

13-Valent Pneumococcal Conjugate Vaccine (PCV13) in Preterm Versus Term Infants

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abstract

OBJECTIVES: This study evaluated the immune response and safety profile of 13-valent pneumococcal conjugate vaccine (PCV13) in preterm infants compared with term infants.

METHODS: This Phase IV, open-label, 2-arm, multicenter, parallel-group study enrolled 200 healthy infants (preterm, $n = 100$; term, $n = 100$) aged 42 to 98 days. All subjects received PCV13 at ages 2, 3, 4 (infant series), and 12 (toddler dose [TD]) months, together with routine vaccines (diphtheria-tetanus-acellular pertussis, hepatitis B, inactivated poliovirus, and *Haemophilus influenzae* type b vaccine and meningococcal group C conjugate vaccine).

RESULTS: Most subjects achieved an anticapsular immunoglobulin G (IgG) antibody concentration $\geq 0.35 \mu\text{g/mL}$ for all serotypes: $>85\%$ after the infant series (except preterm infants for serotypes 5, 6A, and 6B) and $>97\%$ after TD (except for serotype 3). Preterm infants had overall lower IgG geometric mean concentrations compared with term infants; however, geometric mean fold increases after TD were similar for all serotypes. Opsonophagocytic activity results were consistent with IgG results and titers increased after TD in both groups for all serotypes, including serotype 3. PCV13 was generally well tolerated, with similar safety profiles in all preterm subgroups.

CONCLUSIONS: Immune responses were lower in preterm infants than in term infants. However, the majority of subjects in both groups achieved both pneumococcal serotype-specific IgG antibody levels after the infant series that exceeded the World Health Organization-established threshold of protection and functional antibody responses. Responses were uniformly higher after TD, reinforcing the importance of a timely booster dose. PCV13 was well tolerated regardless of gestational age.



WHAT'S KNOWN ON THIS SUBJECT: Preterm infants are at an increased risk of infections; therefore, vaccination is of particular importance. Because immune response data reported for preterm infants may vary according to gestational age and vaccination timing, vaccine responses in this population warrant additional research.

WHAT THIS STUDY ADDS: This study evaluated 13-valent pneumococcal conjugate vaccine in preterm infants. Results suggest that this vaccine was well tolerated and immunogenic; most subjects achieved serotype-specific immunoglobulin G antibody levels and functional antibody responses likely to correlate with protection against invasive disease.

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Dr Martín-Torres provided clinical coordination of the recruiting network, subjects, and samples, as well as contributed to the design and development of the manuscript (which included review of drafts); Dr Czajka was involved in recruiting subjects, collecting data, and reviewing the manuscript drafts; Dr Center participated in the study design, monitored the safety of participating subjects during the study, participated in analysis and interpretation of the data, and contributed to manuscript development (which included review and revision of drafts); Dr Bernaola Iturbe approved the final protocol, participated as an investigator in the clinical trial, recruited and followed up with subjects, and reviewed the manuscript drafts;

Preterm infants are at increased risk for invasive pneumococcal disease (IPD), particularly infants born at <32 weeks of gestation.^{1,2} This risk may be due to several factors, including reduced materno-fetal transfer of pneumococcal antibodies³ and a decreased response to *Streptococcus pneumoniae* due to an immature immune system.⁴ Studies evaluating immune responses of preterm infants receiving pneumococcal vaccinations are scarce, and methodologic differences limit interpretation of the findings.^{2,5-7} However, the data suggest that gestational age (GA) and vaccination timing (eg, allowing for immune maturation) may affect the ability of preterm infants to respond adequately to immunization. To the best of our knowledge, to date, no study has evaluated the 13-valent pneumococcal conjugate vaccine (PCV13) in preterm infants.

The present study evaluated the immunogenicity, safety, and tolerability of a dose schedule of PCV13 given with routine concomitant vaccines to preterm and term infants at 2, 3, 4, and 12 months of age.

METHODS

Objectives

The study's primary and secondary objectives were to describe the pneumococcal immune response induced by PCV13 when measured 1 month after the infant series and 1 month after the toddler dose, respectively, in preterm infants compared with term infants (≥ 37 weeks of gestation). Safety was evaluated in preterm and term infants, as measured by the incidence rates of local reactions, systemic events, and adverse events (AEs).

Study Design and Subjects

This open-label, Phase IV, 2-arm, multicenter, parallel-group study was approved by institutional review

boards and/or independent ethics committees. It was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonisation, the Good Clinical Practice Guideline, and all local regulatory requirements.

Subjects were designated preterm or term based on GA at birth. At inclusion, all subjects were considered in generally healthy condition according to investigator judgment based on medical history and physical examination. Exclusion criteria included contraindication to routine pediatric vaccines, bleeding diathesis, history of culture-proven disease caused by *S pneumoniae*, immune deficiency or suppression, and any serious chronic disorders or major illnesses. Between October 2010 and February 2011, a total of 100 subjects per group were screened and enrolled across 5 sites in Poland (50 term and 50 preterm) and 6 sites in Spain (50 term and 50 preterm). Preterm infants were classified according to GA (32 to <37 completed weeks; 29 to <32 weeks; and <29 weeks). Medical history characteristics were collected for all subjects at enrollment. All subjects received PCV13 at 2, 3, 4 (infant series), and 12 (toddler dose) months of age. A long-term follow-up period to evaluate antibody persistence at 12 and 24 months after the toddler dose was ongoing at the time of the present report.

Vaccines Administered

The 13-valent pneumococcal conjugate vaccine (Prevnar 13, Wyeth Pharmaceuticals Inc, Collegeville, PA; lot number E09498) contains polysaccharides of pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to a nontoxic form of diphtheria toxin cross-reactive material 197. Each 0.5-mL dose, supplied as a single-dose syringe, contains 2.2 μg of each serotype, except type 6B, which contains 4.4 μg . PCV13 was administered by

intramuscular injection in the left anterolateral thigh muscle. In accordance with local routine vaccination plans, subjects also received 2 licensed vaccines in the right thigh: diphtheria-tetanus-acellular pertussis, hepatitis B, inactivated poliovirus, and *Haemophilus influenzae* type b vaccine (Infanrix hexa, GlaxoSmithKline Biologicals, Rixensart, Belgium) at 2, 3, 4, and 12 months of age and meningococcal group C oligosaccharide conjugate vaccine (Meningitec, Wyeth Pharmaceuticals Inc) at 2, 4, and 12 months of age.

