

Maintenance of an Immunogenic Response to Pneumococcal Vaccination in Children With Sickle Cell Disease

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Summary: Patients with sickle cell disease (SCD) are at increased risk for invasive pneumococcal disease because of splenic dysfunction. To mitigate this risk, patients are protected with prophylactic penicillin until completion of pneumococcal vaccination series. The objective of this study was to assess the maintenance of a protective immune response to pneumococcal vaccination in children with SCD. A retrospective review was conducted between June 2019 and June 2020 of all patients with SCD patients for whom it had been 5 ± 1 year since completion of PPSV23 vaccination series. A total of 41 patients were analyzed. The majority of children (68%) were able to maintain an adequate immune response. There was no identifiable disease characteristic associated with maintenance of an appropriate immunogenic response. This study finds that patients with SCD are able to maintain an adequate immune response at the 5 ± 1 year time point from completion of PPSV23 vaccination series. Similarly, patients were not found to have an increased rate of invasive pneumococcal disease even if not meeting criteria for adequate pneumococcal serum titer levels. Maintenance of pneumococcal titers suggests that there may not be a need for revaccination at the 5-year time point in this patient population.

Key Words: sickle cell disease, pneumococcal, vaccine, immune response, children

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The complications of sickle cell disease (SCD), which include severe pain, acute chest syndrome, and stroke, can be devastating.¹ Patients with SCD are also particularly vulnerable to infections by encapsulated bacteria, especially *Streptococcus pneumoniae*, because of splenic dysfunction caused by autoinfarction of the spleen.

Penicillin prophylaxis, as well as pneumococcal vaccination, is paramount to preventing invasive pneumococcal disease (IPD) and associated morbidity and mortality in children with SCD.^{2,3} Pneumococcal polysaccharide vaccine (PPSV23) was a pneumococcal vaccine that was inclusive of various *pneumococcal* strains, but was noted to not have a

protective immune response in children younger than 2 years of age.⁴ This led to the initial use of the 7-valent pneumococcal conjugate vaccine (PCV7) in patients under 2 years of age, which was replaced with the 13-valent pneumococcal conjugate vaccine (PCV13) in 2010.²⁻⁴

The Advisory Committee on Immunization Practices (ACIP) recommends all infants should complete a series of PCV13, typically completed by 15 months of age. PCV13 only covers a portion of the numerous strains of pneumococcal disease, however, the introduction of this vaccine was found to result in a 64% overall reduction in IPD.⁴ Because of splenic dysfunction resulting in increased vulnerability to *pneumococcal* infections, patients with SCD also receive PPSV23 at 2 and 5 years of age to cover a broader set of pneumococcal serotypes.⁵⁻⁷

After completion of the pneumococcal vaccine series, most patients with SCD will have prophylactic penicillin discontinued, unless they have had surgical removal of their spleen or history of IPD, in which case lifelong penicillin prophylaxis is often prescribed.^{2,8} Previous studies have suggested that patients with SCD do not maintain an adequate immune response 5 years or more from the last pneumococcal vaccine, implying patients are not appropriately protected against pneumococcal disease after this time. As a result of these findings, some institutions are choosing to administer PPSV23 every 5 years after the initial 2 doses. However, prior studies were conducted in adult cohorts or only analyzed groups who had received PCV7 or PPSV23 vaccines and not PCV13 vaccination.^{9,10} Little is known about how long children with SCD maintain an adequate immune response to pneumococcal vaccination, particularly following the introduction of PCV13. The objective of this study was to determine if the introduction of PCV13 into the routine vaccination schedule for children with SCD affects maintenance of immunogenicity and if there are any clinical factors which influence a child's ability to maintain an adequate immune response.

MATERIALS AND METHODS

This retrospective study reviewed all patients with SCD who were seen at the Riley Hospital for Children Comprehensive Sickle Cell Program between June 2019 and June 2020. Demographic data such as age, sex, and sickle cell genotype were collected, as well as, hemoglobin (g/dL), hemoglobin F percent, and serum pneumococcal titers that were obtained as part of the patient's routine comprehensive sickle cell clinic appointments. This study was considered exempt by the Indiana University Institutional Review Board. Inclusion criteria were any patient with SCD who completed a 2-dose PPSV23 series within 5 ± 1 year.

