] This and other PCV13 trials were not designed to assess effect of antipyretic use on immu-

nogenicity; posthoc analysis did not show any decreased immune response to PCV7 or PCV13 (Supplemental Text 1).

Since the licensure of Prevnar, nasopharyngeal carriage with serotype 6C has been reported in the United States and United Kingdom,[34–36] and rates of IPD attributable to 6C have increased in people age 5 or older in the United States.[37,38] Although antibody to 6B provides some cross-protection to 6A, it does not seem to protect against 6C.[38] The impact of serotype 6A in PCV13 on disease caused by serotype 6C will be determined on the basis of surveillance for IPD in the context of widespread use of PCV13.

Finally, the safety analysis presented no notable concerns for subjects who received PCV13. Overall, observations indicate that the safety profile of PCV13 is similar to that of PCV7.

CONCLUSIONS

Data from this study support that PCV13 will be as effective as PCV7 in preventing disease caused by serotypes common to both vaccines. PCV13 has a safety profile comparable to PCV7. In addition, PCV13 should mediate protection against the 6 additional serotypes, all of which are important worldwide causes of severe pneumococcal disease.

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