Immunogenicity Assessment

Blood samples were obtained 1 month after the third dose (~5 months of age), just before the toddler dose (~12 months of age), and 1 month after the toddler dose (~13 months of age). Blood samples were collected according to the Directive 2001/20/EC relating to ethical considerations for clinical trials performed in children.⁸ Immune responses, measured by using serotype-specific serum concentrations of anticapsular immunoglobulin G (IgG) and opsonophagocytic activity (OPA) titers to the 13 pneumococcal serotypes in PCV13, were determined for each blood sample. Anticapsular IgG-binding antibody concentrations were measured at each time point by using an enzyme-linked immunosorbent assay with results expressed in micrograms per milliliter⁹; an OPA microcolony assay¹⁰ was used to determine functional antibody (OPA) responses to the 13 pneumococcal serotypes, and results were expressed as OPA titers. OPA assays were only performed when serum volume was adequate to conduct the assay. Because of limits on the volume of sera available, the OPA assays were prioritized for the 6 additional serotypes (1, 3, 5, 6A, 7F, and 19A), followed by the 7 common serotypes

(4, 6B, 9V, 14, 18C, 19F, and 23F). The IgG and OPA testing was performed by Pfizer's Vaccine Research clinical testing laboratory.

Safety Assessment

Parents/legal guardians recorded local reactions (redness, swelling, and tenderness at injection site), systemic events (decreased appetite, irritability, increased sleep, and fever), and antipyretic medication use in an electronic diary on the evening of vaccination and for the next 6 days. AEs and serious AEs (SAEs) were collected from the signing of the informed consent form to 1 month after the toddler dose.

Statistical Analysis

Sample size estimation was based on the proportion of subjects achieving an IgG concentration $\geq 0.35 \mu\text{g/mL}$, the threshold of protection established by the World Health Organization by using pooled data from 3 efficacy trials of pneumococcal conjugate vaccines^{11,12} and in a previous PCV13 study.¹³ A sample size of 80 evaluable subjects per group was determined to provide an estimation of the proportion for each serotype to be within 7.6% precision with a 2-sided 95% confidence interval (CI). Assuming a dropout rate of 20%, 200 subjects were enrolled to ensure that 160 subjects were evaluable (received all assigned vaccinations, had blood drawn as required, had ≥ 1 valid and determinate assay result for the analysis, and had no major protocol violations).

For each serotype, the proportion of subjects achieving an IgG concentration $\geq 0.35 \mu\text{g/mL}$ measured 1 month after the infant series was calculated with an exact, 2-sided 95% CI. The between-group difference in the proportion was computed with an exact, unconditional, 2-sided 95% CI and *P* value.¹⁴ The geometric mean concentration (GMC) ratio of the 2 groups with 2-sided 95% CIs were calculated for each serotype. The

same immunogenicity analyses were performed 1 month after the toddler dose. For the 3 preterm subgroups, the aforementioned descriptive statistics were summarized according to preterm subgroup after the infant series and after the toddler dose. OPA results after the infant series and toddler dose were analyzed as for IgG data.

All subjects who received ≥ 1 dose of PCV13 were included in the safety population. The proportion of subjects with local reactions and systemic events was summarized for each group. AEs were categorized according to the *Medical Dictionary for Regulatory Activities* and summarized according to group for the infant series and toddler dose. Comparisons between preterm and term infants were constructed by using Fisher's exact test for proportions. Proportions were derived for the preterm subgroups, with no formal between-subgroup comparisons. All statistical analyses were performed by using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Preterm Versus Term Infants

Two hundred subjects were screened and enrolled (100 per group);

preterm infants were additionally classified into preterm subgroups according to GA at birth (32 to <37 weeks, $n = 25$; 29 to <32 weeks, $n = 50$; and <29 weeks, $n = 25$). All subjects were white. Mean GA was 30.8 weeks (range: 26.0–36.3 weeks) among preterm infants and 39.5 weeks (range: 37.0–42.0 weeks) among term infants, with a mean birth weight of 1.5 and 3.3 kg, respectively. The number of reported medical history characteristics was higher for preterm infants (83.0%) than for term infants (43.0%) (Table 1, Supplemental Table 6). All subjects completed the infant series; 98% completed the toddler dose. Subject disposition is presented in Fig 1.

One month after the infant series, $>85\%$ of subjects achieved an IgG antibody concentration $\geq 0.35 \mu\text{g/mL}$ (Table 2); the proportion of responders was statistically significantly lower, however, among preterm infants for serotypes 5, 6A, and 6B compared with term infants. One month after the toddler dose, the proportion of subjects in both the term and preterm groups achieving the $0.35\text{-}\mu\text{g/mL}$ threshold was $>97\%$ for all serotypes except serotype 3, with no statistically significant between-group differences (Supplemental Table 7).

TABLE 1 Demographic and Clinical Characteristics: Evaluable Infant Immunogenicity Population

Characteristic	Preterm ($n = 99$)	Term ($n = 98$)	Total ($N = 197$)
Gender, n (%)			
Female	48 (48.5)	55 (56.1)	103 (52.3)
Male	51 (51.5)	43 (43.9)	94 (47.7)
Ethnicity, n (%)			
White	99 (100)	98 (100)	197 (100)
Age at 2-mo dose, mo ^a	1.8 ± 0.6	1.5 ± 0.5	1.7 ± 0.6
Age at 12-mo dose, mo ^a	11.6 ± 0.5	11.6 ± 0.5	11.6 ± 0.5
GA, wk ^a	30.8 ± 2.6	39.5 ± 1.4	35.1 ± 4.8
Weight at birth, kg	1.5 ± 0.5	3.3 ± 0.5	2.4 ± 1.0
Any baseline medical history, n (%) ^b	83 (83)	43 (43)	126 (63)
Respiratory, thoracic, and mediastinal disorders, %	68.0		
Infections and infestations, %	42.0	16.0	
Congenital, familial, and genetic disorders, %		11.0	

Baseline medical history includes any chronic or significant condition or any relevant surgical procedures occurring before randomization and administration of PCV13. The 2 most common diagnoses by medical history category are shown for each group.

