Circulating Antibody 1 and 2 Years After Vaccination With the 13-Valent Pneumococcal Conjugate Vaccine in Preterm Compared With Term Infants

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Background: Premature infants have lower short-term immune responses to vaccination than term infants, but patterns of antibody persistence in preterm infants over longer periods are not well established. This study assessed the persistence of antibody response to the 13-valent pneumococcal conjugate vaccine (PCV13) in formerly preterm versus term infants.

Methods: In total, 100 preterm and 100 term infants received PCV13 with routine vaccines at ages 2, 3, 4 and 12 months. Serotype-specific anticapsular immunoglobulin G (IgG)–binding antibodies and opsonophagocytic activity were determined 1 and 2 years after the last PCV13 dose.

Results: At 1 and 2 years after the last vaccination (toddler dose), IgG geometric mean concentrations (GMCs) for all serotypes had declined from levels measured 1 month after the toddler dose but remained above pre-toddler dose levels. IgG GMCs were significantly lower in preterm than term subjects for a majority of serotypes at both follow-up time points. IgG GMCs increased in both groups for some serotypes from the 1-year to 2-year follow-up, whereas others declined. Opsonophagocytic activity results supported the IgG results.

Conclusions: The routine (3 + 1) vaccination schedule is likely to offer long-term protection against invasive pneumococcal disease in preterm infants and should be initiated regardless of gestational age or weight at birth, without delay of the toddler dose.

Key Words: preterm infants, pneumococcal conjugate vaccine, immunization, immunogenicity

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Premature birth is a risk factor for invasive pneumococcal disease, particularly for infants born before 32-week gestation.[1] Gestational age (GA) and vaccine timing may affect immune responses to vaccines in preterm infants,[1–5] due in part to their immature immune systems.[6,7] A small number of studies have evaluated immunogenicity of pneumococcal conjugate vaccines in preterm infants, but differences in vaccines administered, dose scheduling and GA of enrolled infants may limit their interpretation.[1–4,8,9] We recently published a study of immune responses to the 13-valent pneumococcal conjugate vaccine (PCV13) in preterm versus term infants after a 4-dose vaccination series at 2, 3, 4 and 12 months of age. In that report, PCV13 vaccination elicited protective immune responses in preterm infants, but serotype-specific antibody levels were generally lower in preterm infants than their term counterparts 1 month after the third dose. One month after the fourth dose, differences remained but were less pronounced.[10]

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To date, no studies have examined the long-term persistence of immune responses to PCV13 in formerly preterm infants.

The current report presents results from the follow-up phase of the previously published vaccination phase of the study. Immune responses to PCV13 were assessed in formerly preterm and term infants 1 and 2 years after the last vaccination, corresponding to approximately 2 and 3 years of age.

MATERIALS AND METHODS

Objectives

The objectives of this follow-up phase of the study were to describe the persistence of antipneumococcal antibody responses elicited by PCV13 1 and 2 years after the fourth dose (toddler dose) in formerly preterm infants compared with term infants.

Study Design and Subjects

This open-label, phase 4, 2-arm, multicenter, parallel-group study was conducted at 6 sites in Spain and 5 sites in Poland between October 2010 and January 2014. The study was approved by institutional review board(s) and/or independent ethics committee(s) and conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonisation, Good Clinical Practice guidelines and all local regulatory requirements. Written informed consent was obtained from all parent(s) or legal guardian(s) before enrollment and before performance of any study-related procedures.

For the vaccination phase of the study, 100 term and 100 preterm infants (50 per group in each study country) were recruited from investigators' patient populations and enrolled. Retention after the fourth vaccine dose was encouraged by periodic communications to the study sites and to parents. Subjects withdrawn from the study during the vaccination or follow-up phases were not replaced, regardless of the reason for withdrawal. At inclusion, all 200 subjects were considered to be generally healthy 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 *Streptococcus pneumoniae*, immune deficiency or suppression and any serious chronic disorders or major illnesses. Subjects were stratified into a preterm or term group based on GA at birth; subjects completing <37-week gestation were considered preterm. Preterm infants were additionally stratified into subgroups based on GA of <29 weeks, 29–<32 weeks and 32–<37 weeks. All subjects had received PCV13 at 2, 3, 4 (infant series) and 12 (toddler dose) months of chronologic age.

