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13-Valent Pneumococcal Conjugate Vaccine (PCV13) is Immunogenic and Safe in Children 6-17 Years of Age With Sickle Cell Disease Previously Vaccinated With 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV23): Results of a Phase 3 Study

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Background. A large population of older children with sickle cell disease (SCD) is currently vaccinated with only 23-valent pneumococcal polysaccharide vaccine (PPSV23). In immunocompetent adults, PPSV23 vaccination reduces immune responses to subsequent vaccination with a pneumococcal vaccine. The 13-valent pneumococcal conjugate vaccine (PCV13), which addresses this limitation, may offer an advantage to this population at high risk of pneumococcal disease. [This article was corrected after initial online publication with an erratum. The National Clinical Trial (NCT) number was omitted from the article abstract. That number is NCT00918580.] ***Procedure.*** Children with SCD 6–17 years of age previously vaccinated with PPSV23 at least 6 months before study enrollment received two doses of PCV13 6 months apart. Anti-pneumococcal polysaccharide immunoglobulin G (IgG) geometric mean concentrations (GMCs) and opsonophagocytic activity (OPA) geometric mean titers (GMTs) were measured before, 1 month after each administration, and 1 year after the second administration. ***Results.*** Following each PCV13 administration, IgG GMCs and OPA GMTs significantly increased, and antibody levels after doses 1 and 2 were generally comparable. Antibody levels declined over the year following dose 2. At 1 year after the second administration, OPA GMTs for all and IgG GMCs for most serotypes remained above pre-vaccination levels. Most adverse events were due to vaso-occlusive crises, a characteristic of the underlying condition of SCD. ***Conclusions.*** Children with SCD who were previously vaccinated with PPSV23 responded well to 1 PCV13 dose, and a second dose did not increase antibody response. PCV13 antibodies persisted above pre-vaccination levels for all serotypes 1 year after dose 2. Children with SCD may benefit from at least one dose of PCV13. Pediatr Blood Cancer 2015;62:1427–1436. © 2015 Wiley Periodicals, Inc.

Key words: 13-valent pneumococcal conjugate vaccine; 23-valent pneumococcal polysaccharide vaccine; hydroxycarbamide; immunogenicity; safety; sickle cell disease

INTRODUCTION

Children with sickle cell disease (SCD) are at increased risk of invasive pneumococcal disease (IPD), in part due to functional asplenia [1]. In North America, *Streptococcus pneumoniae* infection was the leading cause of death in SCD children in the 1980s [2]. Interventions aimed at reducing pneumococcal disease in this population have focused primarily on prophylactic penicillin and pneumococcal vaccination. Early studies documented that prophylactic penicillin significantly reduced the risk of pneumococcal infection, particularly useful in children under 5 years of age who are at greatest risk [3,4]. However, the burden of IPD-associated morbidity and mortality among SCD children continues to be a challenge [5].

The 23-valent pneumococcal polysaccharide vaccine (PPSV23) was recommended for children $\geq$2 years of age with functional or anatomic asplenia, including SCD, as a preventative strategy [6]. PPSV23 was the only vaccine option until 2000, when the 7-valent pneumococcal conjugate vaccine (PCV7) was introduced. PCV7, unlike PPSV23, is effective in individuals aged <2 years [7]

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Conflict of Interest Statement: AF, AG, DAS, EAE, QJ, and WCG are current employees of Pfizer and may hold stock options. AP and PH are recipients of grants from Pfizer. MDM has served on an advisory council, review panel, or Speaker's Bureau for Norvartis. AI has received research support from Eli Lilly and Hast Therapeutics, and participated in a Speaker's Bureau and received honoraria from Novartis. NH is a grant investigator for Pfizer, Gilead, and Sanofi Pasteur MSD, and has served on an advisory council or review panel for Gilead. DR is a consultant for Eli Lilly and has received support from Novartis. CD holds stock in Pfizer and Amgen, has received research support from Pfizer and Glycomimetics, and has consulted for Glycomimetics. AT is a grant investigator for Pfizer, has received research grants from Pfizer, Sanofi Pasteur MSD, and GlaxoSmithKline, and has served on an advisory council or review panel for Sanofi Pasteur MSD. MA, JL, NK, MG, BI, PT, and SA have no conflicts of interest.

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because it incorporates capsular polysaccharides conjugated to the immunogenic protein carrier nontoxic diphtheria toxin cross-reacting material 197 (CRM_{197}), which elicits a T cell-dependent immune response [8].

After PCV7 introduction in the US in 2000, several reports documented a decrease in IPD in children with SCD. Halasa et al. [9] reported a 90.8% decrease in IPD rates in SCD children aged <2 years and a 93.4% decrease in children aged <5 years between the pre-PCV7 period (1995–1999) and the post-PCV7 period (2001–2004). An observational study of children in the United States (US) aged $\leq$10 years with SCD approximated 81% vaccine effectiveness against IPD (Confidence Interval [CI] = 19%–96%) in children who received $\geq$1 dose of PCV7 [10]. An analysis of data from African American children <18 years of age with SCD collected in the Active Bacterial Core surveillance (ABCs) areas from 1998–2009 estimated a 53% decline in IPD rates in this population since the introduction of PCV7 [11]. However, an increase in IPD due to pneumococcal serotypes not included in PCV7 was observed in 2011 [12].