^a Mean \pm SD.

^b Values presented for all enrolled subjects; $n = 100$ per group.

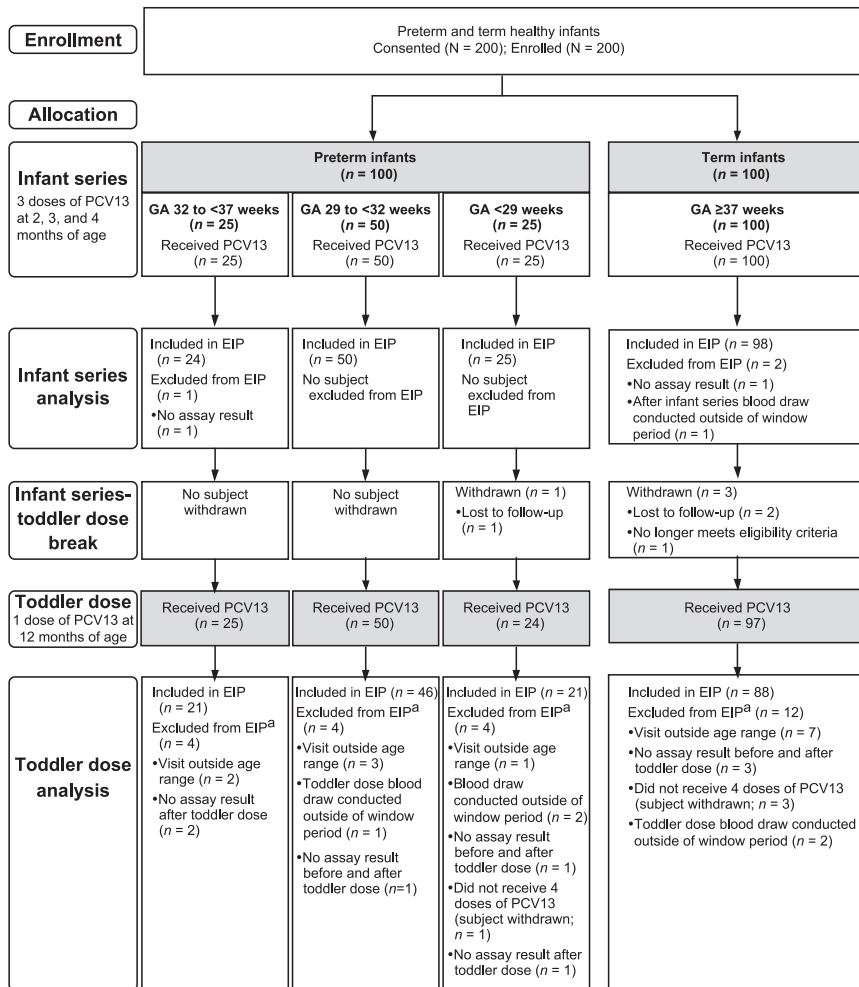


FIGURE 1 Subject disposition and reasons for exclusion. EIP, evaluable immunogenicity population. ^aSubjects could have been excluded for >1 reason.

Pneumococcal IgG GMCs measured 1 month after the infant series, before the toddler dose, and 1 month after the toddler dose were significantly lower for ≥ 1 time point in preterm subjects versus term subjects for all serotypes except 14 and 18C and for all time points for 6 of 13 serotypes (6B, 9V, 19F, 23F, 5, and 6A) (Table 3). After the toddler dose, a booster response (ie, post-toddler dose GMC higher than post-infant series GMC) was observed in both preterm and term infants for all serotypes except serotype 3. IgG GMCs to serotype 3 in both groups were lower after the toddler dose than after the infant series.

There were fewer between-group differences in OPA geometric mean

titers (GMTs) after the infant series or before the toddler dose, with GMT ratios approximating 1 for all but 4 serotypes (14, 18C, 5, and 6A) (Supplemental Table 8). Compared with IgG antibody responses after the infant series, OPA GMTs increased after the toddler dose in both term and preterm infants for all serotypes, including serotype 3; preterm infants had OPA GMTs that were significantly lower, however, than term infants for 6 of the 13 serotypes (4, 18C, 1, 5, 6A, and 19A).

Preterm Subgroups

For all preterm subgroups, >85% of subjects achieved an IgG antibody concentration $\geq 0.35 \mu\text{g/mL}$ 1 month after the infant series for all serotypes

except 3, 5, 6A, 6B, and 23F. For serotypes 6A and 6B, the proportion of subjects achieving this threshold was lower with lower GA (Supplemental Table 9), although no formal statistical analyses were completed. One month after the toddler dose, the proportion of subjects achieving an antibody response $\geq 0.35 \mu\text{g/mL}$ was >95% for all 3 preterm subgroups for all serotypes except serotype 3, which was lower with lower GA (Supplemental Table 10).

IgG GMCs 1 month after the infant series were higher for subjects with 32 to <37 weeks' GA than those with 29 to <32 weeks' GA and <29 weeks' GA for all serotypes (Supplemental Fig 2). Before the toddler dose, IgG GMCs were low in the preterm subgroups. After the toddler dose, a booster response was observed for all serotypes except serotype 3 in all preterm subgroups and serotypes 4 and 18C in the <29 weeks' GA subgroup. Postbooster GMCs were higher in subjects with 32 to <37 weeks' GA than in the other 2 preterm subgroups.

In contrast to IgG GMCs, which seemed to vary with decreasing GA in some serotypes, a similar consistent trend was not found in OPA GMTs across preterm subgroups (Supplemental Fig 3). OPA GMTs were low and increased for all serotypes in all preterm subgroups after the toddler dose, although no differences based on GA were observed.

