MAJOR ARTICLE

Comparative Immunogenicity and Efficacy of 13-Valent and 7-Valent Pneumococcal Conjugate Vaccines in Reducing Nasopharyngeal Colonization: A Randomized Double-Blind Trial

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Background. The 13-valent pneumococcal conjugate vaccine (PCV13) was licensed to replace the 7-valent pneumococcal conjugate vaccine (PCV7) based on serological noninferiority criteria. To date no randomized PCV13 pediatric trial has included clinical endpoints.

Methods. This randomized double-blind trial compared the impact of PCV13 versus PCV7 on nasopharyngeal (NP) colonization and immunogenicity. Healthy infants were randomized (1:1) to receive PCV7 or PCV13 at ages 2, 4, 6, and 12 months; NP swabs were collected at 2, 4, 6, 7, 12, 13, 18, and 24 months, and blood was drawn at 7 and 13 months. Rates of NP acquisition and prevalence, and serotype-specific immunoglobulin G (IgG) concentrations were assessed.

Results. The per protocol analysis population included 881 PCV13 and 873 PCV7 recipients. PCV13 significantly reduced NP acquisition of the additional PCV13 serotypes 1, 6A, 7F, and 19A; the cross-reacting serotype 6C; and the common PCV7 serotype 19F. For serotype 3, and the other PCV7 serotypes, there were no significant differences between the vaccine groups. There were too few serotype 5 events to draw inference. The impact on prevalence at predefined time points was similar to that observed with NP acquisition. PCV13 elicited significantly higher IgG responses for PCV13 additional serotypes and serotype 19F, and similar or lower responses for 6/7 PCV7 serotypes.

Conclusions. PCV13 resulted in lower acquisition and prevalence of NP colonization than PCV7 did for 4 additional PCV13 serotypes, and serotypes 6C and 19F. It was comparable with PCV7 for all other common serotypes. These findings predict vaccine effectiveness through both direct and indirect protection.

Clinical Trials Registration. NCT00508742.

Keywords. *S. pneumoniae*; pneumococcal conjugate vaccine; nasopharyngeal colonization; serotype prevalence; immunogenicity.

Streptococcus pneumoniae is a leading bacterial cause of invasive disease, pneumonia, and acute otitis media in children [1]. *S. pneumoniae* colonizes the nasopharynx, particularly in young children, where it serves as a reservoir for person-to-person transmission [2].

The 7-valent, 9-valent, and 10-valent pneumococcal conjugate vaccines (PCVs) are effective in preventing vaccine-type pneumococcal disease and reducing nasopharyngeal (NP) colonization [3]. The introduction of 7-valent PCV (PCV7) into vaccination programs resulted in reduction in disease due both to the direct protection of those vaccinated and indirect protection through lower carriage rates and reduced *S. pneumoniae* transmission (herd effect) [2]. However, there was

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a need for expanded serotype vaccines to broaden protection [4–7]. To address this unmet medical need, a 13-valent PCV (PCV13) was developed. PCV13 has been licensed globally based on safety and immunogenicity trials in comparison with PCV7. None of the licensure studies had a clinical endpoint. This clinical trial was conducted during PCV13 development to assess its impact, compared with PCV7, on pneumococcal colonization; which may be considered an early predictor of vaccine effectiveness [2]. This study is unique because it is the only double-blind, randomized clinical trial of PCV13 assessing the impact on NP colonization, thus eliminating the bias that is generally associated with postmarketing ecological studies evaluating the impact of PCVs on NP colonization after introduction into vaccination programs.

METHODS

Trial Design

This randomized double-blind trial was conducted in Israel by a single coordinating center overseeing activities at 11 clinical sites. The trial was approved by the Institutional Ethics Committee of the Soroka University Medical Center and the National Ethics Committee. PCV13 was not available in Israel during the period when subjects were to be vaccinated, which allowed for comparison with licensed PCV7.

Participants

Healthy, approximately 2-month-old infants (age range, 42–98 days) were enrolled after their parent(s)/legal guardian(s) provided informed consent. Participants were ineligible if they had any contraindication to vaccination, a known or suspected immune deficiency or suppression, a history of disease caused by *S. pneumoniae*, a severe chronic disorder including a severe congenital malformation or a neurological disorder, or a history of seizures; had received blood products or gamma globulins; were participating in another investigational trial; or were direct descendants of study-site personnel.

Vaccines

PCV13 or PCV7 was administered at ages 2, 4, 6, and 12 months by intramuscular injection into the anterolateral left thigh. Other pediatric vaccines were administered according to national recommendations into the anterolateral right thigh. PCV7 contains saccharides from pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, each individually conjugated to CRM197. PCV13 contains saccharides from the pneumococcal serotypes in PCV7 plus serotypes 1, 3, 5, 6A, 7F, and 19A, each individually conjugated to CRM197. Both vaccines were manufactured by Pfizer Inc and are formulated to contain 2.2 μg of each saccharide, except for 4.4 μg of serotype 6B, 5 mM succinate buffer, and 0.125 mg of aluminum as aluminum phosphate per 0.5-mL dose. PCV13 also included 0.02% polysorbate 80 as an excipient. PCV13 and PCV7 used in this study were identical in appearance.