An expanded serotype pneumococcal conjugate vaccine composed of 13 serotypes (PCV13) was developed to decrease the burden of pneumococcal disease caused by the six additional serotypes not included in PCV7. In 2007–2009, before the introduction of PCV13, data from the US ABCs documented that children 6–18 years of age with SCD had an increased relative risk (RR = 27; CI = 9–73) of IPD caused by PCV13 serotypes compared with similar-aged children without SCD [13]. Therefore, this study was designed to evaluate the safety, tolerability, and immunogenicity of PCV13 when given to subjects with SCD who were naïve to PCV and had previously received at least one dose of PPSV23. Because PPSV23 has been shown to reduce immune responses to subsequent vaccination with PCV7 in immunocompetent adult populations [14,15], a 2-dose regimen of PCV13 was evaluated to determine whether a second dose given 6 months after the initial dose would substantially increase the serum antibodies and overcome any impact of prior PPSV23 on the ability to respond to PCV13.

METHODS

Study Design and Population

This was an open-label, single-arm, multicenter phase 3 study conducted in seven countries from November 2009 to March 2013 to assess the immunogenicity and safety of PCV13 in children aged 6 to <18 years with SCD who had previously received at least one dose of PPSV23. Informed consent and, where applicable, assent, was obtained for all subjects. Inclusion criteria included diagnosis of SCD and documented vaccination with PPSV23 at least 6 months before enrollment. Participants were excluded if they had a history of culture-proven invasive disease caused by *S. pneumoniae* within the last year or previous vaccination with a pneumococcal conjugate vaccine, major illness or condition that substantially increased the risk associated with the subject's ability to participate or may preclude assessment of the subject's vaccine response (such as suspected immunodeficiency, receipt of immunosuppressive therapy, or history of hematopoietic stem cell transplantation), or active hepatitis C infection requiring interferon or ribavirin treatment.

Concomitant vaccination with licensed vaccines per local or national recommendations was permitted. Receipt of the pandemic influenza A (H1N1) vaccine was permitted if given at least 14 days before or 7 days after the study vaccine. Administration of a pneumococcal non-study vaccine was not permitted during the study.

The study was conducted in accordance with the Declaration of Helsinki and was designed and performed in compliance with Good Clinical Practice and applicable local regulatory requirements. The final protocol, any amendments, and the informed consent form were approved by the Institutional Review Board(s) or Independent Ethics Committee(s) at each participating investigational center.

Study Objectives

The study objectives were to compare anti-pneumococcal responses to each PCV13 serotype by measuring immunoglobulin G (IgG) concentrations and opsonophagocytic activity (OPA) titers 1 month after the first dose relative to 1 month after the second dose of PCV13, and to describe the anti-pneumococcal responses before and 1 month after each dose. The protocol was amended while the study was ongoing to include an assessment of antibody persistence (as measured by IgG concentrations and OPA titers) at 1 year after the second PCV13 dose in subjects who were still active in the study at the time of the amendment.

Safety objectives were to measure incidence rates of local reactions, systemic events, adverse events (AEs), and serious AEs (SAEs). Local reactions included pain, redness, and swelling at the injection site; systemic events included fever, vomiting, diarrhea, headache, fatigue, muscle pain, and joint pain. AEs were defined as any untoward medical occurrence, including but not limited to abnormal test findings, progression or worsening of underlying disease, and clinically significant symptoms and signs. SAEs were any untoward medical occurrence that is life-threatening, requires inpatient hospitalization, or results in significant disability, birth defect, or death. Participants recorded local reactions and systemic events for 7 days after each dose in an electronic diary. AEs and SAEs were collected at the investigational sites: all AEs up to 1 month after each vaccination, and newly diagnosed chronic medical conditions at 6 months after each vaccination and 1 year after the second PCV13 dose. SAEs were collected throughout the study.

Vaccine and Administration

Subjects received two doses of PCV13 approximately 6 months apart. PCV13 (Prevenar13/Prevnar 13®, Wyeth Vaccines, Pearl River, NY; Lot numbers 7-5095-009 A and E09498) contains capsular polysaccharides of pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23 F individually conjugated to CRM_{197}. Each 0.5-ml dose contained 2.2 μg of each serotype, except for 6B, which is included at 4.4 μg. Each dose is formulated in 5 mM succinate buffer with 0.02% polysorbate 80, and 0.125 mg aluminum as aluminum phosphate. PCV13 was supplied in single-dose syringes and stored at 2°C–8°C. Vaccine was administered by intramuscular injection.

Sample Size Estimation

Study sample size was not powered for hypothesis testing. Inclusion of at least 80 subjects in the evaluable immunogenicity population provided a range of 21–37% precision of the 95%CIs of the antibody geometric mean fold rises (GMFRs) across the 13 serotypes.

Population Analysis

The evaluable immunogenicity population was the primary population for immunogenicity analyses and comprised eligible subjects who received both doses of study vaccine and no prohibited medications or vaccines, had no major protocol violations, had blood drawn within the specified periods, and had valid and determinate assay result. All vaccinated subjects with available safety data were analyzed.

Immunogenicity Analysis

The immunogenicity endpoints for the study were the anti-pneumococcal polysaccharide IgG geometric mean concentrations (GMCs) and OPA geometric mean titers (GMTs) to the 13 serotypes contained in PCV13 at each blood sampling determined using validated IgG and OPA assays [16,17].

For the comparison of immune responses elicited by each dose, the GMFRs from 1 month after dose 1 to 1 month after dose 2 were calculated for subjects with data for both blood draws. The GMFRs from before to after dose 1, from before to after dose 2, and the differences in those GMFRs were determined for subjects who had data for both blood draws, before and after each dose. The GMFRs from before dose 1 to 1 year after dose 2 were also calculated as a post hoc analysis for subjects with data for both blood draws. All immunogenicity endpoints were summarized with corresponding 95% CIs. All analyses were descriptive and were performed with the SAS software package. No imputations were performed for missing data.