Safety Results

The proportion of subjects with local reactions within 7 days after each vaccination was comparable in the preterm and term groups and tended to decrease after each dose in the infant series. The majority of local reactions were mild or moderate (Table 4). Systemic events occurred in a similar percentage of subjects in both groups during the infant series, except for decreased appetite and

TABLE 2 Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration $\geq 0.35 \mu\text{g/mL}$ 1 Month After the Infant Series: Evaluable Immunogenicity Population

Serotype	Preterm ($n = 98-99$) ^a	Term ($n = 97$) ^a	Difference ^b (95% CI)
	%	%	
PCV7 serotypes			
4	96.97	98.97	-2.00 (-7.65 to 2.88)
6B	72.73	87.63	-14.90 (-26.40 to -3.21)
9V	96.97	96.91	0.06 (-5.84 to 6.05)
14	100.00	97.94	2.06 (-1.71 to 7.25)
18C	96.97	94.85	2.12 (-4.09 to 8.89)
19F	98.99	98.97	0.02 (-4.54 to 4.68)
23F	85.86	92.78	-6.92 (-16.19 to 1.89)
Additional PCV13 serotypes			
1	93.94	95.88	-1.94 (-9.07 to 4.86)
3	85.86	90.72	-4.86 (-14.40 to 4.39)
5	71.72	90.72	-19.00 (-30.10 to -7.16)
6A	82.65	94.85	-12.19 (-21.66 to -3.26)
7F	98.99	98.97	0.02 (-4.54 to 4.68)
19A	98.99	98.97	0.02 (-4.54 to 4.68)

^a Number of subjects with a determinate IgG antibody concentration to the given serotype.

^b Difference in proportions: preterm minus term, expressed as a percentage.

irritability or decreased sleep, which were significantly more frequent in the preterm group. The most common systemic event at all doses for both groups was irritability or decreased sleep. The majority of systemic events were mild, with <10% of subjects overall reporting a severe reaction. No subject had fever >40°C during the infant series; 1 term subject experienced fever >40°C during the toddler dose.

During the infant series, 59% of preterm subjects and 55% of term subjects reported an AE ($P = .70$) (Table 5). Infections, especially respiratory infections, were the most common AEs in both groups. Gastrointestinal disorders occurred significantly more frequently among preterm infants than among term infants ($P = .04$).

In the period between the infant series blood draw and the toddler dose, approximately equal proportions of subjects experienced AEs ($P = .67$) (Table 5). The most common AEs in both groups were infections. During the toddler dose (from vaccination through the toddler blood draw), 31% of preterm subjects and 27% of term subjects experienced AEs ($P = .53$). During this

period, 1 subject in the preterm group experienced a vaccine-related AE (rash).

Overall, SAEs occurred in more preterm subjects than in term subjects (14% vs 5%, respectively, during the infant series; $P = .051$) (Table 5). Only 1% to 2% of subjects experienced SAEs during the toddler dose (1 event of diarrhea in a term infant and 2 events of respiratory infection in the preterm group). One term subject and 1 preterm subject experienced febrile convulsions (139 days after dose 3 and 17 days after dose 4, respectively); neither event was considered vaccine related due to the presence of a simultaneous acute febrile illness (bronchopneumonia and respiratory tract infection, respectively). Infections were the most common SAEs at all doses, with lower respiratory tract infections predominating. During and after the infant series, SAEs of bronchiolitis, pneumonia, and upper respiratory tract infections were reported in 6, 5, and 2 preterm infants, respectively, and by 2, 1, and 0 term infants. SAEs classified as gastrointestinal disorders were reported for 4 preterm infants and 1 term infant throughout the study.

DISCUSSION

This study is the first to evaluate the immunogenicity and safety of PCV13 in preterm infants, a vulnerable population with special respiratory morbidity risk.¹⁵ Previous studies in preterm infants have shown a reduced response to other conjugate vaccines, including those targeting *H influenzae* type b¹⁶ and *Neisseria meningitidis* serogroup C.¹⁷ These data, together with the increased risk of IPD in preterm infants,^{2,18} highlight the need to ensure that preterm infants are immunized and respond adequately to vaccination against *S pneumoniae*.

The current results suggest that preterm infants respond adequately to PCV13 given in a 4-dose series at 2, 3, 4, and 12 months of age. Not unexpectedly, differences between preterm and term infants were observed, with IgG GMCs significantly lower in preterm subjects versus term subjects for 11 of 13 serotypes at ≥ 1 time point and ~50% of serotypes at all measured time points. For some serotypes, lower responses corresponded with lower GA. Although post-toddler dose IgG GMC responses varied according to serotype and GA, the results suggest that adequate priming occurs among preterm infants which is comparable to term infants administered the same vaccination schedule. Differences in IgG response between preterm and term infants almost disappeared after toddler vaccination, emphasizing the importance of timely administration of the booster dose.

In contrast, there were fewer between-group differences in OPA GMTs after the infant series or before the toddler dose; GMTs increased after the toddler dose in both the term and preterm groups, although OPA GMTs were lower among preterm than term infants for 6 of the 13 serotypes. This finding suggests that despite a lower ability to generate serotype-specific antibodies as term infants, the functionality

TABLE 3 Comparison of Antipneumococcal IgG GMCs and GMRs According to Time Point: Evaluable Immunogenicity Population