Vaccines Administered

As previously described, subjects received the PCV13 (Prevnar 13, Wyeth Vaccines; Lot Number E09498, Wyeth Pharmaceuticals Inc., Collegeville, PA), which contains polysaccharides from 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 (CRM_{197}).[10] The diphtheria-tetanus-acellular pertussis, hepatitis B, inactivated poliovirus, *Haemophilus influenzae* type b vaccine (DTaP-IPV-HBV-Hib; Infanrix Hexa, GlaxoSmithKline Biologicals, Rixensart, Belgium) and meningococcal group C oligosaccharide conjugate vaccine (Meningitec, Wyeth Pharmaceuticals Inc., Collegeville, PA) were also administered according to recommended schedules. Rotavirus vaccine (not required in either country)[11] could have been given at any time; measles, mumps, rubella vaccine (recommended in both countries) and varicella vaccine (recommended in Poland for specific at-risk groups 9 months to 12 years of age; recommended in Spain for at-risk groups and from 12 years of age) could have been given according to each country's national vaccination schedule.

Prior and Concomitant Medicines

Antipyretic medications, topical inhaled corticosteroids and blood transfusions were permitted during the course of the study. Palivizumab could have been given at any time as appropriate.

Immunogenicity Assessment

Serum antibody persistence was evaluated approximately 12 and 24 months after the toddler (fourth) dose of PCV13. Persistence of immune responses to the 13 pneumococcal serotypes in PCV13 were measured by serotype-specific concentrations of anticapsular immunoglobulin G (IgG) and opsonophagocytic activity (OPA) titers, as previously described.[10] The IgG and OPA testing were performed by Pfizer's Vaccine Research Clinical Testing Laboratory (Pearl River, NY) and Pharmaceutical Product Development Inc. (Richmond, VA).

Statistical Analyses

For each serotype, the proportion of subjects achieving IgG concentration ≥0.35 μg/mL measured 1 and 2 years after the toddler dose was calculated with an exact, 2-sided 95% confidence interval (CI). CIs are back transformations of confidence levels based on the Student's *t* test distribution for the mean logarithm of the concentrations. The difference in the proportion between preterm and term subjects was computed with an exact, unconditional, 2-sided 95% CI.[12] The geometric mean concentration (GMC) ratio of the preterm and term groups was calculated for each serotype with a 2-sided 95% CI. Comparisons between preterm and term groups were constructed using geometric mean ratios and 95% CI at each persistence time point as data permitted. Differences between preterm and term groups were considered significantly lower if the upper limit of the 95% CI of the comparison was <1.0, and significantly higher if the lower limit of the 95% CI of the comparison was >1.0. Preterm subgroup data were summarized descriptively, but no formal comparisons were constructed. OPA data were similarly analyzed as for IgG data.

RESULTS

Subjects

A total of 200 subjects were enrolled in this study, 100 each in the preterm and term groups. Within the preterm subgroups, 25 were in the 32- to <37-week GA subgroup, 50 were in the 29- to <32-week GA subgroup and 25 were in the <29-week GA subgroup. All subjects were white; mean GA was 30.8 weeks (range: 26.0–36.3) among preterm infants and 39.4 weeks (range: 37.0–42.0) for term infants (Table 1). Subject disposition for term infants and preterm infants by GA is presented in Figure, Supplemental Digital Content 1, http://links.lww.com/INF/C605. A total of 196 subjects (98.0%) received the toddler vaccination dose and completed the blood draw 1 month later. In both groups, 88 subjects (88.0%) completed the 1-year follow-up, and 81 preterm (81.0%) and 80 term (80.0%) subjects completed the 2-year follow-up visit. The most commonly reported reason for withdrawal from the study at any point after the vaccination phase was "no longer willing to participate." Loss to follow-up and lack of continued eligibility were also cited; no subject withdrew because of safety reasons.

Immunogenicity: Preterm Versus Term Subjects

The proportion of subjects with pneumococcal IgG concentration ≥0.35 μg/mL was statistically significantly lower in formerly preterm infants at the 1-year follow-up visit for serotypes 3, 4, 9V, 18C, 19A and 23F and at the 2-year follow-up for serotypes 18C, 19A and 23F (Table, Supplemental Digital Content 2, http://links.lww.com/INF/C606). Compared with before the toddler dose, pneumococcal IgG GMCs for preterm and term infants were higher

TABLE 1. Demographic and Clinical Characteristics: Evaluable Posttoddler Immunogenicity Population

Characteristic	1-yr Follow-up			2-yr Follow-up		
	Preterm n = 80	Term n = 80	Total n = 160	Preterm n = 71	Term n = 71	Total n = 142
Sex, n (%)						
Female	36 (45.0)	47 (58.8)	83 (51.9)	32 (45.1)	42 (59.2)	74 (52.1)
Ethnicity, n (%)						
White	80 (100.0)	80 (100.0)	160 (100.0)	71 (100.0)	71 (100.0)	142 (100.0)
Mean age at 2-mo dose (SD), mo	1.8 (0.6)	1.6 (0.5)	1.7 (0.5)	1.8 (0.6)	1.6 (0.5)	1.7 (0.6)
Mean gestational age (SD), wk	30.8 (2.6)	39.4 (1.4)	35.1 (4.8)	30.8 (2.7)	39.4 (1.5)	35.1 (4.8)
Mean weight at birth (SD), kg	1.5 (0.5)	3.3 (0.5)	2.4 (1.0)	1.5 (0.6)	3.3 (0.5)	2.4 (1.0)

SD indicates standard deviation.