Nasopharyngeal Cultures, Blood Sampling, and Laboratory Testing

NP swabs were collected from participants at ages 2, 4, 6, 7, 12, 13, 18, and 24 months using flexible Dacron-tipped swabs; swabs and cultures were prepared as previously described [8]. All cultured swab samples that tested positive for *S. pneumoniae* were taken forward for serotyping by the Quellung reaction [9] using antisera (Statens Serum Institut, Copenhagen, Denmark). Isolates with negative reactions to all pooled serum samples and to omni serum were considered to be nontypeable. All isolates testing positive by Quellung reaction to serotype 6A were further characterized by polymerase chain reaction testing to differentiate between 6A or 6C, as previously described [4].

Blood samples were obtained at age 7 and 13 months (approximately 1 month after the infant series and toddler dose, respectively). Standardized enzyme-linked immunosorbent assay (ELISA) was used to determine serum concentrations of anticapsular-binding immunoglobulin G (IgG) antibodies for each pneumococcal serotype included in PCV13, using the international reference serum 89-SF. ELISA used a C polysaccharide-containing cell wall extract plus serotype 22F capsular polysaccharide as absorbents [10, 11].

Outcomes

The impact of PCV13 and PCV7 on newly identified NP acquisition of serotypes, combined or as single serotypes, was assessed by measuring the proportion of participants with a new acquisition from 1 month after the infant series (age 7 months) to 24 months of age. A new acquisition was defined as detection of a given serotype that was not previously identified at baseline (ages 2, 4, and 6 months), or at any other time point before the detection. Therefore, only 1 new acquisition was counted for each serotype per participant [8, 12]. Initially, the primary endpoint was new acquisition of serotypes 6A and 19A combined. However, during the study a new capsular serotype within serogroup 6, serotype 6C, was identified, which needed to be distinguished from serotype 6A [13, 14]. The primary objective was, therefore, modified to NP acquisition of serotypes 6A, 6C, and 19A combined. New acquisition for other serotypes and serotype combinations was also assessed.

The prevalence of NP colonization was calculated at each visit at age 7, 12, 13, 18, and 24 months as the proportion of positive cultures relative to the total number of nonmissing cultures. A post hoc analysis compared the cumulative prevalence of colonization between the vaccine groups. Cumulative prevalence was defined as the percentage of participants observed to

carry a serotype or combination of serotypes at any time from the age 7 months visit up to and including a given time point.

For immunogenicity endpoints, IgG concentrations were measured and geometric mean concentrations (GMCs) calculated. Safety endpoints included the incidence of medically important and related adverse events (AEs), those resulting in withdrawal, those associated with antibiotic use, and all serious AEs (SAEs), which were collected by the investigator at each visit.

Sample Size

The target sample size was approximately 1864 participants randomized to treatment, with an estimated 1640 evaluable participants. Using a 2-sided type I error rate of 0.05, a sample size of 820 participants per group was expected to provide ≥90% power to show reduction of new acquisitions of serotypes 6A, 6C, and 19A combined.

Randomization and Blinding

In this double-blind study, subjects were randomized to vaccine groups in a 1:1 ratio of PCV13:PCV7. Allocation of subjects to vaccine groups was performed using a manual randomization envelope system using 8 treatment letters that represent a 1:1 ratio of PCV7:PCV13. Randomization envelopes were used in sequential order at each site to assign the subject's randomization number and a treatment letter.

Statistical Methods

The primary per protocol NP culture analysis included eligible healthy infants who received the treatment to which they were randomized, had at least 1 NP swab for the proposed analysis, and had no other major protocol violations. The proportion of participants within each vaccine group with new acquisition 1 month after the infant series (age 7 months) to 24 months of age was summarized for single serotypes and combined serotypes. The rate ratio (PCV13:PCV7) was calculated and 95% confidence intervals (CIs) were derived using an exact procedure based on the method of Chan and Zhang [15].

Prevalence of NP colonization at 7, 12, 13, 18, and 24 months of age for single and combined serotypes was calculated based on the proportion of subjects with positive culture findings. Odds ratios (PCV13:PCV7) were derived and 2-sided 95% CIs constructed using logistic regression. Cumulative prevalence of NP colonization was derived using the percentage of subjects observed to carry a serotype (or combination of serotypes). The rate ratio (PCV13:PCV7) was summarized and 2-sided 95% CIs were calculated.

Serotype-specific IgG antibody concentrations were logarithmically transformed for analysis. Two-sided CIs for the ratio of GMCs PCV13:PCV7 were constructed by back-transformation of the CIs for the difference of the 2 logarithmically transformed assay results.

AEs were categorized according to the Medical Dictionary for Regulatory Activities and summarized by vaccine group for each vaccination separately. Comparisons between groups were performed using a 2-sided Fisher exact test.

Statistics were derived using SAS (version 9.2) and Proc StatXact (version 8.1).

RESULTS

Participants

Between February 2008 and September 2009, a total of 1866 healthy infants were randomly assigned to receive PCV13 or PCV7. The last study visit was September 2011. Participant flow is shown in Figure 1. The demographic characteristics of the per protocol analysis populations were similar (Table 1).