Serotype		Preterm GMC (95% CI) ^a (<i>n</i> = 81–99) ^b	Term GMC (95% CI) ^a (<i>n</i> = 83–97) ^b	Comparison of Preterm Versus Term GMR (95% CI) ^c
PCV7 serotypes				
4	1 mo after infant series	1.96 (1.67 to 2.31)	2.46 (2.04 to 2.97)	0.80 (0.62 to 1.02)
	Immediately before toddler dose	0.31 (0.26 to 0.37) ^d	0.41 (0.34 to 0.49) ^d	0.76 (0.60 to 0.97) ^d
	1 mo after toddler dose	2.57 (2.18 to 3.03) ^d	3.97 (3.32 to 4.74) ^d	0.65 (0.51 to 0.82) ^d
6B	1 mo after infant series	0.73 (0.55 to 0.97) ^d	1.30 (1.00 to 1.67) ^d	0.56 (0.38 to 0.82) ^d
	Immediately before toddler dose	0.48 (0.39 to 0.58) ^d	0.94 (0.79 to 1.11) ^d	0.51 (0.39 to 0.66) ^d
	1 mo after toddler dose	4.42 (3.64 to 5.37) ^d	7.27 (6.09 to 8.68) ^d	0.61 (0.47 to 0.79) ^d
9V	1 mo after infant series	1.26 (1.08 to 1.47) ^d	1.70 (1.45 to 2.00) ^d	0.74 (0.59 to 0.93) ^d
	Immediately before toddler dose	0.39 (0.33 to 0.46) ^d	0.62 (0.53 to 0.72) ^d	0.64 (0.51 to 0.80) ^d
	1 mo after toddler dose	2.30 (1.99 to 2.66) ^d	3.06 (2.62 to 3.56) ^d	0.75 (0.61 to 0.93) ^d
14	1 mo after infant series	7.48 (6.23 to 8.99)	6.08 (4.82 to 7.67)	1.23 (0.92 to 1.65)
	Immediately before toddler dose	2.02 (1.68 to 2.43)	2.36 (1.94 to 2.87)	0.86 (0.66 to 1.12)
	1 mo after toddler dose	9.24 (7.66 to 11.14)	11.02 (9.44 to 12.86)	0.84 (0.66 to 1.07)
18C	1 mo after infant series	1.93 (1.66 to 2.24)	1.93 (1.62 to 2.29)	1.00 (0.80 to 1.25)
	Immediately before toddler dose	0.32 (0.28 to 0.37)	0.30 (0.26 to 0.36)	1.06 (0.85 to 1.32)
	1 mo after toddler dose	2.37 (2.02 to 2.79)	2.81 (2.32 to 3.40)	0.84 (0.66 to 1.08)
19F	1 mo after infant series	2.21 (1.89 to 2.58) ^d	3.05 (2.62 to 3.55) ^d	0.72 (0.58 to 0.90) ^d
	Immediately before toddler dose	0.68 (0.57 to 0.80) ^d	0.93 (0.79 to 1.10) ^d	0.73 (0.58 to 0.92) ^d
	1 mo after toddler dose	7.38 (6.23 to 8.76) ^d	11.67 (9.47 to 14.36) ^d	0.63 (0.48 to 0.83) ^d
23F	1 mo after infant series	0.86 (0.69 to 1.07) ^d	1.36 (1.10 to 1.68) ^d	0.64 (0.47 to 0.86) ^d
	Immediately before toddler dose	0.24 (0.18 to 0.31) ^d	0.40 (0.33 to 0.48) ^d	0.60 (0.43 to 0.83) ^d
	1 mo after toddler dose	2.45 (2.01 to 2.98) ^d	4.03 (3.36 to 4.85) ^d	0.61 (0.46 to 0.79) ^d
Additional PCV13 serotypes				
1	1 mo after infant series	1.26 (1.06 to 1.48) ^d	1.79 (1.50 to 2.13) ^d	0.70 (0.55 to 0.89) ^d
	Immediately before toddler dose	0.39 (0.34 to 0.46)	0.41 (0.35 to 0.48)	0.96 (0.77 to 1.20)
	1 mo after toddler dose	3.32 (2.83 to 3.89)	4.09 (3.42 to 4.89)	0.81 (0.64 to 1.03)
3	1 mo after infant series	0.83 (0.70 to 0.98)	0.86 (0.75 to 1.00)	0.96 (0.77 to 1.19)
	Immediately before toddler dose	0.07 (0.05 to 0.09) ^d	0.11 (0.09 to 0.14) ^d	0.60 (0.41 to 0.87) ^d
	1 mo after toddler dose	0.52 (0.44 to 0.62)	0.57 (0.49 to 0.65)	0.92 (0.73 to 1.15)
5	1 mo after infant series	0.56 (0.44 to 0.70) ^d	1.03 (0.87 to 1.22) ^d	0.54 (0.40 to 0.72) ^d
	Immediately before toddler dose	0.74 (0.64 to 0.87) ^d	1.06 (0.90 to 1.26) ^d	0.70 (0.56 to 0.88) ^d
	1 mo after toddler dose	2.63 (2.28 to 3.02) ^d	3.72 (3.19 to 4.33) ^d	0.71 (0.58 to 0.87) ^d
6A	1 mo after infant series	1.22 (0.98 to 1.53) ^d	2.01 (1.65 to 2.46) ^d	0.61 (0.45 to 0.82) ^d
	Immediately before toddler dose	0.54 (0.45 to 0.65) ^d	1.01 (0.82 to 1.24) ^d	0.54 (0.41 to 0.70) ^d
	1 mo after toddler dose	5.64 (4.86 to 6.54) ^d	7.84 (6.59 to 9.33) ^d	0.72 (0.57 to 0.90) ^d
7F	1 mo after infant series	2.14 (1.81 to 2.53) ^d	3.02 (2.63 to 3.48) ^d	0.71 (0.57 to 0.88) ^d
	Immediately before toddler dose	0.72 (0.63 to 0.82)	0.84 (0.73 to 0.96)	0.86 (0.71 to 1.03)
	1 mo after toddler dose	4.25 (3.75 to 4.82)	5.13 (4.48 to 5.87)	0.83 (0.69 to 1.00)
19A	1 mo after infant series	2.85 (2.44 to 3.33)	3.35 (2.85 to 3.94)	0.85 (0.68 to 1.07)
	Immediately before toddler dose	0.86 (0.72 to 1.03) ^d	1.57 (1.27 to 1.92) ^d	0.55 (0.42 to 0.72) ^d
	1 mo after toddler dose	5.57 (4.66 to 6.65) ^d	8.84 (7.45 to 10.48) ^d	0.63 (0.49 to 0.81) ^d

GMR, geometric mean ratio.