(higher point estimate without overlapping CIs) or similar (CIs overlap) at the 1-year and 2-year follow-up visits for all serotypes except serotypes 4 and 14 at 2 years after the toddler dose. IgG GMCs in both infant groups at the 1-year and 2-year follow-up visits were lower (lower point estimate without overlapping CIs) than GMCs 1 month after the toddler dose for all serotypes. IgG GMCs in preterm infants compared with term infants had lower point estimates with overlapping CIs at both follow-up time points for serotypes 1, 3, 4, 7F and 14. Compared with term infants, IgG GMCs in preterm infants were statistically significantly lower at both follow-up time points for serotypes 6B, 18C, 19A, 19F and 23F; IgG GMCs for serotypes 5, 6A and 9V were statistically significantly lower in preterm infants at the 1-year follow-up only (Table 2 and Fig. 1).

At the 1-year and 2-year follow-up time points for preterm and term infants, pneumococcal OPA geometric mean titers (GMTs) were higher than or similar to those before the toddler dose for all serotypes. Compared with 1 month after the toddler dose, however, OPA GMTs at the 1-year and 2-year follow-up visits in both groups were lower for all serotypes. Formerly preterm infants had statistically significantly lower OPA GMTs at the 1-year follow-up for serotypes 6A, 18C, 19A and 23F and at the 2-year follow-up for serotypes 5 and 19A when compared with GMTs for term infants (Table 3 and Fig., Supplemental Digital Content 3, http://links.lww.com/INF/C607).

Immunogenicity: Preterm Subgroups

In all subgroups at the 1-year and 2-year follow-up time points, GMCs were higher than or similar to those before the toddler dose for all serotypes except serotype 7F (lower than before the toddler dose). GMCs in all subgroups for all serotypes declined from 1 month after the toddler dose to the 1-year follow-up (Table, Supplemental Digital Content 4, http://links.lww.com/INF/C608, which shows pneumococcal IgG GMCs through 2 years after the toddler dose). At both follow-up time points, no discernable patterns were observed in IgG GMCs for any serotype across preterm subgroups based on GA.

For both follow-up time points, OPA GMTs for all serotypes were higher than or similar to those before the toddler dose and lower than GMTs 1 month after the toddler dose. At both follow-up time points, no discernable patterns were observed in OPA GMTs for any serotype across preterm subgroups based on GA (Table, Supplemental Digital Content 5, http://links.lww.com/INF/C609, which shows pneumococcal OPA GMTs through 2 years after the toddler dose).

DISCUSSION

This study is the first to examine the persistence of immune responses to PCV13 serotypes in preterm and term infants. The vaccination phase of the study demonstrated that preterm infants are able to generate an immune response to PCV13 that is likely to protect against invasive pneumococcal disease. However, IgG GMCs were lower in preterm than term infants for nearly half of the serotypes at all time points. Differences in OPA GMTs between term and preterm infants were not as great, suggesting that despite the quantitative differences observed for IgG antibody, the functionality of the antibody raised by immunization of preterm infants is more closely similar to that of a term infant.[10]

The lower IgG GMCs observed shortly after vaccination persisted in preterm infants 1 and 2 years after the last vaccine dose. Consistent with the first phase of the study, fewer differences were noted in OPA responses between the study groups at both the 1-year and 2-year follow-ups. These observations suggest comparable retention of functional antibodies in both groups up to 2 years after the toddler dose.