Nasopharyngeal Colonization

PCV13 Additional Serotypes Plus Serotype 6C

PCV13 compared with PCV7 significantly reduced rates of newly identified NP acquisition within 7–24 months of age for additional serotypes 6A, 6C, and 19A combined; PCV13 additional serotypes (1, 3, 5, 6A, 7F, and 19A) and serotype 6C combined; and single serotypes 1, 6A, 6C, 7F, and 19A (Table 2). For serotype 3 there were no differences in NP acquisition rates between the vaccine groups. There were too few NP acquisition events of serotype 5 to draw inference.

NP prevalence was significantly lower in the PCV13 group than in the PCV7 group at all predetermined points for PCV13 additional serotypes combined and for serotype 6C (Figure 2). For single serotypes, carriage in PCV13 recipients was significantly lower at ≥3 predetermined points for serotypes 6A and 19A (Figure 2). For single serotypes 1, 6C, and 7F, the differences in prevalence at each age point were not significant, although they were generally lower in the PCV13 group.

Findings for impact of PCV13 on cumulative prevalence for each additional serotype were consistent with the significant reductions observed by PCV13 on newly identified NP acquisition. For serotype 3, there were no differences in rates between the vaccine groups (Figure 3, Supplementary Table 1).

Common PCV13 and PCV7 Serotypes

For the common serotypes combined and for single serotypes 4, 6B, 9V, 14, 18C, and 23F, there were no significant differences in rates of newly identified NP acquisition between the vaccine groups. For serotype 19F, PCV13 significantly reduced the rate of NP acquisition compared with PCV7 (Table 2).

The NP prevalence at predefined age points of the common serotypes combined (Figure 2) and as single serotypes was similar between the 2 vaccine groups with the exception of

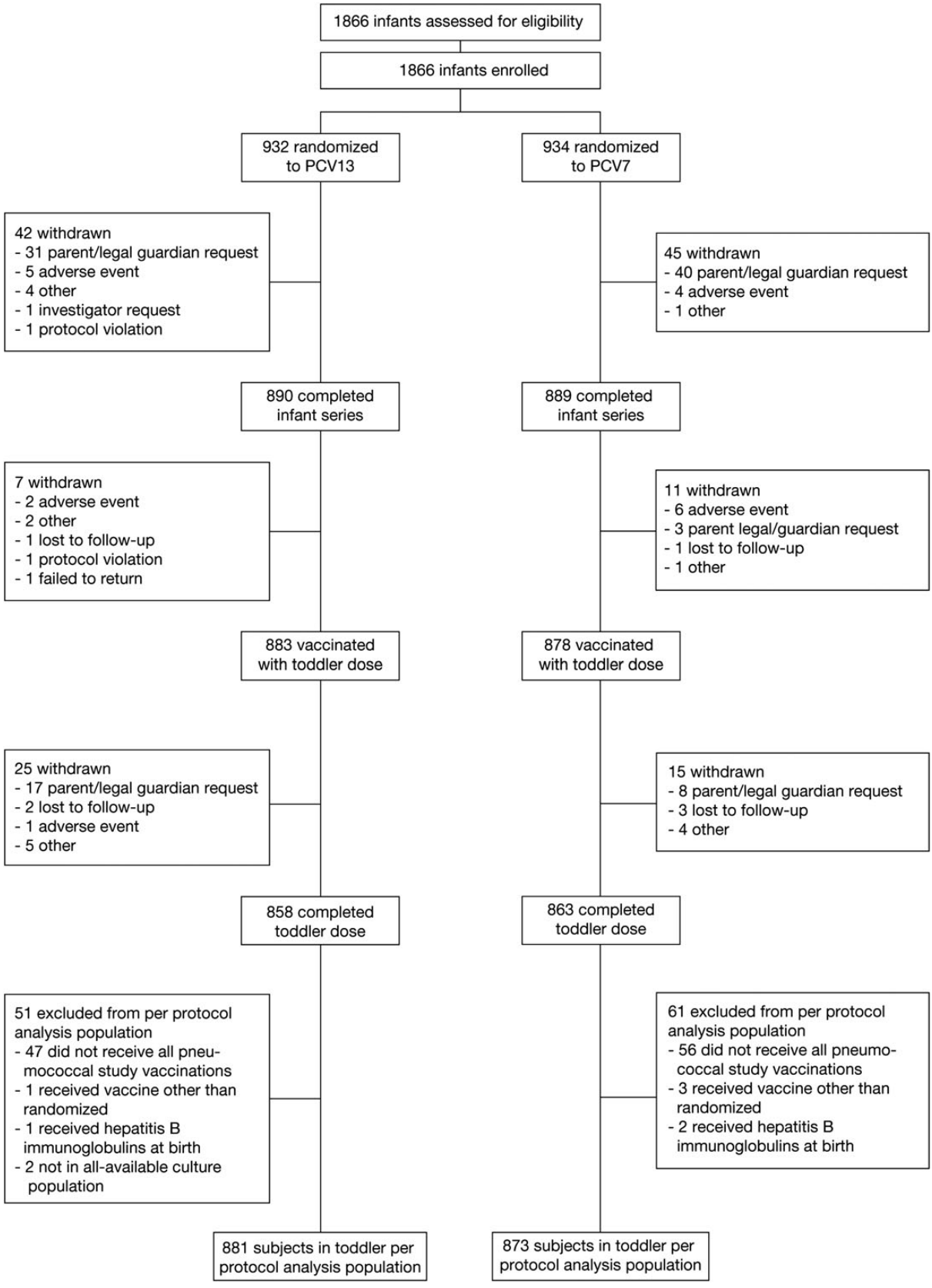


Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram. Abbreviations: PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