The above analyses were repeated to evaluate the influence of the number of previous PPSV23 doses on the immune responses to PCV13. However, a meaningful analysis could not be conducted, as very few subjects received more than 1 PPSV23 dose (2–6 doses). A post hoc analysis conducted on the evaluable immunogenicity population explored the impact of the interval between the most recent PPSV23 dose given before study entry and the first dose of PCV13. The analysis was performed by plotting the IgG or OPA antibody levels (logarithm transformed data) for each subject against the interval (months) between the most recent PPSV23 dose and the first dose of PCV13. The Pearson correlation coefficient was calculated for each plot.

Long-term hydroxycarbamide use is common among SCD patients to reduce pain and other complications, and bone marrow suppression is a possible side effect of this therapy [18]. Therefore, a post hoc analysis to assess effects of concomitant hydroxycarbamide use on PCV13 immune responses was performed between subgroups of subjects who did or did not provide documented use of hydroxycarbamide during the study period overlapping the two PCV13 doses.

Safety Analysis

The percentages of subjects with local reactions, systemic events, AEs, and SAEs were descriptively summarized.

RESULTS

Baseline Characteristics and Disposition of Subjects

A total of 158 subjects were vaccinated with the first dose of PCV13 in 18 centers: five each in the US and United Kingdom, two each in Italy, Lebanon, and Egypt, and one each in France and Saudi Arabia. The majority of subjects enrolled were previously vaccinated with one dose of PPSV23 (92.4%), with 12 subjects receiving more than one dose (range: 2–6). The mean age (±SD) at enrollment was 13.3 (±3.08) years. One hundred forty-six (92.4%) subjects completed the 1-month visit after dose 2 (Table I). Because the 1-year visit was added while the study was underway, some subjects had already completed the study or, when given the opportunity to reconsent for the 1-year visit, decided not to continue, leaving 87 (55.1%) subjects completing the 1-year visit after dose 2 (Table I). The time between the most recent dose of PPSV23 and the first dose of PCV13 was 3.5 (±2.60) years, with a median of 2.9 years and a range of 6 months to 11.8 years.

Immunogenicity Responses

The evaluable immunogenicity population consisted of 138 of 158 (87.3%) enrolled subjects 1 month after dose 2, and 81 (51.3%) subjects who completed the 1-year follow-up after dose 2. In response to dose 1, both IgG GMCs and OPA GMTs increased (Fig. 1) and were statistically significantly higher compared with pre-vaccination levels. IgG GMCs and OPA GMTs declined over the next 6 months, but remained above pre-vaccination levels for all serotypes. In response to dose 2, both IgG GMCs and OPA GMTs rose again for all serotypes (Fig. 1) and were statistically significantly higher compared with before dose 2. The GMFRs for dose 2 were significantly lower than the GMFRs for dose 1.

The IgG GMCs after dose 2 were similar to or lower than those after dose 1 for all serotypes. For serotypes 1, 3, 4, 5, 7F, 9V, 14, 18C, and 19 A, IgG GMCs after dose 2 were statistically significantly lower than those after dose 1 (upper limit of the 95%CI was <1) (Table II). In contrast, OPA GMTs after dose 2 were similar to or higher than those after dose 1 for all serotypes. For serotypes 1, 7F, 9V, and 23 F, OPA GMTs after dose 2 were statistically significantly higher than those after dose 1 (lower limit of the 95%CI was >1) (Table III).

Immune responses declined between 1 month and 1 year after dose 2 (Fig. 1). The IgG GMCs at 1 year after dose 2 were statistically significantly higher than those before dose 1 for all serotypes, except serotypes 3 and 5 for which the values were numerically similar (Table II). For all serotypes, the OPA GMTs 1 year after dose 2 were statistically significantly higher than those before dose 1 (Table III).

Analysis of immune response versus time interval between the most recent dose of PPSV23 and PCV13 dose 1 did not reveal a consistent and/or substantial trend for the 2 immune response variables. Pearson correlation coefficients ranged from −0.02 (serotype 3) to 0.24 (serotype 23F) for IgG concentrations, and from −0.05 (serotype 3) to 0.23 (serotype 1) for OPA titers. The patterns were generally similar for all vaccine serotypes.

The evaluable immunogenicity population included 76 subjects reporting hydroxycarbamide use at the time of both PCV13 administrations and during the period between the 2 vaccine doses, and 59 subjects who did not report hydroxycarbamide use. The analysis revealed no impact of hydroxycarbamide use on IgG concentrations or OPA titers following administration of either dose of PCV13.

Safety

At least one local reaction was reported by >88% of subjects after each dose, with pain at the injection site reported most frequently (>85% after each dose) (Fig. 2A). After each dose, the

TABLE I. Disposition and Demographic Characteristics of Enrolled Subjects (N = 158)

		Years	
Age at enrollment	Mean (±SD) Range	13.3 (±3.08) 6.0, 17.9	
		n	%
Sex	Male	82	51.9
	Female	76	48.1
Race	Black	67	42.4
	White[a]	56	35.4
	Other[b]	35	22.2
Number of previous PPSV23 doses	1 dose	146	92.4
	2–6 doses	12	7.6
Vaccinated subjects	1 dose of PCV13	158	100.0
	2 doses of PCV13	146	92.4
Withdrawn subjects	Before dose 2 of PCV13	12	7.6
	Reason: adverse event	1	0.6
	After dose 2 of PCV13[c]	2	1.3
Completed visits	1 month after dose 2	146	92.4
	6 months after last dose[d]	147	93.0
	Did not continue in the study	58	36.7
	Continued in the study	89	56.3
	1 year after dose 2	87	55.1

SD, standard deviation; PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine. [a]All from Lebanon. [b]Majority from Egypt. [c]Failed to return between 6 months and 1 year after dose 2. [d]1 subject did not receive dose 2 but completed the 6-month follow-up telephone call.

percentages of subjects reporting swelling (49.1% and 53.6%, respectively) and redness (23.7% and 26.9%, respectively) were similar. Most local reactions were mild. Systemic events were reported by >87% of subjects after each dose (Fig. 2B). Muscle pain, fatigue, and headache were reported by >50% of subjects after each dose. Most systemic events were mild or moderate. Fever >40.0°C was reported by only one subject after each vaccine dose. One subject experienced injection site pain and systemic events (muscle pain, headache, joint pain, fatigue, fever, and vomiting) within 7 days following dose 1 and was withdrawn by the parents (Table I).