^a GMCs were calculated by using all subjects with available data for the specified blood draw. CIs are back-transformations of confidence levels based on Student's *t* distribution for the mean logarithm of the concentrations.^b Number of subjects with a determinate IgG antibody concentration to the given serotype.^c Preterm significantly lower than term; upper limit of 95% CI of GMR <1.0.^d Serotypes/time points with significant differences between groups.

(ie, killing ability) of the antibody generated in preterm infants is comparable to term infants after the infant series. The reason for the difference observed after the toddler dose is not clear but may be reflective of a lower number of clones established after priming and, therefore, less ability for clonal expansion on boosting. The smaller number of subjects contributing sera

to the OPA analyses may further limit the between-group comparisons.

For serotype 3, lower IgG GMCs were observed after the booster dose than after the infant series, although postbooster GMCs were higher than pre-toddler dose levels in both preterm and term infants; however, the post-toddler dose OPA GMT was higher than or similar to that measured after the infant series. This

unique response pattern observed for serotype 3 is consistent with findings from other studies.^{19,20} Despite this observed phenomenon, studies of early vaccine effectiveness suggest that disease protection is afforded by direct vaccination against serotype 3.^{21,22}

Although several methodologic differences exist when comparing this study with previous studies of

TABLE 4 Subjects Reporting Local Reactions, Systemic Events, and Antipyretic Use Within 7 Days of Vaccination

Variable	Dose 1 Infant Series		Dose 2 Infant Series		Dose 3 Infant Series		Toddler Dose	
	Preterm (n = 86–98) ^a	Term (n = 85–99) ^a	Preterm (n = 73–97) ^a	Term (n = 76–96) ^a	Preterm (n = 73–94) ^a	Term (n = 77–95) ^a	Preterm (n = 74–93) ^a	Term (n = 69–92) ^a
Local reactions, %								
Tenderness ^b								
Any	48.9	42.0	48.2	38.6	39.0	28.6	69.8	55.3
Mild	46.2	31.8 ^c	43.5	31.0	35.8	26.2	66.3	51.8
Moderate	17.8	16.5	14.3	15.7	9.3	5.1	20.8	11.4
Severe	0	0	0	1.3	0	0	2.7	0
Swelling ^d								
Any	39.4	29.2	35.7	42.7	30.1	41.2	43.2	35.0
Mild	37.4	28.1	33.7	42.7	26.8	41.2	38.8	32.9
Moderate	8.8	8.2	8.0	2.6	5.3	5.1	13.2	9.5
Severe	0	0	0	0	0	0	1.4	0
Redness ^d								
Any	33.7	29.9	28.0	40.2	32.9	46.0	51.8	49.4
Mild	32.2	28.7	28.0	37.8	32.9	46.0	51.8	48.2
Moderate	3.4	4.7	2.7	2.6	1.4	3.8	6.7	10.7
Severe	0	0	0	0	0	0	0	0
Any of the above	66.3	57.6	62.9	60.7	51.7	52.2	75.3	68.2
Systemic events, %								
Fever								
≥38°C	11.6	13.6	27.8	31.6	27.8	30.9	28.8	43.6
>38°C to 39°C	10.5	13.6	27.8	30.4	26.9	30.9	27.5	42.9 ^e
>39°C to 40°C	1.2	0	0	1.3	1.3	2.6	1.4	4.2
>40°C	0	0	0	0	0	0	0	1.4
Decreased appetite ^e								
Any	60.9	41.6 ^c	61.8	46.4 ^c	48.8	47.6	57.5	60.5
Mild	54.9	35.2 ^c	55.7	41.7	36.6	46.4	50.0	56.0
Moderate	20.5	17.2	25.3	19.2	17.6	16.5	25.6	23.3
Severe	1.2	0	1.4	0	1.4	1.3	1.3	1.4
Increased sleep ^f								
Any	67.7	69.5	74.1	64.0	52.3	58.0	57.8	65.1
Mild	60.4	61.3	69.9	59.1	48.9	51.7	53.7	59.5
Moderate	29.9	30.7	34.6	29.5	16.9	20.0	18.4	24.3
Severe	2.3	2.4	2.7	1.3	1.4	1.3	0	2.9
Irritability or decreased sleep ^g								
Any	84.2	82.5	89.5	77.9 ^c	79.3	81.1	84.4	80.2
Mild	77.4	69.5	81.1	71.7	72.2	74.7	74.4	76.4
Moderate	43.5	47.3	64.7	44.2 ^c	33.8	35.6	44.9	45.0
Severe	8.1	5.9	17.6	2.6 ^c	6.8	6.4	6.6	4.3
Antipyretic medication use	24.4	24.4	48.8	45.8	40.5	38.3	48.8	50.6
Any systemic event ^h	90.8	90.9	95.9	88.5	87.2	90.5	90.3	89.1

^a Number of subjects reporting the specific characteristic.

^b Mild, hurts if gently touched with no crying; moderate, hurts if gently touched with crying; severe, causes limitation of limb movement.

^c Significant difference between preterm and term groups ($P \leq .05$).

^d Mild, 0.5 to 2.0 cm; moderate, 2.5 to 7.0 cm; severe, >7.0 cm.

^e Mild, loss of appetite but no decreased oral intake; moderate, decreased oral intake; severe, refusal to feed.

^f Mild, increased or prolonged sleeping bouts; moderate, slightly subdued, interfering with daily activity; severe, disabling, not interested in usual daily activity.

^g Mild, easily consolable; moderate, requiring increased attention; severe, inconsolable, crying that cannot be comforted.

^h Includes fever $\geq 38^\circ\text{C}$, decreased appetite, increased sleep, and irritability or decreased sleep.