Table 1 Demographic Characteristics of the Per Protocol Analysis Populations

Characteristic	Vaccine Group as Randomized		
	PCV13 (n = 881)	PCV7 (n = 873)	Total (N = 1754)
Sex, No. (%)			
Female	452 (51.3)	438 (50.2)	890 (50.7)
Male	429 (48.7)	435 (49.8)	864 (49.3)
Age, mo, mean (±SD)			
Dose 1	2.2 (0.3)	2.2 (0.3)	2.2 (0.3)
Dose 2	3.9 (0.4)	3.9 (0.4)	3.9 (0.4)
Dose 3	5.7 (0.5)	5.7 (0.5)	5.7 (0.5)
Toddler dose[a]	12.5 (0.5)	12.5 (0.6)	12.5 (0.6)
Weight, kg, mean (±SD) at enrollment	5.2 (0.7)	5.2 (0.7)	5.2 (0.7)
Ethnicity, No. (%)			
Jewish children	583 (66.2)	571 (65.4)	1154 (65.8)
Bedouin children	295 (33.5)	300 (34.4)	595 (33.9)
Others	3 (0.3)	2 (0.2)	5 (0.3)

Abbreviations: PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; SD, standard deviation.

[a] Toddler dose mean age (±SD) was calculated using the safety population (PCV13, n = 884; PCV7, n = 877; N = 1761).

serotype 19F. Serotype 19F had a lower prevalence in the PCV13 group compared with the PCV7 group at all age points, and significantly lower at 12 and 13 months of age (Figure 2).

Findings for impact of PCV13 on cumulative prevalence for each common serotype were consistent with those of PCV13 on newly identified NP acquisition, with significant reductions for serotype 19F only (Figure 3, Supplementary Table 1).

Nonvaccine Serotypes

Overall rates of newly identified NP acquisition of nonvaccine serotypes combined were significantly higher in the PCV13 group compared with the PCV7 group (Table 2). Similar findings were observed for cumulative prevalence of NP colonization (Supplementary Table 1). For prevalence of nonvaccine serotypes combined at predefined time points, trends toward higher prevalence in the PCV13 group were significant at 24 months only (Figure 2).

The most common nonvaccine serotypes across groups were serotypes 15A, 15B/C, 16F, 23A, 35B, and 38, which, when combined, constituted 49.0% and 44.4% of all nonvaccine serotypes in the PCV13 and PCV7 groups, respectively. No significant differences for single serotypes between groups were observed except for serotype 15B/C, for which rates were significantly higher in the PCV13 group (Supplementary Table 2).

All Serotypes Combined (Overall Pneumococcal Carriage)

For all serotypes combined, there were no differences in rates of newly identified NP acquisition or in the cumulative prevalence between the 2 vaccine groups (Table 2, Supplementary Table 1).

Immunogenicity

For each of the additional serotypes, PCV13 elicited statistically significantly higher IgG responses than PCV7 (Table 3). For the common serotypes, PCV13 elicited similar (serotypes 4, 6B, 9V, and 18C) or significantly lower (serotypes 14 and 23F) IgG responses than after PCV7 administration, with the exception of 19F where IgG concentrations were significantly higher after PCV13.

Safety

Overall there were no significant differences between PCV13 and PCV7 groups in the incidence of AEs collected in this study. There was 1 unrelated case of sudden death of unknown cause in the PCV13 group. None of the reported SAEs was considered related to the study vaccines.

DISCUSSION

This clinical trial showed that PCV13 compared with PCV7 significantly reduced NP colonization of the additional PCV13 serotypes (and serotype 6C) combined; this was due to significant reductions in single serotypes 1, 6A, 6C, 7F, and 19A. In addition, a significant reduction in the common PCV7 serotype 19F was observed, where the IgG GMCs in PCV13 recipients were higher than in PCV7 recipients. There was no significant difference between the vaccine groups for serotype 3 and for the other 6 common PCV7 serotypes. There were too few serotype 5 events to draw inference.

Our assessment was based on rates of newly identified NP acquisition, prevalence, and cumulative prevalence. Serotype 6C, although not a PCV13 serotype, was included in the assessment, as during the study (and prior to unblinding the study) it became apparent that this serotype, which is structurally similar to 6A, could now be distinguished from 6A and should be assessed separately [14]. Of the PCV13 additional serotypes that are important causes of pneumococcal disease, not all were carried frequently. Serotypes 6A and 19A were most frequently carried.

Although reduction in NP acquisition may be predictive of direct protection for vaccinated individuals, assessment of prevalence and cumulative prevalence may be more predictive of indirect effects on the community as prevalence and cumulative prevalence better reflect the period during which individuals may transmit the organism. Reduction in carriage is associated with disease reduction in adults and nonvaccinated children [2].