The few studies assessing immunogenicity of PCVs in preterm infants have evaluated mostly PCV7 and have reported inconsistent results, possibly owing to heterogeneity in vaccination schedules and GA of enrolled infants. Two studies including infants with a GA ≥32 weeks identified no differences in PCV7 immune responses between preterm and term infants,[1,2] whereas a third study reported comparable proportions of responders above a given antibody concentration threshold in preterm and term infants, except for 1 serotype.[3] However, Ruggeberg et al.[4] observed significantly lower IgG GMCs in preterm infants 1 month after the toddler dose for 3 serotypes. Similar to that study, the current study also enrolled extremely premature infants (GA: ≥26 weeks) and reported significantly lower pneumococcal IgG GMCs in preterm subjects 1 month after the toddler dose.[10]

Antibody persistence is an important component of both direct and herd protection.[13] However, relatively few studies have evaluated persistence of vaccine immune responses in formerly preterm infants. Antibody persistence has been reported for children up to 7 years of age for antigens in other routine pediatric vaccines, including *H. influenzae* type b polyribosylribitol phosphate, hepatitis B surface antigen, polio antigens (serotypes 1, 2 and 3), diphtheria toxoid, pertussis antigens (filamentous hemagglutinin, pertactin and pertussis toxoid) and tetanus toxoid. Although antibody levels were frequently lower in formerly preterm infants, continued seroprotection was inferred for those antigens for which minimal protective thresholds have been established.[6,14,15]

Polysaccharide conjugate vaccines stimulate circulating antibody production and induce anamnestic immune responses.[16] A limitation of the current study is the measurement of only circulating antibody and not immune memory. However, the report by Ruggeberg et al.[4] in which preterm infants were vaccinated with an infant series of PCV7 followed by a 23-valent pneumococcal polysaccharide vaccine (PPSV23) booster provides clinical evidence that PCV7 establishes immune memory and suggests that PCV13, by extension, is likely to induce immune memory as well. Other studies in term infants provide further evidence for the establishment of immune memory by conjugate pneumococcal vaccines after a booster dose of PPSV23[17,18] or PCV13.[19] Immune memory responses to natural pneumococcal challenge, although not tested in this study, may also play an important role in assuring protection against disease.

Circulating antibody levels in preterm and term infants fluctuated by serotype between the 1-year and 2-year follow-up time points, which may indicate natural boosting through exposure to circulating pneumococci. Moreover, capsular polysaccharides may stimulate antibody production differently than exposure to

TABLE 2. Comparison of Antipneumococcal IgG GMCs and GMRs by Time Point: Evaluable Immunogenicity Population