The Sickle Cell Program's vaccination guidelines follow the recommendations outlined by ACIP, the American Academy of Pediatrics (AAP), and the National Heart,

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Lung, and Blood Institute (NHLBI). All children with SCD complete a PCV13 vaccination series. PPSV23 vaccination was given at 2 and 5 years of age, or 2 doses 3 to 5 years apart if vaccination is initiated at a later age. In addition, if children with SCD were initially vaccinated with PCV7 they were administered PCV13, per ACIP and AAP catch-up recommendations.¹¹ Vaccination records for this study were obtained through the Children and Hoosier Immunization Registry Program (CHIRP), Indiana's online vaccination database, and confirmed with the electronic medical record. Patients without a confirmed immunization history were excluded.

The Sickle Cell Program's guidelines for hydroxyurea use are congruent with NHLBI guidelines with initiation typically occurring between 9 and 12 months for all children with Hb SS or SB0 disease. However, for the cohort in this study, many were beyond this age range when these guidelines were implemented in our clinic, and therefore, offered HU at later ages. Dosing is escalated to the maximum tolerated dose based on laboratory and clinical responses.

Pneumococcal titers were measured by ARUP laboratory. Adequate maintenance of immune response was defined as having serum immunoglobulin (Ig)G levels ≥ 1.3 $\mu\text{g/mL}$ for at least 50% (12 or greater) of the 23 pneumococcal serotypes. This was determined as an adequate cut-off based on prior studies, consultation with a immunology expert, and per ARUP lab standards (<http://ltd.aruplab.com/Tests/Pub/2005779>).⁹

Descriptive statistics were used to analyze demographic data. Patients were divided into adequate or inadequate immune response groups based on the titer criteria mentioned. The Fisher exact test or *t* test was used to compare demographic and disease characteristics between immune response groups. All analyses were performed using STATA 15, and *P*-values <0.05 were considered statistically significant.

RESULTS

Forty-seven patients had serum samples collected, of which 6 were excluded because of discrepant immunization records. The mean age was 12 years old (± 2.9), with ~50% being female (Table 1). The majority (71%) had Hb SS genotype. Ten patients (24%) had anatomic asplenia. Twenty-five patients (61%) were prescribed hydroxyurea.

Of the 41 patients analyzed, 68% had an adequate immune response 5 ± 1 years after completion of a 2-dose

TABLE 1. Demographics

Baseline Characteristic	N (Total = 41), n (%)
Female	20 (49)
Age	12 y (± 2.9)
Genotype	
SS	29 (71)
SC	9 (22)
SB0	1 (2)
SB+	2 (5)
Anatomic asplenia	10 (24)
Hydroxyurea use	25 (61)
Chronic transfusion therapy	6 (15)
History of bacteremia	3 (7.3)
Vaccine received	
PCV7 only	5 (12)
PCV7 +PCV13	26 (63)
PCV13 only	10 (24)

TABLE 2. Immunogenic Response and Clinical Characteristics

Characteristic	Serotype Outcome, n (%)		<i>P</i>
	Adequate Response	Inadequate Response	
Overall titer response, n=41	28 (68)	13 (32)	—
PCV7 vaccine, n=31	20 (65)	11 (35)	0.458
PCV13 vaccine, n=36	24 (67)	12 (33)	1
Bacteremia, n=3	1 (33)	2 (66)	0.232
Hydroxyurea therapy, n=25	15 (60)	10 (40)	0.187
Chronic transfusions, n=6	5 (83)	1 (17)	0.645
Anatomic Asplenia, n=10	7 (78)	3 (22)	0.692
Time in years from the last PPSV23 vaccine	4.99 \pm 0.838	5.42 \pm 1.19	0.195

PPSV23 vaccination series. The average time in years from last dose of PPSV23 for those in the adequate immune response group was 4.99 versus 5.42 in the inadequate immune response group, but this difference was not statistically significant.

The majority of patients (63%) had received a combination of PCV7 and PCV13 before PPSV23. A total of 36 patients received PCV13, either alone or in combination with PCV7 vaccination, 67% of whom demonstrated an adequate titer response. There was no statistically significant difference in titer response between those who received PCV13 alone, those who received PCV13 following initial PCV7 vaccination, and those who received PCV7 only (62%, 73%, and 80% relatively) (Table 2). There were 7 patients who received a catch-up PCV13 dose after the 2 doses of PPSV23, 3 of whom had inadequate titers. Regardless of overall titer adequacy, the majority of serotypes for which these 7 patients had adequate responses are present in the PCV13 vaccination. More so, many of these serotypes are covered by PCV7 and PPSV23, as well. Figure 1 depicts the percent of patients with adequate titer levels for each serotype based on the vaccination combination they received. There was no statistical difference between the vaccination subgroups and adequate serotype titer levels for any one specific serotype.