These data support findings from recent surveillance studies where significant reductions in the prevalence of NP colonization

Table 2. Comparison of Subjects With Newly Identified Nasopharyngeal Acquisition of a Pneumococcal Serotype, 1 Month After Infant Series (7–24 Months of Age)

Serotype or Combination of Serotypes	No.[a]	PCV13 (n = 801–881), % (95% CI)	No.[a]	PCV7 (n = 804–873), % (95% CI)	Rate Ratio (95% CI)
PCV13 and PCV7 common serotypes					
4	4	0.5 (.1–1.2)	5	0.6 (.2–1.3)	0.79 (.18–3.29)
6B	43	5.4 (3.9–7.2)	60	7.5 (5.7–9.5)	0.72 (.49–1.05)
9V	17	2.0 (1.2–3.1)	17	2.0 (1.2–3.1)	1.00 (.49–2.07)
14	50	5.9 (4.4–7.8)	37	4.4 (3.1–6.0)	1.35 (.89–2.07)
18C	15	1.7 (1.0–2.8)	15	1.8 (1.0–2.9)	0.98 (.47–2.06)
19F	66	7.9 (6.2–10.0)	101	12.2 (10.0–14.6)	0.65 (.48–.87)
23F	37	4.4 (3.1–6.0)	26	3.2 (2.1–4.6)	1.39 (.85–2.31)
PCV13 additional serotypes plus serotype 6C					
1	0	0.0 (.0–.4)	8	0.9 (.4–1.8)	0.00 (NE–.44)
3	16	1.8 (1.1–3.0)	16	1.9 (1.1–3.0)	0.99 (.48–2.06)
5	1	0.1 (.0–.6)	2	0.2 (.0–.8)	0.50 (.02–5.54)
6A	63	7.7 (5.9–9.7)	106	13.2 (10.9–15.7)	0.58 (.43–.78)
6C	23	2.7 (1.7–4.0)	51	6.0 (4.5–7.8)	0.44 (.27–.71)
7F	3	0.3 (.1–1.0)	11	1.3 (.6–2.3)	0.27 (.04–.90)
19A	105	12.6 (10.4–15.1)	190	22.9 (20.1–25.9)	0.55 (.44–.68)
Serotype combinations					
6A/C	79	9.0 (7.2–11.1)	151	17.3 (14.8–20.0)	0.52 (.40–.67)
6A/C or 19A	128	20.0 (17.4–22.8)	230	36.0 (32.8–39.3)	0.56 (.47–.65)
1, 3, 5, 6A/C, 7F, or 19A	192	21.8 (19.1–24.7)	335	38.4 (35.1–41.7)	0.57 (.49–0.66)
4, 6B, 9V, 14, 18C, 19F, or 23F	208	23.6 (20.8–26.6)	239	27.4 (24.4–30.5)	0.86 (.73–1.01)
PCV13 vaccine serotypes	360	40.9 (37.6–44.2)	499	57.2 (53.8–60.5)	0.71 (.65–.79)
Nonvaccine serotypes	665	75.5 (72.5–78.3)	609	69.8 (66.6–72.8)	1.08 (1.02–1.15)
All serotypes		**85.2 (82.7–87.5)**		**85.3 (82.8–87.6)**	**1.00 (.96–1.04)**

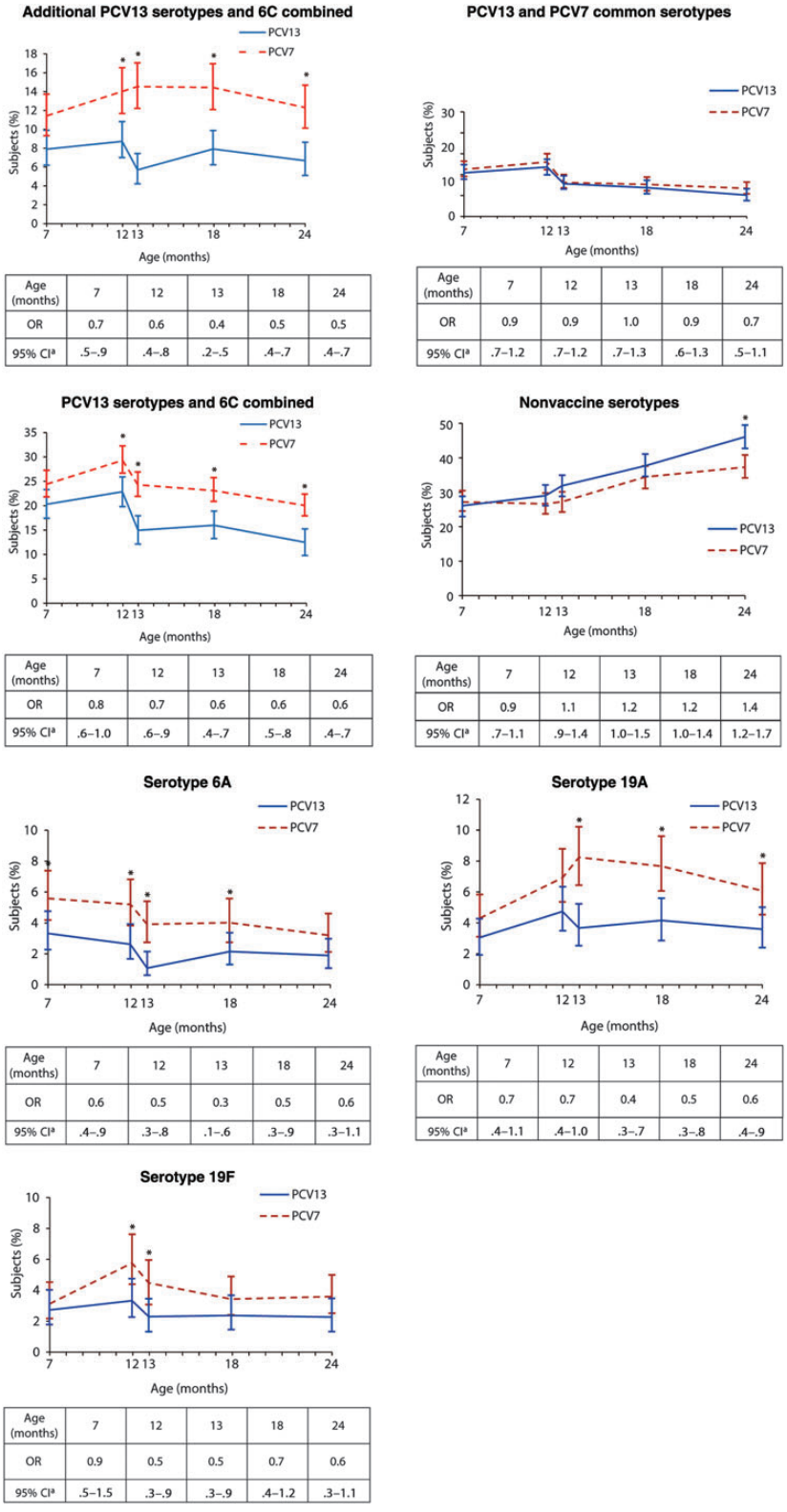
Abbreviations: CI, confidence interval; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