Serotype	Preterm GMC (95% CI)* n† = 65–86	Term GMC (95% CI)* n† = 63–87	Comparison Preterm to Term GMR (95% CI)‡
PCV7 serotypes			
4			
Before toddler dose	0.31 (0.26–0.37)	0.41 (0.34–0.49)	0.76 (0.60–0.97)§
1 mo after toddler dose	2.57 (2.18–3.03)	3.97 (3.32–4.74)	0.65 (0.51–0.82)§
1 yr after toddler dose	0.30 (0.25–0.36)	0.37 (0.31–0.44)	0.81 (0.63–1.04)
2 yr after toddler dose	0.19 (0.16–0.23)	0.24 (0.20–0.29)	0.80 (0.61–1.03)
6B			
Before toddler dose	0.48 (0.39–0.58)	0.94 (0.79–1.11)	0.51 (0.39–0.66)§
1 mo after toddler dose	4.42 (3.64–5.37)	7.27 (6.09–8.68)	0.61 (0.47–0.79)§
1 yr after toddler dose	1.26 (1.02–1.57)	2.01 (1.69–2.39)	0.63 (0.48–0.83)§
2 yr after toddler dose	1.44 (1.13–1.85)	2.70 (2.10–3.48)	0.53 (0.38–0.76)§
9V			
Before toddler dose	0.39 (0.33–0.46)	0.62 (0.53–0.72)	0.64 (0.51–0.80)§
1 mo after toddler dose	2.30 (1.99–2.66)	3.06 (2.62–3.56)	0.75 (0.61–0.93)§
1 yr after toddler dose	0.61 (0.48–0.78)	0.98 (0.82–1.19)	0.62 (0.46–0.84)§
2 yr after toddler dose	0.74 (0.58–0.94)	0.99 (0.80–1.23)	0.74 (0.54–1.03)
14			
Before toddler dose	2.02 (1.68–2.43)	2.36 (1.94–2.87)	0.86 (0.66–1.12)
1 mo after toddler dose	9.24 (7.66–11.14)	11.02 (9.44–12.86)	0.84 (0.66–1.07)
1 yr after toddler dose	1.43 (1.15–1.78)	1.73 (1.40–2.14)	0.83 (0.61–1.12)
2 yr after toddler dose	1.06 (0.78–1.43)	1.37 (1.03–1.82)	0.77 (0.51–1.17)
18C			
Before toddler dose	0.32 (0.28–0.37)	0.30 (0.26–0.36)	1.06 (0.85–1.32)
1 mo after toddler dose	2.37 (2.02–2.79)	2.81 (2.32–3.40)	0.84 (0.66–1.08)
1 yr after toddler dose	0.33 (0.27–0.41)	0.66 (0.54–0.81)	0.50 (0.37–0.67)§
2 yr after toddler dose	0.32 (0.24–0.42)	0.57 (0.47–0.69)	0.56 (0.40–0.78)§
19F			
Before toddler dose	0.68 (0.57–0.80)	0.93 (0.79–1.10)	0.73 (0.58–0.92)§
1 mo after toddler dose	7.38 (6.23–8.76)	11.67 (9.47–14.36)	0.63 (0.48–0.83)§
1 yr after toddler dose	0.96 (0.80–1.15)	1.78 (1.40–2.26)	0.54 (0.40–0.72)§
2 yr after toddler dose	1.10 (0.83–1.46)	2.43 (1.71–3.44)	0.45 (0.29–0.71)§
23F			
Before toddler dose	0.24 (0.18–0.31)	0.40 (0.33–0.48)	0.60 (0.43–0.83)§
1 mo after toddler dose	2.45 (2.01–2.98)	4.03 (3.36–4.85)	0.61 (0.46–0.79)§
1 yr after toddler dose	0.59 (0.47–0.74)	1.24 (1.01–1.52)	0.47 (0.35–0.64)§
2 yr after toddler dose	1.03 (0.77–1.38)	1.83 (1.42–2.37)	0.56 (0.38–0.83)§
Additional PCV13 serotypes			
1			
Before toddler dose	0.39 (0.34–0.46)	0.41 (0.35–0.48)	0.96 (0.77–1.20)
1 mo after toddler dose	3.32 (2.83–3.89)	4.09 (3.42–4.89)	0.81 (0.64–1.03)
1 yr after toddler dose	0.40 (0.35–0.46)	0.53 (0.45–0.62)	0.76 (0.61–0.94)§
2 yr after toddler dose	0.32 (0.26–0.38)	0.39 (0.32–0.47)	0.82 (0.63–1.07)
3			
Before toddler dose	0.07 (0.05–0.09)	0.11 (0.09–0.14)	0.60 (0.41–0.87)§
1 mo after toddler dose	0.52 (0.44–0.62)	0.57 (0.49–0.65)	0.92 (0.73–1.15)
1 yr after toddler dose	0.13 (0.10–0.17)	0.22 (0.16–0.30)	0.59 (0.39–0.90)§
2 yr after toddler dose	0.17 (0.12–0.25)	0.27 (0.18–0.40)	0.66 (0.39–1.11)
5			
Before toddler dose	0.74 (0.64–0.87)	1.06 (0.90–1.26)	0.70 (0.56–0.88)§
1 mo after toddler dose	2.63 (2.28–3.02)	3.72 (3.19–4.33)	0.71 (0.58–0.87)§
1 yr after toddler dose	1.10 (0.91–1.32)	1.63 (1.35–1.97)	0.67 (0.52–0.87)§
2 yr after toddler dose	1.34 (1.07–1.68)	1.97 (1.60–2.41)	0.68 (0.50–0.92)§
6A			
Before toddler dose	0.54 (0.45–0.65)	1.01 (0.82–1.24)	0.54 (0.41–0.70)§
1 mo after toddler dose	5.64 (4.86–6.54)	7.84 (6.59–9.33)	0.72 (0.57–0.90)§
1 yr after toddler dose	1.08 (0.89–1.32)	1.59 (1.34–1.90)	0.68 (0.52–0.88)§
2 yr after toddler dose	1.41 (1.09–1.82)	2.10 (1.64–2.70)	0.67 (0.47–0.95)§
7F			
Before toddler dose	0.72 (0.63–0.82)	0.84 (0.73–0.96)	0.86 (0.71–1.03)
1 mo after toddler dose	4.25 (3.75–4.82)	5.13 (4.48–5.87)	0.83 (0.69–1.00)
1 yr after toddler dose	0.68 (0.59–0.80)	0.83 (0.72–0.96)	0.82 (0.67–1.02)
2 yr after toddler dose	0.60 (0.50–0.71)	0.67 (0.57–0.80)	0.89 (0.70–1.13)
19A			
Before toddler dose	0.86 (0.72–1.03)	1.57 (1.27–1.92)	0.55 (0.42–0.72)§
1 mo after toddler dose	5.57 (4.66–6.65)	8.84 (7.45–10.48)	0.63 (0.49–0.81)§
1 yr after toddler dose	1.61 (1.22–2.12)	3.16 (2.53–3.95)	0.51 (0.36–0.72)§
2 yr after toddler dose	2.33 (1.76–3.10)	4.36 (3.40–5.61)	0.53 (0.37–0.78)§

*GMCs were calculated using all subjects with available data for the specified blood draw. CIs are back transformations of confidence levels based on the Student's *t* test distribution for the mean logarithm of the concentrations.