There were no statistically significant associations with sex, age, genotype, anatomic asplenia, hydroxyurea use, or chronic transfusions (Table 2). Three patients had documented non-pneumococcal bacterial infections, but no patients had serious pneumococcal infections. Two of the patients with non-pneumococcal bacteremia had inadequate pneumococcal immune responses.

Evaluation of an appropriately maintained immunogenic response to individual serotypes between the 2 groups of inadequate versus adequate maintenance is depicted in Table 3. Between the 2 groups of patients some serotypes were more likely to have maintained an adequate titer response as indicated by *P*-value <0.05 , however, there was no association between vaccination patterns for that difference.

DISCUSSION

The inclusion of SCD on statewide newborn screens resulted in the ability of health care providers to initiate early penicillin prophylaxis until the completion of the

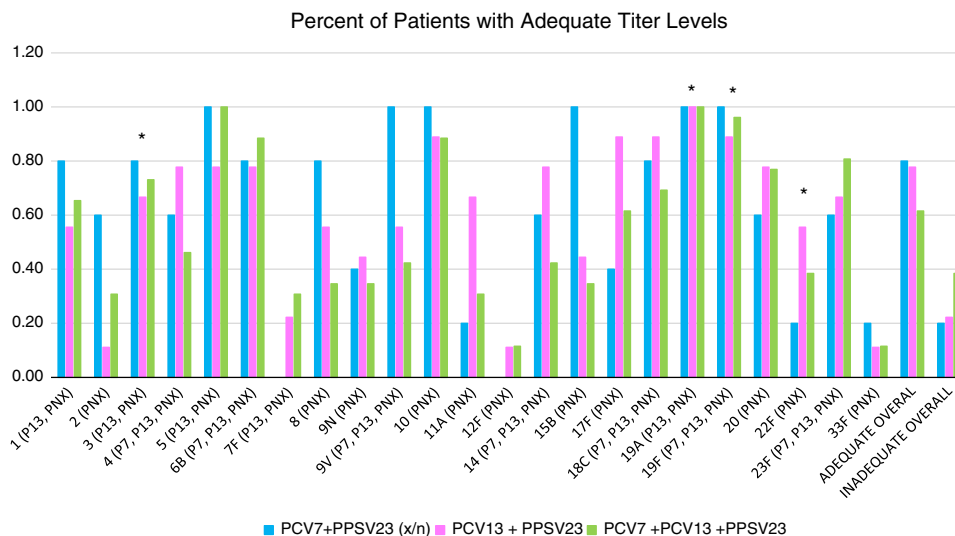


FIGURE 1. Percent of patients with adequate titer levels for specific pneumococcal serotypes based on vaccination history. *The most common vaccine targetable serotypes that resulted in cases of invasive pneumococcal disease in children younger than 5 years of age in the state of Indiana between 2014 and 2018.

pneumococcal vaccine series.⁸ Despite these interventions, little is known about the ability to retain pneumococcal immunity in this patient population.¹² Because of conflicting evidence about need for revaccination, timing of revaccination, and pneumococcal titer maintenance, no widely accepted standard regarding revaccination in the SCD population has been established.^{13,14}

We found that the majority (68%) of children with SCD were able to maintain an appropriate immunogenic response, up to 5 ± 1 year from the completion of their second PPSV23 vaccine.^{9,14} To our knowledge, this is the first study that analyzes maintenance of pneumococcal immunogenicity in children since the introduction of PCV13 as standard practice. Previous studies, such as Rao et al,¹³ found one third of children with SCD in their cohort had suboptimal levels of pneumococcal titers when measured 3 to 7 years after the first booster of PPSV23. Santoro et al,⁹ also noted this drop in protective titer levels with only 36% of children having adequate titer levels at an average of 37 months postcompletion pneumococcal vaccination. However, both studies were completed when PCV13 was not the standard pneumococcal vaccination for children. Robinson and Lanzkron¹⁰ similarly evaluated an adult SCD cohort who had received PCV13 vaccination, and found 68% of the patients studied had appropriate pneumococcal titer levels at 5 years post pneumococcal vaccination. The reported ‘nonresponders’ were mostly in patients who had more than a 5-year interval from their last pneumococcal vaccination. Our data also indicates that patients with inadequate titers had on average a longer interval of time since last PPSV23 vaccination at 5.42 years compared with patients with adequate titer levels with an average of 4.99 years since last PPSV23 vaccination. However, this was not a statistically significant difference, and potentially confounded by our more stringent definition for adequate titers (≥ 1.3 µg/mL as opposed to Robinson and Lanzkron¹⁰ of ≥ 1 µg/mL). The results of our 7 patients who received PCV13 vaccination after PPSV23 vaccination find that 4/7 (57%) had an adequate maintenance of titer response. When looking at all 7 of these patients regardless of adequate titer maintenance, it was noted that of the serotypes that had adequate maintenance of titer response, the majority were from PCV13 vaccinations. This potentially implies that PPSV23 before PCV13 vaccination may act as a primer, improving maintenance of titer response. This is in line with prior studies that have found PCV13 vaccine post-PPSV23 vaccination resulted in higher titer levels, again implying