[a] No. of subjects with at least 1 determinate nasopharyngeal culture result for any of the given serotypes or combinations.

of PCV13 serotypes 19A, 7F, and 6C, with no significant reductions for serotype 3, were observed with PCV13 compared with PCV7 recipients during acute otitis media episodes [16]. Similarly, reductions in carriage of PCV13 serotypes, particularly serotype 19A, were observed following introduction of PCV13 in Atlanta, Georgia [17], and Boston, Massachusetts [18]. These findings are also consistent with efficacy data from surveillance studies of invasive pneumococcal disease (IPD) rates in children pre– and post–PVC13 introduction in the United Kingdom, the United States, and Germany, which showed reduced rates of IPD overall, and IPD caused primarily by PCV13 serotypes 19A and 7F [19–21]. Furthermore, Moore et al observed a 45%–65% reduction in IPD across all adult age groups caused primarily by serotypes 19A and 7F, supporting herd protection due to low carriage of these serotypes in vaccinees [20].

The increase in NP colonization of nonvaccine serotypes observed in this study in the PCV13 compared with PCV7 group has been reported elsewhere following PCV administration [8, 22]. In this study nonvaccine serotypes 15A, 15B/C, 16F, 23A, 35B, and 38 were most commonly observed in both vaccine groups, with only serotype 15B/C significantly higher in the PCV13 group. The disease replacement that has been observed since the introduction of PCV7 was due mainly to the serotypes in PCV13 (mostly serotypes 7F and 19A); other serotypes that are not in PCV13 have not usually caused as much disease [6]. Several serotypes, including 3 of the most common nonvaccine serotypes in our study (15A, 15B/C, and 35B) were also frequently observed after PCV13 introduction in France [16].

The IgG immune responses elicited by PCV13 compared with PCV7 correspond with the impact on NP colonization. For the 6 additional PCV13 serotypes and common serotype 19F, PCV13 was significantly more immunogenic than PCV7 and this corresponded with a significant impact on NP colonization for the majority of these serotypes; the exceptions were for serotype 5, for which there were too few acquisitions to draw inference, and serotype 3 where no impact on colonization was observed. Overall serotype 3 elicited the lowest immune response of the PCV13 serotypes. Whether the immune responses to serotype 3 will be associated with an impact on serotype 3 disease will need to be closely monitored. For common



Additional PCV13 serotypes and 6C combined					
Age (months)	7	12	13	18	24
OR	0.7	0.6	0.4	0.5	0.5
95% CI[a]	.5–.9	.4–.8	.2–.5	.4–.7	.4–.7

PCV13 and PCV7 common serotypes					
Age (months)	7	12	13	18	24
OR	0.9	0.9	1.0	0.9	0.7
95% CI[a]	.7–1.2	.7–1.2	.7–1.3	.6–1.3	.5–1.1

PCV13 serotypes and 6C combined					
Age (months)	7	12	13	18	24
OR	0.8	0.7	0.6	0.6	0.6
95% CI[a]	.6–1.0	.6–.9	.4–.7	.5–.8	.4–.7

Nonvaccine serotypes					
Age (months)	7	12	13	18	24
OR	0.9	1.1	1.2	1.2	1.4
95% CI[a]	.7–1.1	.9–1.4	1.0–1.5	1.0–1.4	1.2–1.7

Serotype 6A					
Age (months)	7	12	13	18	24
OR	0.6	0.5	0.3	0.5	0.6
95% CI[a]	.4–.9	.3–.8	.1–.6	.3–.9	.3–1.1

Serotype 19A					
Age (months)	7	12	13	18	24
OR	0.7	0.7	0.4	0.5	0.6
95% CI[a]	.4–1.1	.4–1.0	.3–.7	.3–.8	.4–.9