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

‡Preterm significantly lower than term: upper limit of 95% CI of GMR <1.0.

§Serotypes/time points with significant differences between groups.

GMR indicates geometric mean ratio.

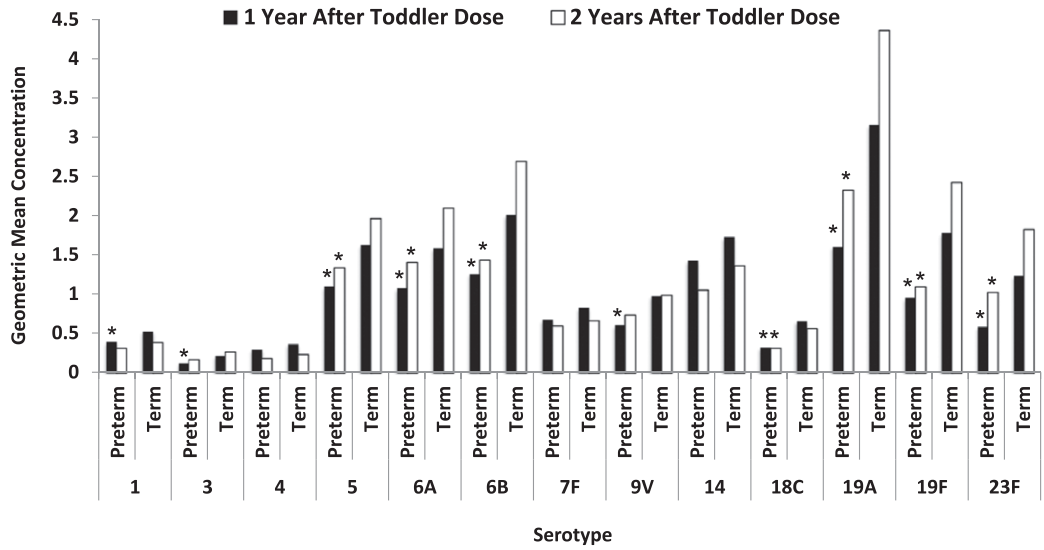

FIGURE 1. Comparison of antipneumococcal IgG GMCs in preterm and term infants at 1 and 2 years after vaccination. IgG GMCs are presented by time point, serotype and preterm/term gestational age group. Asterisks indicate significantly lower values in preterm compared with term infants.

the PCV13 conjugate protein at the toddler dose, leading to heterogeneity in serotype-specific IgG levels with time. Heterogeneity in persistence may stem from potential differences in quality and quantity of B cells elicited by intact bacteria compared with pneumococcal conjugate vaccine antigens.[20] In a study of infants immunized with the meningococcal serogroup C protein conjugate vaccine (MnC-CRM_{197}), MnC-specific memory B cells and antibody levels after priming correlated with antibody persistence at 1 year of age, suggesting that initial responses predict antibody persistence.[21] In addition, the strength of immune responses to pneumococcal antigens may vary with age and serotype.[22]

Differences between preterm and term infants for certain serotypes may have been less evident 1 month after the toddler dose because of the postbooster spike in antibody concentrations that possibly muted any between-group differences. Differences may only become apparent as antibody levels wane with time. Nevertheless, the antibody concentrations achieved after PCV13 vaccination of preterm infants are protective and similar to those detected in term infants.

A strength of this study is its parallel-group design, which allowed direct comparisons between preterm and term subjects. Moreover, the 2-year follow-up period provided an extended analysis window after vaccination in which to evaluate the persistence of antibody responses in subjects born as early as 26-week gestation. Although circulating antibody concentrations were significantly lower in preterm infants for 7 serotypes, antibody concentrations at the 1- and 2-year follow-ups generally remained higher than those before the toddler dose, and no trends were observed toward decreased antibody concentrations with increasing prematurity. A larger sample size, however, may be necessary to identify significant trends in immune responses based on GA.

Further study of long-term antibody persistence and additional epidemiologic studies are still needed to confirm that antibody persistence correlates with long-term protection against *S. pneumoniae* by PCV13 vaccination of preterm infants. Because of a lack of expert consensus regarding the threshold of protection for individual pneumococcal serotypes, the current study defined the threshold of protection as the aggregate correlate of protection established by the World Health Organization (IgG concentrations ≥0.35 μg/mL based on prelicensure studies).[23] Two studies have evaluated protection based on IgG titers by individual serotype,[24,25] but a lack of official guidance regarding which criteria to use prompted the application of the World Health Organization–recommended threshold.