AEs were reported by 39.2% of subjects in the 6 months after dose 1, 29.9% in the 6 months after dose 2, and 19.5% between 6 and 12 months after dose 2. Most AEs were vaso-occlusive crises, as were most SAEs. Sickle cell anaemia with crisis and vascular occlusion SAEs were reported by a similar proportion of subjects during the 6 months after doses 1 and 2, and between 6 and 12 months after dose 2 (Table IV). None were assessed as related to study vaccine. The only SAE considered by the investigator to be related to study vaccine was a case of osteomyelitis and back pain that occurred 14 days after dose 1 and resolved. During the study period, all SAEs resolved and no deaths occurred.

DISCUSSION

PCV13 elicited an immune response against all vaccine serotypes in children with SCD aged 6–17 years who had been previously vaccinated with one or more doses of PPSV23 at least 6 months before enrollment. Both anticapsular IgG binding and functional antibodies (OPA) increased significantly after a single dose of PCV13. Antibody concentrations then declined as expected over the 6 months following dose 1, but remained higher than the pre-dose levels. Both binding and functional antibodies increased again after the second dose of PCV13. Increases in IgG antibodies and OPA titers from before to after dose 2 (GMFRs) were lower than those observed from before to after dose 1. The IgG GMCs after dose 2 were similar to or lower than those after dose 1, and the OPA GMTs after dose 2 were similar to or higher than those after dose 1. Overall, the antibody responses 1 month after each dose were generally comparable. Notably, IgG concentrations at 1 year after the second dose remained higher than levels before dose 1 for 11 of 13 serotypes, and OPA titers remained above the pre-PCV13 baseline for all serotypes. This observation reflects a persistent antibody response 1 year after 2 doses of PCV13 that are administered 6 months apart.

The OPA responses seen 1 month after dose 1 in this study are numerically lower than OPA responses to PCV13 observed in a study of healthy subjects aged 5–9 years who had previously received PCV7, or aged 10–17 years who were naïve to pneumococcal vaccination [19]. The observed lower immune response to PCV13 in the present study may be due to previous PPSV23 vaccination, as reported in PCV13-vaccinated adults ≥60 years of age who had previously received PPSV23 [20,21]. A similar study showed PPSV23 to decrease responses to PCV7 administered 1 year later in older adults [15]. Similar observations