7-valent pneumococcal conjugate vaccine (PCV7) in preterm versus term infants, including the schedule, timing, and type of vaccine administered, immunogenicity results are consistent with our findings.^{5–7} Despite observed differences in IgG responses, previous studies suggest that

preterm infants can be adequately protected against IPD after receiving a pneumococcal polysaccharide conjugate vaccine. Shinefield et al² reported a vaccine efficacy of 100% in ~4400 preterm infants who received 3 doses of PCV7 with routine vaccinations. In a subset of subjects who had

immunogenicity measured, >95% of preterm infants had IgG GMCs $\geq 0.15 \mu\text{g/mL}$, with no difference between preterm and term infants. In an observational study, Rückinger et al²³ found that an infant series of PCV7 prevented IPD in preterm infants, suggesting that pneumococcal polysaccharide

TABLE 5 AEs and SAEs Reported by >5% of Subjects in Any Group at Any Dose

AE	Infant Series		After Infant Series		Toddler Dose	
	Preterm (n = 100)	Term (n = 100)	Preterm (n = 100)	Term (n = 100)	Preterm (n = 99)	Term (n = 97)
Adverse Event, %						
Any event ^a	59.0	55.0	18.0	15.0	31.3	26.8
Gastrointestinal disorders	13.0	4.0 ^b	3.0	1.0	2.0	5.2
General disorders and administration site conditions	7.0	7.0	1.0	0	1.0	1.0
Infections and infestations	45.0	41.0	14.0	11.0	27.3	21.6
Bronchiolitis	11.0	8.0	1.0	1.0	2.0	0
Gastroenteritis	1.0	6.0	3.0	0	3.0	2.1
Nasopharyngitis	6.0	5.0	0	2.0	6.1	4.1
Respiratory tract infection	8.0	9.0	4.0	0	3.0	1.0
Upper respiratory tract infection	10.0	10.0	1.0	0	5.1	4.1
Skin and subcutaneous tissue disorders	7.0	5.0	0	2.0	1.0	0
SAE, %						
Any event	14.0	5.0	8.0	9.0	2.0	1.0
Infections and infestations	12.0	5.0	7.0	7.0	2.0	0

^a Number of subjects reporting ≥ 1 event.

^b Significant difference between preterm and term groups in percentages of subjects reporting an event ($P \leq .05$).

conjugate vaccines can provide functional protection despite a lower quantitative immune response than in term infants.

Similar to results from studies with PCV7,^{2,5-7,23} PCV13 was generally well tolerated in preterm infants, with no new safety concerns observed. Local reactions and systemic events, including fever, were predominantly mild and had comparable incidences in preterm and term infants. During the infant series, there was a nonsignificant difference in the incidence of any SAE (preterm: 14.0%; full term: 5.0%; $P = .051$); these events were mainly respiratory and gastrointestinal infections. This finding is not unexpected, as the study was conducted during the winter months when the incidence of these types of infections peaks.²⁴⁻²⁶ Preterm infants have an increased susceptibility to respiratory infections and are more likely than term infants to have a clinical course that may necessitate hospitalization. Overall, the safety profile observed reflects expected AEs for young infants.

One strength of the present study was its parallel-group design that enabled a direct comparison of immune responses in preterm and term

infants. This study evaluated preterm infants with a GA of <29 weeks, an underrepresented population in previous pneumococcal conjugate vaccine studies. One possible limitation of this study was the inclusion of white study subjects only. In addition, the sample size did not allow subgroup comparisons for other outcomes such as OPA GMTs or the identification of rare AEs. Also, because infant weight at the time of vaccination was not measured, the relation between weight and PCV13 response, if any, is unknown. Finally, palivizumab prophylaxis was administered to ~25% of the preterm infants. Whether this treatment influenced immune responses to PCV13 is unclear; however, because palivizumab contains monoclonal antibodies specific for respiratory syncytial virus, interference with PCV13 immune responses is unlikely.²⁷ Moreover, other studies have shown comparable immune responses to PCV7 and the meningococcal groups C and Y and Haemophilus b tetanus toxoid conjugate vaccine in term infants compared with preterm infants who were permitted palivizumab prophylaxis.^{6,28}

In future studies, stratifying the results of our study according to

baseline medical conditions may provide further insight into vaccination in this vulnerable population. Epidemiologic studies in preterm infants are also needed to confirm that PCV13 is effective in this population.

CONCLUSIONS

Although the immune response to PCV13 one month after the infant series was lower in preterm infants versus term infants, it is likely to provide adequate protection against disease. Although post-toddler dose responses varied according to serotype and GA, priming after an infant series of PCV13 was similar for preterm and term infants. Although the IgG concentrations for serotype 3 after the toddler dose were lower than those achieved after the infant series, the functional OPA antibody levels suggest a similar likelihood of protection for both preterm and term infants. PCV13 was generally well tolerated in the preterm infants when administered on an accelerated schedule, and the observed AEs were consistent with childhood illnesses common in this population. These results reinforce the importance of timely pneumococcal vaccination for all infants, including those born prematurely.

ACKNOWLEDGMENTS

The authors thank the infants who participated in the study and their families, as well as the clinical staff that assisted each investigator during the study. The authors also thank the other investigators and team members who contributed to the successful conduct and completion of this study, including: Susana Ares and Esperanza Escribano (Hospital La Paz, Madrid); Maria Concepcion Goni Orayen and Laura Moreno Galarraga (Complejo Hospitalario de Navarra, Pamplona); Marta Bouzon Alejandro, Maria Lopez Sousa, Olalla Elena Lopez Suarez, Nazareth Martinon Torres, and Lorenzo Redondo Collazo (Complejo Hospitalario

Universitario de Santiago, A Coruña); Jose Luis Gomez Llorente (Complejo Hospitalario de Torrecárdenas, Almería); Aleksandra Matyla-Radzevska (Specjalistyczny ZOZ nad Matka i Dzieckiem Przychodnia Wieków Rozwojowego, Poznań); Agnieszka Spychalowicz (Hanna Czajka Indywidualna Praktyka Lekarska, Kraków); Marzena Ambicka-Ciba, Magdalena Orzechowska, and Henryk Szymanski (Szpital im Sw Jadwigi Slaskiej Oddział Dziecięcy, Trzebnica); Tomasz Czerniak, Agnieszka Jalowska, Julia Seniuta, Kinga Sikorska-Socha, Karolina Szel-Bernach, Zofia Szymanska-Toczek, Izabela Zaleska, and Kamila Zyzak (Samodzielny Publiczny Szpital

Kliniczny nr 1 we Wrocławiu, Wrocław); Oscar Blanco Barca, Eva Gonzalez Colmenero, and Maria Suarez Albo (Complejo Hospitalario Xeral Cies, Pontevedra); Maria Isabel Gonzalez Tome, Pablo Rojo Conejo, Jesus Ruiz Contreras, and Maria Jose Torres Valdivieso (Hospital 12 de Octubre, Madrid); Jerzy Pejcz (Hospital Swietej Jadwigi Slaskiej, Trzebnica); and Natacha Ledren-Narayanin, Katarzyna Juszcak, and Enrique Ramos (Pfizer, Inc). This study was supported by Pfizer Inc. Editorial/medical writing support was provided by Nicole Gudleski O'Regan, PhD, of Complete Healthcare Communications, Inc, and was funded by Pfizer Inc.