Immune responses elicited by PCV13 in preterm and term infants persisted up to 2 years after the toddler dose, although differences were observed between the 2 groups. Antipneumococcal IgG levels in preterm infants were generally lower than in term infants, but fewer differences in OPA were seen between the groups. A recent study by Voysey et al.[26] reported generally higher IgG levels and OPA titers among girls than boys up to 1 year after the toddler dose. The current study was not designed to evaluate immune responses by sex, and while the proportion of female preterm (45%) and term (60%) subjects was slightly different, the majority of subjects in both groups had IgG levels and OPA titers at 1 and 2 years after the toddler dose that are likely to confer protection against vaccine-type pneumococcal disease.

Preterm infants may be at a relative disadvantage when vaccinated in infancy, but generate persistent pneumococcal antibody responses that are functionally comparable to those of term infants. While it might have been possible to identify pneumococcal disease occurring among study participants by virtue of protocol-specified safety reporting requirements, the number of such infections would likely be low. Moreover, determining the etiology of infections among this group of children was not a specific objective of the current study, which was designed to effectively capture antibody responses. However, responses observed in preterm infants are likely to afford protection; this may be confirmed with epidemiologic studies.

Overall, these results emphasize the need for timely vaccination of infants against *S. pneumoniae* starting at the chronologic age of 2 months, regardless of GA or weight at birth, and reinforce the importance of giving the toddler dose at the earliest possible opportunity. A routine vaccination schedule including a 3-dose primary series followed by a toddler dose at approximately 12 months is likely to offer long-term protection against invasive pneumococcal disease in preterm infants as well as their term infant counterparts.

TABLE 3. Comparison of Antipneumococcal OPA GMTs and GMRs by Time Point: Evaluable Immunogenicity Population