Serotype 19F					
Age (months)	7	12	13	18	24
OR	0.9	0.5	0.5	0.7	0.6
95% CI[a]	.5–1.5	.3–.9	.3–.9	.4–1.2	.3–1.1

Figure 2. Prevalence of 13-valent pneumococcal conjugate vaccine (PCV13) additional serotypes and 6C; 7-valent pneumococcal conjugate vaccine (PCV7) and PCV13 common serotypes; PCV13 serotypes and 6C combined and nonvaccine serotypes; and single serotypes 6A, 19A, and 19F in each vaccine group at predefined time points. *Difference in serotype prevalence between vaccine groups was significant (upper limit of odds ratio confidence interval [CI] <1 or lower limit of 95% CI >1). [a]Two-sided CI for the odds ratio of PCV13:PCV7. Abbreviations: CI, confidence interval; OR, odds ratio; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

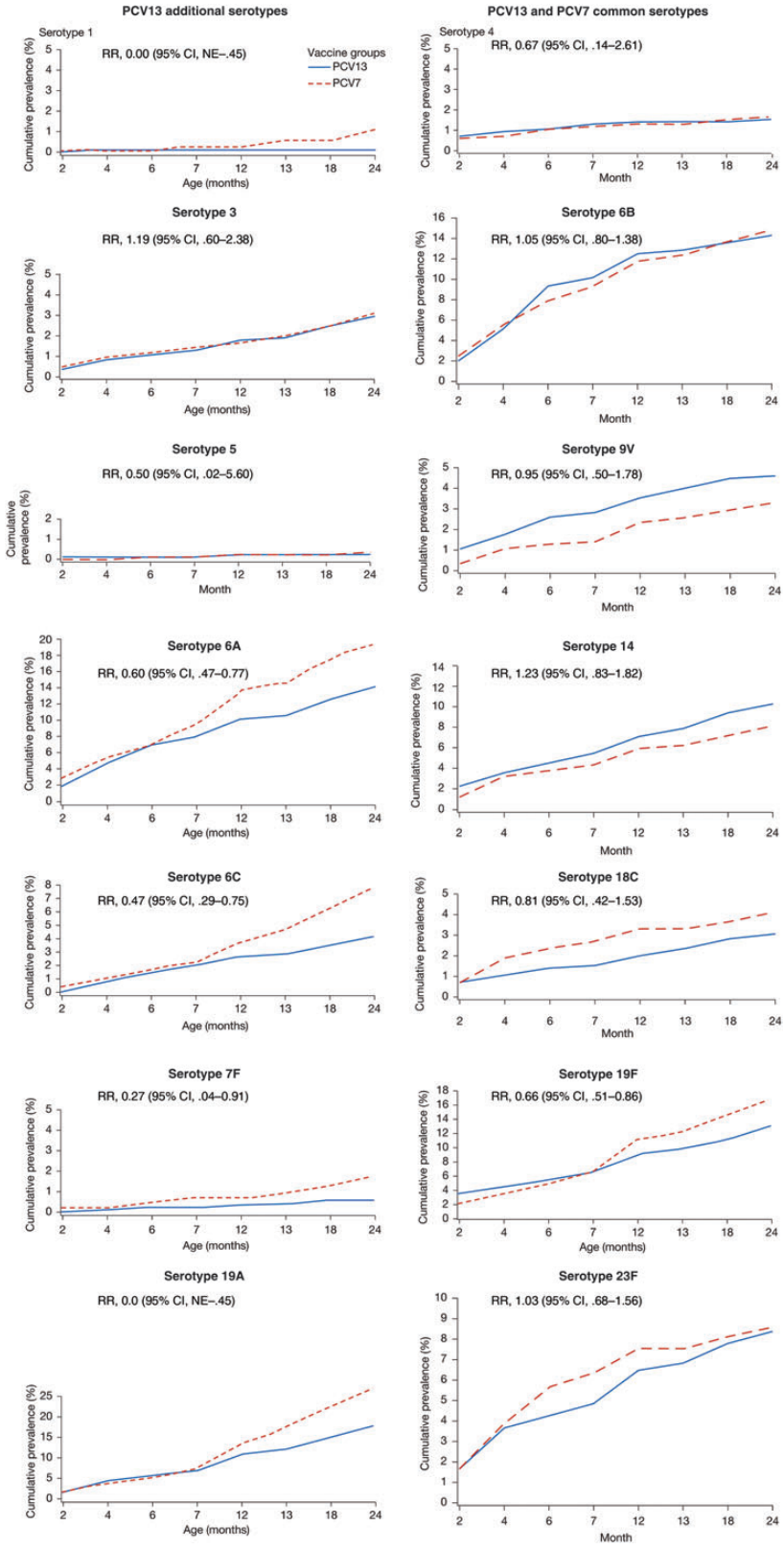


Figure 3. The impact of 13-valent pneumococcal conjugate vaccine (PCV13) and 7-valent pneumococcal conjugate vaccine (PCV7) on cumulative prevalence of nasopharyngeal acquisition for additional PCV13 serotypes 1, 3, 5, 6A, 6C, 7F, and 19A and common serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F measured from 7 months to 24 months of age. Abbreviations: CI, confidence interval; NE, not estimable; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; RR, rate ratio.