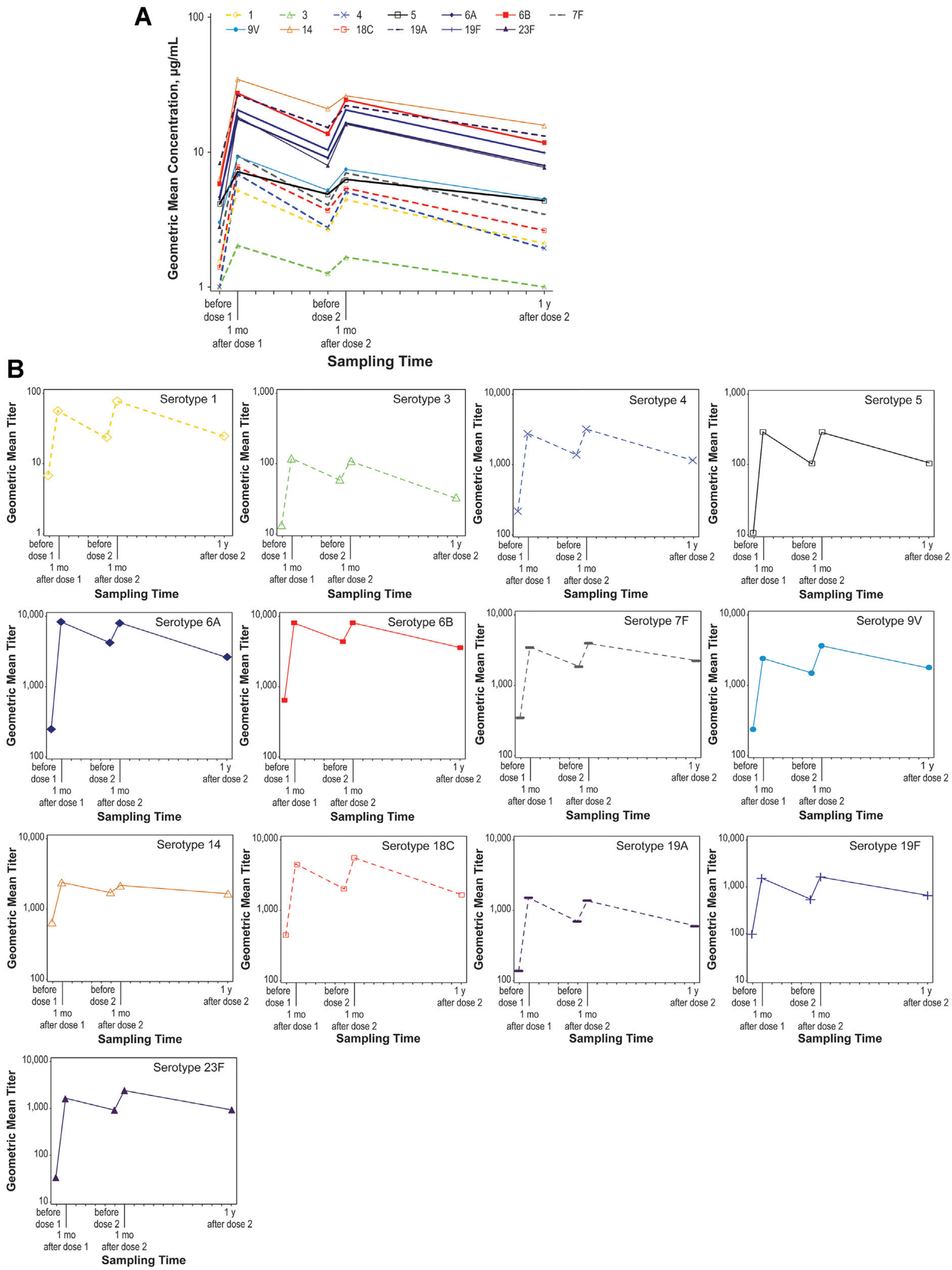

Fig. 1. Pneumococcal IgG GMCs and OPA GMTs at each sampling time for PCV13 (evaluable immunogenicity population). IgG = immunoglobulin G; GMC = geometric mean concentration; OPA = opsonophagocytic activity; GMT = geometric mean titer; PCV13 = 13-valent pneumococcal conjugate vaccine.

TABLE II. Pneumococcal IgG GMCs and GMFRs Following Vaccination With PCV13

	GMC[a] (μg/ml) (n[b] = 134–137)				GMC[a] (μg/ml) (n[b] = 64–78)			
Serotype	After dose 1	After dose 2	GMFR[c]	(95% CI[d])	Before dose 1	1 year after dose 2	GMFR[c]	(95% CI[d])
1	5.15	4.51	0.88	(0.77, 0.99)[e]	1.44	2.24	1.55	(1.24, 1.95)[f]
3	2.03	1.67	0.82	(0.75, 0.90)[e]	1.04	1.03	0.99	(0.76, 1.29)
4	6.81	5.09	0.75	(0.66, 0.84)[e]	0.95	2.02	2.12	(1.64, 2.75)[f]
5	7.05	6.33	0.90	(0.82, 0.98)[e]	4.33	4.33	1.00	(0.89, 1.12)
6A	17.25	16.37	0.95	(0.82, 1.10)	5.23	8.89	1.70	(1.42, 2.03)[f]
6B	27.14	24.24	0.89	(0.78, 1.02)	5.49	11.64	2.12	(1.74, 2.59)[f]
7F	9.37	7.06	0.75	(0.67, 0.85)[e]	2.03	3.34	1.65	(1.39, 1.95)[f]
9V	9.04	7.46	0.82	(0.75, 0.91)[e]	3.00	4.49	1.50	(1.28, 1.76)[f]
14	34.74	26.19	0.75	(0.67, 0.85)[e]	5.58	16.96	3.04	(2.21, 4.17)[f]
18C	7.74	5.44	0.70	(0.62, 0.80)[e]	1.29	2.72	2.11	(1.73, 2.59)[f]
19A	26.73	22.19	0.83	(0.74, 0.93)[e]	7.86	13.55	1.72	(1.43, 2.08)[f]
19F	19.61	20.56	1.05	(0.91, 1.20)	4.29	11.29	2.63	(2.10, 3.29)[f]
23F	17.80	16.18	0.91	(0.77, 1.08)	2.92	7.75	2.66	(2.14, 3.30)[f]

IgG, immunoglobulin G; GMC, geometric mean concentration; GMFR, geometric mean fold rise; PCV13, 13-valent pneumococcal conjugate vaccine; CI, confidence interval. [a]GMCs calculated using all evaluable subjects with data for both blood draws. [b]n = Number of evaluable subjects with determinate IgG concentration to the specified serotype at both blood draws. [c]GMFRs calculated using all evaluable subjects with data from both blood draws. [d]CIs are back transformations of a confidence interval based on the Student *t*-distribution for the mean logarithm of the concentrations, or the mean fold rise. [e]Upper limit of the 95% CI for the GMFR is <1. [f]Lower limit of the 95% CI for the GMFR is >1.

were made in a study of PCV13-vaccinated 7-year-old children who had been previously primed and boosted with a PCV9-meningococcal C (MnCC) vaccine between 3–12 months of age, or primed with PCV9-MnCC and boosted with PPSV23. The PCV9/PPSV23/PCV13 group exhibited reduced IgG and OPA immune responses compared with the PCV9/PCV9/PCV13 group [22]. In our study population, altered immune function associated with functional or anatomic asplenia cannot be ruled out as a contributor to the reduced immune responses observed. However, infants with SCD are generally able to mount PCV immune responses measured as IgG binding and OPA functional antibody responses that are as robust as those of healthy infants [23,24].