Drs Blazquez Gamero and Concheiro-Guisán participated as investigators in the clinical trial, recruited and followed up with subjects, and reviewed the manuscript drafts; Dr Gimenez-Sanchez approved the final protocol, participated as an investigator in the clinical trial, recruited and followed up with subjects, and reviewed the manuscript drafts; Dr Majda-Stanisławska gathered subjects and data for the study and reviewed the manuscript drafts; Dr Omeñaca approved the final protocol, participated as an investigator in the clinical trial, recruited and followed up with subjects, and reviewed the manuscript drafts; Drs Szenborn and Wysocki were involved in recruiting subjects, collecting data, and reviewing the manuscript drafts; Dr Giardina provided immunoassay results for the study and contributed to the development of the manuscript; Dr Patterson participated in the study design and the analysis and interpretation of the data, and contributed to manuscript development (which included review of drafts); Dr Gruber supported the concept and design of the study, participated in data analysis, and contributed to manuscript development; and Drs Scott and Gurtman participated in the study design, monitored the safety of participating subjects during the study, participated in analysis and interpretation of the data, and contributed to manuscript development (including review of drafts). All authors approved the final manuscript as submitted.

This trial has been registered at www.clinicaltrials.gov (identifier NCT01193335) and at www.clinicaltrialsregister.eu/ (EudraCT no. 2009-017332-41).

www.pediatrics.org/cgi/doi/10.1542/peds.2014-2941

DOI: 10.1542/peds.2014-2941

Accepted for publication Jan 27, 2015

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: Dr Martinón-Torres's research activities have been supported by grants from Instituto Carlos III (Intensificación de la actividad investigadora) and Fondo de Investigación Sanitaria (PI10/00540 and PI13/02382) del plan nacional de I+D+I and "fondos FEDER." He has received research grants and/or honoraria as a consultant/advisor and/or speaker and for conducting vaccine trials from GlaxoSmithKline, Sanofi Pasteur MSD, Sanofi Pasteur, Pfizer Inc/Wyeth, Novartis, and MedImmune Inc. Dr Czajka has served as a principal investigator in clinical studies sponsored by Pfizer, Novartis, and GlaxoSmithKline; Dr Wysocki has served as principal investigator in clinical trials sponsored by GlaxoSmithKline, Pfizer, and Novartis and has received grants from these vaccine producers for participation in conferences; Dr Majda-Stanisławska has served as principal investigator in clinical trials sponsored by Pfizer; Dr Omeñaca has served as principal investigator in clinical trials sponsored by GlaxoSmithKline; Dr Bernaola Iturbe has served as a principal investigator in clinical studies sponsored by Pfizer and has lectured for Pfizer, GlaxoSmithKline, and Sanofi Pasteur MSD; Dr Blazquez Gamero has conducted vaccine trials from Pfizer/Wyeth, Novartis, and GlaxoSmithKline; Dr Gimenez-Sanchez has received grants and honoraria from Pfizer, GlaxoSmithKline, Novartis, and Sanofi Pasteur MSD for participation in conferences and advisory committees; Dr Szenborn has served as principal investigator in clinical trials sponsored by GlaxoSmithKline, Pfizer, Baxter, and Novartis and has received grants from these vaccine producers and from Sanofi Pasteur for participation in conferences; and Drs Center, Giardina, Patterson, Gruber, Scott, and Gurtman are employed by Pfizer and hold stock in the company. Dr Concheiro-Guisán has indicated she has no financial relationships relevant to this article to disclose.

FUNDING: Sponsored by Pfizer Inc.

POTENTIAL CONFLICT OF INTEREST: Dr Martín-Torres has received research grants and/or honoraria as a consultant/advisor and/or speaker and for conducting vaccine trials from GlaxoSmithKline, Sanofi Pasteur MSD, Sanofi Pasteur, Pfizer Inc/Wyeth, Novartis, and MedImmune Inc. Dr Czajka has served as a principal investigator in clinical studies sponsored by Pfizer, Novartis, and GlaxoSmithKline; Dr Wysocki has served as principal investigator in clinical trials sponsored by GlaxoSmithKline, Pfizer, and Novartis and has received grants from these vaccine producers for participation in conferences; Dr Majda-Stanislawski has served as principal investigator in clinical trials sponsored by Pfizer; Dr Omeñaca has served as principal investigator in clinical trials sponsored by GlaxoSmithKline; Dr Bernaola Iturbe has served as a principal investigator in clinical studies sponsored by Pfizer and has lectured for Pfizer, GlaxoSmithKline, and Sanofi Pasteur MSD; Dr Blazquez Gamero has conducted vaccine trials from Pfizer/Wyeth, Novartis, and GlaxoSmithKline; Dr Gimenez-Sanchez has received grants and honoraria from Pfizer, GlaxoSmithKline, Novartis, and Sanofi Pasteur MSD for participation in conferences and advisory committees; Dr Szenborn has served as principal investigator in clinical trials sponsored by GlaxoSmithKline, Pfizer, Baxter, and Novartis and has received grants from these vaccine producers and from Sanofi Pasteur for participation in conferences; and Drs Center, Giardina, Patterson, Gruber, Scott, and Gurtman are employed by Pfizer and hold stock in the company. Dr Concheiro-Guisán has indicated she has no potential conflicts of interest to disclose.

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