Table 3. Immunoglobulin G Immune Response for PCV13 Serotypes: Per Protocol Population (PCV7 and PCV13 Common Serotypes, and PCV13 Additional Serotypes)

		PCV13 and PCV7 Common Serotypes						
Response	Group	4	6B	9V	14	18C	19F	23F
Infant series								
IgG GMC, μg/mL	PCV13 (n = 741–765)	2.16	2.26	1.40	5.72	1.49	2.90	1.13
	PCV7 (n = 715–782	2.02	2.30	1.44	6.46	1.47	2.23	1.57
GMC ratio (95% CI)		1.07 (.99–1.15)	0.98 (.87–1.10)	0.98 (.91–1.05)	0.89 (.79–.99)	1.02 (.93–1.11)	1.30 (1.19–1.42)	0.72 (.65–.81)
Toddler dose								
IgG GMC, μg/mL	PCV13 (n = 785–797)	4.84	10.77	3.98	12.11	4.20	11.06	5.79
	PCV7 (n = 674–798	4.91	11.88	4.22	13.64	4.24	5.35	7.77
GMC ratio (95% CI)		0.99 (.90–1.08)	0.91 (.82–1.00)	0.94 (.87–1.02)	0.89 (.81–.98)	0.99 (.90–1.09)	2.07 (1.87–2.29)	0.74 (.67–.83)

		PCV13 Additional Serotypes					
Response	Group	1	3	5	6A	7F	19A
Infant series							
IgG GMC, μg/mL	PCV13 (n = 741–765)	2.08	0.97	1.38	2.53	3.34	1.81
	PCV7 (n = 715–779)	0.02	0.04	0.23	0.36	0.05	0.70
GMC ratio (95% CI)		95.03 (86.63–104.26)	25.46 (22.73–28.52)	6.05 (5.44–6.74)	6.95 (6.25–7.72)	67.52 (61.70–73.88)	2.60 (2.37–2.85)
Toddler dose							
IgG GMC, μg/mL	PCV13 (n = 785–797)	5.20	1.42	4.25	10.48	8.07	8.83
	PCV7 (n = 647–797)	0.04	0.08	0.55	2.20	0.07	2.63
GMC ratio (95% CI)		133.97 (121.16–148.13)	17.76 (15.72–20.05)	7.70 (6.88–8.62)	4.76 (4.28–5.29)	113.75 (101.50–127.48)	3.36 (3.07–3.68)

Abbreviations: CI, confidence interval; GMC, geometric mean concentration; IgG, immunoglobulin G; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

serotypes 14 and 23F with significantly lower immune responses in the PCV13 group, there was a parallel tendency for higher carriage in the PCV13 group, but differences were not statistically significant between vaccine groups.

Of interest, in this study serotype 19F in PCV13 elicited higher IgG responses compared with PCV7 after the infant series and after the toddler dose. Higher responses in PCV13 recipients have not been observed consistently across PCV13 studies after the infant series, but after the toddler dose responses have consistently been higher in PCV13 recipients [23–26]. Haston et al observed similar findings both by ELISA and opsonophagocytic activity (OPA) assays after the infant series in a small study and, based on further OPA analysis with 19A polysaccharide adsorption, suggested that PCV13 may have enhanced activity against serotype 19F due to cross-reactive antibodies induced by 19A [27]. Changes made to optimize the manufacturing processes of serotype 19F in PCV13 compared with PCV7 may have influenced immune responses. In addition, a trend for lower acquisition of serotype 6B was observed in the PCV13 group compared with the PCV7 group. This may have been augmented by cross-reaction with serotype 6A, although this was not reflected by the immune response elicited by serotype 6B, which tended to be lower in the PCV13 group compared with the PCV7 group.

Adverse events collected in this study were consistent with the overall satisfactory safety profile of PCV13; there was no daily assessment of reactogenicity as these data were available from other PCV13 studies and were not the focus of this study [23–25].

Study limitations include the inability to identify co-colonization with multiple serotypes, and the very conservative approach taken in defining new NP acquisition. Thus, there is the possibility that NP acquisitions occurred more frequently than those detected in this study. However, these limitations existed for both arms of the study.

PCV13 resulted in lower acquisition and prevalence of NP colonization than PCV7 for the majority of additional PCV13 serotypes as well as serotypes 6C and 19F, and it was comparable with PCV7 with regards to all other common serotypes. These findings represent the first evidence of a clinical impact of PCV13 associated with immune responses, which may serve as a predictor of vaccine effectiveness through both direct and indirect protection.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. R. D. has received (in the last 5 years) grants/research support from Berna/Crucell, Wyeth/Pfizer, MSD, and Protea; has been a scientific consultant for Berna/Crucell, GlaxoSmithKline (GSK), Novartis, Wyeth/Pfizer, Protea, and MSD and a speaker for Berna/Crucell, GSK, and Wyeth/Pfizer; and is a shareholder of Protea/NASVAX. D. G. has been a speaker for GSK, MSD, Pfizer, and Abbott and a scientific consultant for GSK and A.I.T. (Advance Inhalation Therapy); has received grants from A.I.T., MSD, and Abbott; and is a shareholder of A.I.T. S. P., C. J., A. G., W. C. G., and D. A. S. are employees of Pfizer Inc. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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