TABLE III. Pneumococcal OPA GMTs and GMFRs Following Vaccination With PCV13

	GMT[a] (n[b] = 64–109)				GMT[a] (n[b] = 40–66)			
Serotype	After dose 1	After dose 2	GMFR[c]	(95% CI[d])	Before dose 1	1 year after dose 2	GMFR[c]	(95% CI[d])
1	55	77	1.4	(1.08, 1.80)[e]	6	24	3.8	(2.56, 5.75)[e]
3	106	105	1.0	(0.83, 1.17)	13	34	2.7	(1.73, 4.09)[e]
4	2700	2936	1.1	(0.90, 1.31)	269	1091	4.1	(1.86, 8.89)[e]
5	262	280	1.1	(0.83, 1.37)	11	99	9.0	(5.63, 14.33)[e]
6A	7611	7127	0.9	(0.79, 1.10)	286	2296	8.0	(3.83, 16.88)[e]
6B	7624	7705	1.0	(0.85, 1.20)	888	3446	3.9	(1.80, 8.38)[e]
7F	3224	3692	1.1	(1.01, 1.30)[e]	376	2264	6.0	(3.10, 11.70)[e]
9V	2639	3354	1.3	(1.01, 1.60)[e]	384	1543	4.0	(1.69, 9.58)[e]
14	2295	2096	0.9	(0.80, 1.04)	749	1741	2.3	(1.36, 3.97)[e]
18C	4537	5462	1.2	(1.00, 1.46)	601	1469	2.4	(1.00, 5.94)[e,f]
19A	1424	1300	0.9	(0.80, 1.04)	117	630	5.4	(3.45, 8.44)[e]
19F	1610	1523	0.9	(0.78, 1.15)	105	537	5.1	(2.40, 10.92)[e]
23F	1670	2202	1.3	(1.07, 1.62)[e]	29	844	29.5	(13.57, 64.13)[e]

OPA, opsonophagocytic activity; GMT, geometric mean titer; GMFR, geometric mean fold rise; PCV13, 13-valent pneumococcal conjugate vaccine; CI, confidence interval. [a]GMTs calculated using all evaluable subjects with data for both blood draws. [b]n = Number of evaluable subjects with determinate OPA titer to the specified serotype at both blood draws. [c]GMFRs calculated using all evaluable subjects with data from both blood draws. [d]CIs are back transformations of a confidence interval based on the Student *t* distribution for the mean logarithm of the titers, or the mean fold rise, [e]Lower limit of the 95% CI for the GMFR is >1, [f]1.00 = 1.004.

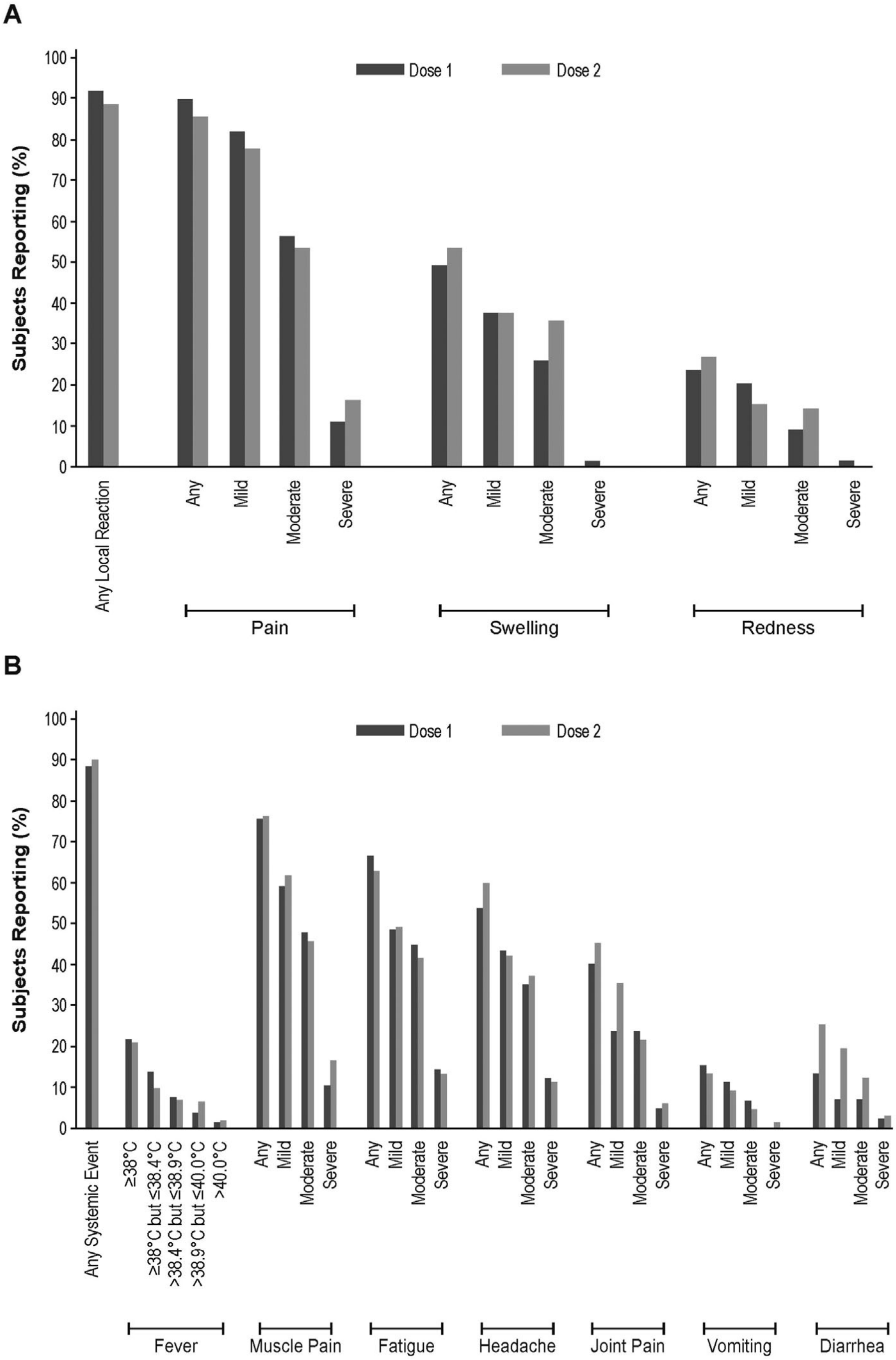

Fig. 2. Subjects reporting local reactions and systemic events within seven days of PCV13 vaccination. (A) Pain: mild, does not interfere with activity; moderate, interferes with activity; and severe, prevents daily activity. Redness and swelling for subjects ≥6–<12 years of age: mild, 0.5–2.0 cm; moderate, 2.5–7.0 cm; and severe, >7.0 cm; for subjects ≥12 years of age: mild, 2.5–5.0 cm; moderate, 5.1–10.0 cm; and severe, >10.0 cm. (B) Vomiting: mild, 1–2 times in 24 hr; moderate, >2 times in 24 hr; and severe, requires IV hydration. Diarrhea: mild, 2–3 loose stools in 24 hr; moderate, 4–5 loose stools in 24 hr; and severe, ≥6 loose stools in 24 hr. Other systemic events: mild, does not interfere with activity; moderate, some interference with activity; and severe, significant, prevents daily routine activity. PCV13 = 13-valent pneumococcal conjugate vaccine.