Serotype	Preterm GMT (95% CI)* n† = 46–81	Term GMT (95% CI)* n† = 45–83	Comparison Preterm to Term GMR (95% CI)‡
PCV7 serotypes			
4			
Before toddler dose	10 (6.0–15.3)	13 (7.9–21.9)	0.7 (0.37–1.44)
1 mo after toddler dose	1154 (879.2–1514.5)	1757 (1329.1–2322.4)	0.7 (0.45–0.97)§
1 yr after toddler dose	24 (12.9–45.5)	29 (15.2–54.5)	0.8 (0.35–2.05)
2 yr after toddler dose	15 (7.0–32.9)	17 (9.0–32.6)	0.9 (0.33–2.37)
6B			
Before toddler dose	12 (6.8–20.1)	15 (8.5–25.6)	0.8 (0.37–1.71)
1 mo after toddler dose	1229 (877.2–1722.1)	1406 (1003.4–1970.3)	0.9 (0.54–1.40)
1 yr after toddler dose	38 (19.0–74.9)	36 (19.2–68.8)	1.0 (0.41–2.63)
2 yr after toddler dose	29 (13.7–59.9)	27 (12.4–58.2)	1.1 (0.37–3.07)
9V			
Before toddler dose	11 (6.2–20.9)	7 (4.9–11.1)	1.5 (0.76–3.12)
1 mo after toddler dose	1871 (1217.8–2873.6)	2542 (1711.6–3775.2)	0.7 (0.41–1.31)
1 yr after toddler dose	141 (67.5–293.1)	244 (126.3–469.7)	0.6 (0.22–1.53)
2 yr after toddler dose	132 (57.5–301.5)	75 (34.7–163.7)	1.7 (0.57–5.36)
14			
Before toddler dose	242 (148.5–394.0)	389 (260.4–582.2)	0.6 (0.33–1.17)
1 mo after toddler dose	1294 (969.0–1728.4)	1651 (1300.1–2097.1)	0.8 (0.54–1.44)
1 yr after toddler dose	276 (169.0–449.4)	372 (236.1–586.5)	0.7 (0.38–1.14)
2 yr after toddler dose	262 (142.0–482.8)	296 (161.6–543.8)	0.9 (0.38–2.07)
18C			
Before toddler dose	32 (16.1–61.7)	51 (26.8–98.3)	0.6 (0.24–1.55)
1 mo after toddler dose	2464 (1696.0–3579.4)	4510 (3399.7–5981.7)	0.5 (0.34–0.87)§
1 yr after toddler dose	33 (16.4–67.4)	121 (56.9–258.1)	0.3 (0.10–0.76)§
2 yr after toddler dose	14 (7.1–25.9)	29 (14.3–57.9)	0.5 (0.18–1.21)
19F			
Before toddler dose	6 (4.1–7.4)	4 (3.8–4.7)	1.3 (0.97–1.77)
1 mo after toddler dose	376 (229.1–617.1)	640 (431.5–948.3)	0.6 (0.31–1.10)
1 yr after toddler dose	11 (6.2–17.7)	18 (9.6–35.4)	0.6 (0.25–1.30)
2 yr after toddler dose	13 (7.4–22.5)	20 (10.1–39.9)	0.6 (0.27–1.53)
23F			
Before toddler dose	11 (6.9–19.0)	16 (9.6–26.6)	0.7 (0.35–1.46)
1 mo after toddler dose	1048 (738.6–1488.0)	1657 (1217.7–2255.0)	0.6 (0.40–1.01)
1 yr after toddler dose	45 (23.7–86.6)	168 (92.4–303.9)	0.3 (0.11–0.65)§
2 yr after toddler dose	60 (29.7–122.2)	135 (71.2–255.3)	0.4 (0.17–1.15)
Additional PCV13 serotypes			
1			
Before toddler dose	6 (4.5–6.8)	4 (3.9–4.8)	1.3 (1.00–1.60)
1 mo after toddler dose	59 (43.7–78.6)	107 (83.0–137.0)	0.5 (0.38–0.81)§
1 yr after toddler dose	5 (4.2–6.3)	5 (4.3–5.8)	1.0 (0.81–1.32)
2 yr after toddler dose	5 (4.1–5.4)	4 (3.9–4.6)	1.1 (0.96–1.31)
3			
Before toddler dose	8 (6.2–10.0)	8 (6.6–10.4)	1.0 (0.68–1.33)
1 mo after toddler dose	114 (97.1–132.7)	121 (103.4–140.4)	0.9 (0.76–1.17)
1 yr after toddler dose	11 (8.6–15.4)	13 (9.2–18.7)	0.9 (0.56–1.37)
2 yr after toddler dose	11 (8.1–15.2)	16 (10.7–24.2)	0.7 (0.41–1.14)
5			
Before toddler dose	5 (4.2–6.0)	5 (4.2–5.6)	1.0 (0.82–1.31)
1 mo after toddler dose	166 (127.9–216.3)	260 (203.9–331.9)	0.6 (0.45–0.91)§
1 yr after toddler dose	8 (5.6–10.4)	10 (7.0–13.3)	0.8 (0.51–1.23)
2 yr after toddler dose	5 (4.1–5.6)	7 (5.4–9.4)	0.7 (0.49–0.92)§
6A			
Before toddler dose	45 (25.2–81.1)	91 (56.6–146.3)	0.5 (0.24–1.04)
1 mo after toddler dose	1978 (1571.5–2489.7)	3154 (2606.0–3816.0)	0.6 (0.47–0.85)§
1 yr after toddler dose	98 (53.0–183.0)	255 (152.9–424.8)	0.4 (0.17–0.86)§
2 yr after toddler dose	42 (21.5–81.1)	102 (53.7–193.4)	0.4 (0.16–1.03)
7F			
Before toddler dose	228 (137.6–377.1)	188 (109.3–323.1)	1.2 (0.58–2.53)
1 mo after toddler dose	2915 (2453.4–3462.7)	3154 (2746.2–3622.4)	0.9 (0.74–1.15)
1 yr after toddler dose	599 (411.0–873.3)	533 (348.3–814.1)	1.1 (0.64–1.97)
2 yr after toddler dose	170 (87.7–330.9)	269 (155.6–463.7)	0.6 (0.27–1.48)
19A			
Before toddler dose	9 (6.3–12.0)	10 (7.1–14.8)	0.8 (0.52–1.37)
1 mo after toddler dose	558 (456.3–682.6)	825 (692.4–983.8)	0.7 (0.52–0.88)§
1 yr after toddler dose	28 (17.2–43.9)	54 (34.2–85.5)	0.5 (0.27–0.97)§
2 yr after toddler dose	22 (13.6–37.1)	50 (30.1–82.6)	0.5 (0.22–0.91)§

*GMTs were calculated using all subjects with available data for the specified blood draw. CIs are back transformations of confidence levels based on the Student's *t* test distribution for the mean logarithm of the titers.

†Number of subjects with a determinate antibody titer to the given serotype.

‡Preterm significantly lower than term: upper limit of 95% CI of GMR <1.0; preterm significantly higher than term: lower limit of 95% CI of GMR >1.0.

§Serotypes/time points with significant differences between groups.

GMR indicates geometric mean ratio.

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