TABLE 3 . Patients With Adequate Immunogenic Response to Individual Serotypes of the PPSV23 Vaccine Based on Overall Response

Serotypes	Adequate Response	Inadequate Response	P
	N = 28, n (%)	N = 13, n (%)	
1*	25 (89)	2 (15)	<0.001
2†	8 (29)	3 (23)	1
3*	25 (89)	4 (31)	<0.001
4*,‡	21 (75)	1 (8)	<0.001
5*	28 (100)	10 (77)	0.027
6B*,‡	25 (89)	10 (77)	0.361
7F*	9 (32)	2 (15)	0.451
8†	18 (64)	1 (8)	0.001
9N†	15 (54)	1 (8)	0.006
9V*,‡	18 (64)	3 (23)	0.02
10A†	27 (96)	9 (69)	0.028
11A†	15 (54)	1 (8)	0.006
12F†	3 (11)	1 (8)	1
14*,‡	18 (64)	5 (38)	0.179
15B†	14 (50)	4 (31)	0.321
17F†	24 (86)	3 (23)	<0.001
18C*,‡	25 (89)	5 (38)	0.001
19A*	28 (100)	13 (100)	1
19F*,‡	27 (96)	12 (92)	0.539
20†	26 (93)	5 (38)	<0.001
22F†	15 (54)	2 (15)	0.039
23F*,‡	25 (89)	7 (54)	0.018
33F†	6 (21)	0	0.152

*Serotypes that are in the PCV13 vaccination.

†Serotypes that are only in the PPSV23 vaccination.

‡Serotypes that are in PCV7 vaccination.

that immunity could be improved with the schedule of the polysaccharide vaccine followed by the conjugate vaccination.¹⁵

Our study did not demonstrate associations between disease characteristics with either an adequate or inadequate immune response, as noted in Table 2. Of particular interest is the lack of significance of spleen status. In the clinical setting of asplenia it was hypothesized that serum anti-pneumococcal polysaccharide (PnPS)-specific memory B cells, both IgM and IgG isotypes, would be decreased and thus, negatively impact long-term titer development.^{16,17} However, our study did not show a statistically significant difference in titer maintenance among patients with anatomic splenectomy and functional asplenia or timing between splenectomy and vaccination, which is in alignment with a study that has shown splenectomy alone is not a reason for loss of memory B cells and decreased IgM anti-pneumococcal antibodies.¹⁸ Rosado et al,¹⁹ found that those vaccinated with the pneumococcal conjugated vaccine post splenectomy were able to restore the pool of anti-PnPS IgG memory B cells.

Of significant clinical importance is the lack of IPD or other serious *S. pneumoniae* infections in our cohort. Prior literature review finds that serotypes 1, 4, 5, 7F, 8, 12F, 14, 18C, and 19A are the most likely serotypes to result in IPD in the general population.²⁰ In Indiana, cases of IPD are reportable, with serotyping performed in children younger than 5 years of age. Statewide data from 2014 to 2018 showed a total of 154 cases of IPD in children younger than 5 years of age. The majority of the cases were because of serotypes not included in either PCV13 or PPSV23. However, 26% were caused by serotypes found in PCV13 and/or PPSV23, the most common of which were 22F (5.8%), 19F (5.2%), 3 (3.2%), and 19A (2.6%) (Fig. 2).²¹ We found that our patients had varying responses with regards to adequate or inadequate titer levels for these specific serotypes, as seen in Figure 1 and Table 3.