In a previous study, subjects who had received PPSV23 5 years before enrollment were given a dose of PCV13 or PPSV23; for 10 of 12 serotypes common to both vaccines, subjects in the PCV13 group had significantly higher OPA titers than subjects who received another dose of PPSV23 [20]. Although healthy subjects previously vaccinated with PPSV23 generated stronger immune responses to a dose of PCV13 compared with PPSV23 [20], a parallel conclusion for pediatric SCD subjects cannot be drawn based on the current study.

Because the majority of the study population had only received one dose of PPSV23, the impact of the number of prior PPSV23 doses on PCV13 responses could not be assessed. No correlation

TABLE IV. Subjects Reporting Serious Adverse Events Throughout the Study

MedDRA system organ class and preferred term	Within 6 months after PCV13 dose 1 N = 158	Within 6 months after PCV13 dose 2 N = 147	Between 6–12 months after PCV13 dose 2 N = 87
	n (%)	n (%)	n (%)
Any	40 (25.3)	34 (23.1)	16 (18.4)
Congenital, familial, and genetic disorders	24 (15.2)	22 (15.0)	11 (12.6)
Sickle cell anaemia with crisis or Vascular occlusion	24 (15.2)	22 (15.0)	11 (12.6)
Other			
Blood and lymphatic system disorders	2 (1.3)	2 (1.4)	0 (0.0)
Anaemia	1 (0.6)	0 (0.0)	0 (0.0)
Haemolytic anaemia	0 (0.0)	1 (0.7)	0 (0.0)
Hypersplenism	0 (0.0)	1 (0.7)	0 (0.0)
Lymphadenopathy	1 (0.6)	0 (0.0)	0 (0.0)
Eye disorders	1 (0.6)	0 (0.0)	0 (0.0)
Visual impairment	1 (0.6)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	5 (3.2)	0 (0.0)	0 (0.0)
Abdominal pain	1 (0.6)	0 (0.0)	0 (0.0)
Constipation	1 (0.6)	0 (0.0)	0 (0.0)
Gastritis	1 (0.6)	0 (0.0)	0 (0.0)
Gingivitis	1 (0.6)	0 (0.0)	0 (0.0)
Hiatus hernia	1 (0.6)	0 (0.0)	0 (0.0)
Nausea	1 (0.6)	0 (0.0)	0 (0.0)
Oesophagitis	1 (0.6)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	6 (3.8)	5 (3.4)	4 (4.6)
Chest pain	0 (0.0)	1 (0.7)	0 (0.0)
Fatigue	1 (0.6)	0 (0.0)	0 (0.0)
Oedema peripheral	0 (0.0)	0 (0.0)	1 (1.1)
Pain	1 (0.6)	2 (1.4)	1 (1.1)
Pyrexia	5 (3.2)	2 (1.4)	3 (3.4)
Hepatobiliary disorders	3 (1.9)	0 (0.0)	1 (1.1)
Cholescystitis	1 (0.6)	0 (0.0)	0 (0.0)
Cholescystitis acute	1 (0.6)	0 (0.0)	1 (1.1)
Hyperbilirubinaemia	1 (0.6)	0 (0.0)	0 (0.0)
Infections and infestations	12 (7.6)	8 (5.4)	6 (6.9)
Bacteraemia	1 (0.6)	1 (0.7)	0 (0.0)
Bone abscess	0 (0.0)	0 (0.0)	1 (1.1)
Bronchitis	1 (0.6)	1 (0.7)	1 (1.1)
Device-related infection	1 (0.6)	0 (0.0)	0 (0.0)
Gastroenteritis	0 (0.0)	1 (0.7)	1 (1.1)
Groin abscess	0 (0.0)	1 (0.7)	0 (0.0)
Hepatitis A	0 (0.0)	1 (0.7)	0 (0.0)
Osteomyelitis	1 (0.6)	0 (0.0)	1 (1.1)
Pharyngitis	1 (0.6)	0 (0.0)	0 (0.0)
Pharyngotonsillitis	1 (0.6)	0 (0.0)	0 (0.0)
Pneumonia	1 (0.6)	2 (1.4)	4 (4.6)
Pyelonephritis	1 (0.6)	0 (0.0)	0 (0.0)
Sinusitis	0 (0.0)	1 (0.7)	0 (0.0)
Staphylococcal bacteraemia	0 (0.0)	1 (0.7)	0 (0.0)
Tonsillitis	1 (0.6)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	2 (1.3)	0 (0.0)	0 (0.0)
Urinary tract infection	1 (0.6)	0 (0.0)	1 (1.1)

TABLE IV. (*Continued*)