Oligbu et al completed a literature review of studies published from 2000 to 2017 which found a prevalence rate of 1.9% for IPD calculated from a review of 475 studies with over 9000 children with SCD.²² The Indiana State Department of Health (ISDH) reports an incidence rate of 8.3 per

100,000 in Indiana for the year of 2018. On average from 2014 to 2018 the incidence rate is 7.84 per 100,000.²³ Our retrospective review found no cases of IPD in our patient population. It is possible we did not see a large number of IPD cases in our SCD cohort, not only because of prophylactic penicillin in those 5 years or under, but also because of maintaining an immune response to common community serotypes.

Our results (Table 3) demonstrate that a patient can be deemed to have an adequate titer response overall, but still remain susceptible to infection for a given individual serotype to which they have an inadequate titer response. The reverse is noted by a 100% retained immunity in our cohort to serotype 19A, regardless of overall immune response status. Of significance serotype 19A is noted to be one of the more common serotypes to result in IPD in the general population.²⁰

A potential limitation of our study is our definition of an adequate immune response; we acknowledge that other sources have used different cut-off values which limits the generalizability of this analysis.^{10,24-26} Another limitation of our study is the lack of longitudinal vaccine titer data, which limits the ability to assess for an inadequate initial immune response to vaccination versus waning antibody titers. The lack of longitudinal vaccine titer data also limits the ability to assess for both the immune response attributable to vaccine versus natural infection. It is also noted that in patients on chronic transfusion protocols we are also unable to discern between passive antibody from a blood donor versus a patients' own antibody titers. Statewide IPD data only reflects serotype information in those <5 years old, which is not reflective of the age group in our cohort, though no cases of IPD were found in our cohort. With only 41 patients it is difficult to assess if our data would accurately reflect the low incidence rate of IPD projected in the SCD patient population. IPD rates and serotype predominance will vary from region to region, which limits the generalizability of our data. Our study is also limited in generalizability because of this being a single institution study, which is evaluating one time point.

Overall, we have found that the majority of patients with SCD are able to maintain appropriate immunogenic

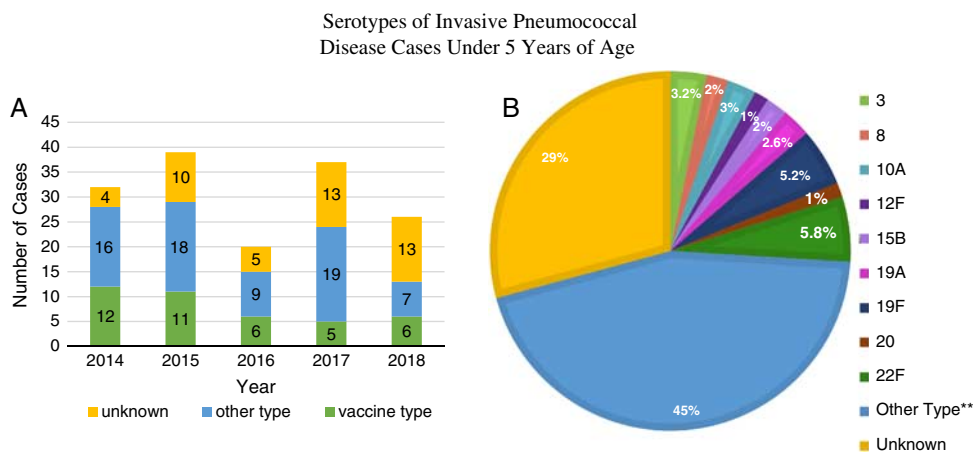


FIGURE 2. Serotypes of invasive pneumococcal disease cases under 5 years of age by year, Indiana, 2014 to 2018. A, Categorized by a vaccine type serotype, unknown serotype, or other/serotype not covered by a vaccine. B, Further categorizes and demonstrates the specific serotypes, unknown, or other type. **Other serotypes not included in either 13-valent pneumococcal conjugate vaccine (PCV13) or PPSV23 as well as isolates that demonstrated cross-reactivity where one single serotype could not be determined.

response to pneumococcal vaccinations 5 years following their initial PPSV23 vaccination series. We did not find any patient-specific disease characteristics that can potentially be used to determine if a patient is more or less likely to maintain an appropriate immunogenic response. However, with low IPD rates and high immunogenicity to the common serotype 19A, additional dosing of PPSV23 post-completion of PPSV23 vaccination series may not be necessary. Future studies include assessing titers over a longer time period to determine trends in loss of an immune response postvaccination, and whether rates of IPD remain low, to further understand the clinical relevance of revaccination.

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