MedDRA system organ class and preferred term	Within 6 months after PCV13 dose 1 N = 158	Within 6 months after PCV13 dose 2 N = 147	Between 6–12 months after PCV13 dose 2 N = 87
	n (%)	n (%)	n (%)
Injury, poisoning, and procedural complications	1 (0.6)	1 (0.7)	0 (0.0)
Overdose	0 (0.0)	1 (0.7)	0 (0.0)
Rib fracture	1 (0.6)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	1 (0.7)	0 (0.0)
Hypocalcaemia	0 (0.0)	1 (0.7)	0 (0.0)
Musculoskeletal and connective tissue disorders	3 (1.9)	6 (4.1)	0 (0.0)
Arthralgia	0 (0.0)	1 (0.7)	0 (0.0)
Back pain	2 (1.3)	1 (0.7)	0 (0.0)
Flank pain	0 (0.0)	1 (0.7)	0 (0.0)
Muscular weakness	0 (0.0)	1 (0.7)	0 (0.0)
Musculoskeletal chest pain	0 (0.0)	2 (1.4)	0 (0.0)
Pain in extremity	1 (0.6)	2 (1.4)	0 (0.0)
Pain in jaw	1 (0.6)	0 (0.0)	0 (0.0)
Nervous system disorders	3 (1.9)	4 (2.7)	1 (1.1)
Cerebral infarction	0 (0.0)	1 (0.7)	0 (0.0)
Cerebrovascular accident	0 (0.0)	0 (0.0)	1 (1.1)
Headache	1 (0.6)	1 (0.7)	0 (0.0)
Hypoaesthesia	0 (0.0)	1 (0.7)	0 (0.0)
Lethargy	1 (0.6)	0 (0.0)	0 (0.0)
Migraine	1 (0.6)	0 (0.0)	0 (0.0)
Unresponsive to stimuli	0 (0.0)	1 (0.7)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	2 (1.4)	0 (0.0)
Pregnancy	0 (0.0)	2 (1.4)	0 (0.0)
Psychiatric disorders	1 (0.6)	0 (0.0)	0 (0.0)
Mental status changes	1 (0.6)	0 (0.0)	0 (0.0)
Renal and urinary disorders	1 (0.6)	3 (2.0)	1 (1.1)
Dysuria	1 (0.6)	0 (0.0)	0 (0.0)
Haematuria	0 (0.0)	1 (0.7)	1 (1.1)
Renal failure	0 (0.0)	1 (0.7)	0 (0.0)
Renal failure chronic	0 (0.0)	1 (0.7)	0 (0.0)
Reproductive system and breast disorders	1 (0.6)	0 (0.0)	0 (0.0)
Priapism	1 (0.6)	0 (0.0)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	4 (2.5)	3 (2.0)	2 (2.3)
Acute chest syndrome	3 (1.9)	2 (1.4)	1 (1.1)
Asthma	1 (0.6)	1 (0.7)	1 (1.1)
Lung infiltration	0 (0.0)	1 (0.7)	0 (0.0)
Respiratory failure	0 (0.0)	1 (0.7)	0 (0.0)

MedDRA, Medical Dictionary for Regulatory Activities; PCV13, 13-valent pneumococcal conjugate vaccine; n (%), Number (percentage) of subjects reporting at least 1 event.

was found between the time since last PPSV23 vaccination and the magnitude of immune responses to first dose of PCV13. The mean interval from the last PPSV23 dose to study enrollment was 3.5 ($\pm$2.6) years, ranging from 0.5 to 11.8 years. Therefore, if the reduced responses to PCV13 observed in this population are due to PPSV23 pre-vaccination, its effect on subsequent PCV13 dosing seems long-lasting. This observation is consistent with findings from a long-term follow-up study in adults aged 60–64 years in whom a second vaccination with PPSV23 administered about 4 years after the initial PPSV23 vaccination resulted in notably lower immune responses than those seen after the initial PPSV23 dose [25].

In contrast, the recall immune responses observed following revaccination with PCV13 [25] or vaccination with PPSV23 after initial PCV13 vaccination [21,25] support the viewpoint that the conjugate vaccine elicits polysaccharide-specific immunological memory and thereby enhances the ability to respond to natural infection. Remarkably, 49% of IPD during 2007–2008 among immunocompromised children 6–18 years of age was caused by PCV13 serotypes [13].

Currently there are no recommendations for concomitant use of hydroxycarbamide with immunizations, and whether this drug may interfere with PCV13 immune response maturation is unknown. A recent study investigating the effects of hydroxycarbamide on immune responses to pneumococcal vaccinations (PPSV23 administered at 24 months after receipt of three doses of PCV7) in infants and young children 10 weeks–24 months of age with SCD did not identify significant differences in IgG responses between the hydroxycarbamide- and placebo-treated subjects [26]. Our study also revealed no impact of concomitant hydroxycarbamide use on antibody responses to PCV13. While the analysis is preliminary, data from our study suggest that effective immunization with PCV13 can be achieved during hydroxycarbamide therapy.

Study limitations include a non-comparative design and the lack of a parallel arm evaluating the effects of a second dose of PPSV23 administered at the same interval as PCV13. This study was designed to administer the study vaccine to subjects previously vaccinated with PPSV23 at least 6 months before enrollment. According to current guidelines, administration of a second dose of PPSV23 < 5 years from the initial vaccination is not recommended in this population [13].

Repeated PCV13 doses in this population were well tolerated, and there were no unanticipated reactions or AEs. Most AEs and SAEs were vaso-occlusive crises, as expected in this population, and were reported at fairly similar rates throughout the study.

CONCLUSION

After a single dose of PCV13, antibody titers significantly increased in young children and adolescents with SCD who had previously received PPSV23. Antibody levels after a second PCV13 dose given 6 months later were comparable to levels after the first dose. Although antibody levels declined over the year following the second dose, they remained above pre-vaccination levels. Based on the study results, this population may benefit from at least one dose of PCV13. Further studies are warranted to evaluate the need for re-vaccination with PCV13 and the interval between doses.

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