Incidence of Invasive Pneumococcal Disease among Individuals with Sickle Cell Disease before and after the Introduction of the Pneumococcal Conjugate Vaccine

Natasha B. Halasa,1 Sadhna M. Shankar,1 Thomas R. Talbot,2,3 Patrick G. Arbogast,4,5 Ed F. Mitchel,3
Winfred C. Wang,6 William Schaffner,2,3 Allen S. Craig,3,6 and Marie R. Griffin2,3,5,7

Departments of 1Pediatrics, 2Medicine, 3Preventive Medicine, and 4Biostatistics, and 5Center for Education and Research on Therapeutics, Vanderbilt University School of Medicine, 6Tennessee Department of Health, and 7Geriatric Research Education and Clinical Center and Clinical Research Center of Excellence, Veterans Affairs, Tennessee Valley Healthcare System, Nashville, and 8Department of Hematology, St. Jude Children’s Research Hospital, Memphis, Tennessee

(See the editorial commentary by Steinberg on pages 1434–5)

Background. We sought to determine the incidence of invasive pneumococcal disease (IPD) among individuals with sickle cell disease (SCD) before and after the introduction of the pneumococcal conjugate vaccine (PCV).

Methods. Individuals with SCD who were enrolled in Tennessee Medicaid from January 1995 through December 2004 were identified using SCD-specific International Classification of Diseases, Ninth Revision, Clinical Modification codes. Population-based surveillance data were used to identify individuals with IPD and were linked to patients with SCD in the Tennessee Medicaid database to determine incidence rates of IPD. Clinical data were collected on all subjects with IPD, and antibiotic susceptibility testing and serotyping were performed on all available pneumococcal isolates.

Results. We identified 2026 individuals with SCD, who constituted 13,687 person-years of follow-up. During the study period, 37 individuals with SCD developed IPD, and 21 of these patients were aged <5 years. In a comparison of the pre-PCV period (1995–1999) with the post-PCV period (2001–2004), the rate of IPD decreased by 90.8% in children aged <2 years (from 3630 to 335 cases per 100,000 person-years; P < .001) and by 93.4% in children aged ≥5 years (from 2044 to 134 cases per 100,000 person-years; P < .001). Rates of IPD for patients with SCD who were aged ≥5 years decreased from 161 cases per 100,000 person-years during the pre-PCV period to 99 cases per 100,000 person-years during the post-PCV period (P = .36).

Conclusion. The rate of IPD among children with SCD who are aged <5 years has decreased markedly since the introduction of routine administration of PCV to young children.

Individuals with sickle cell disease (SCD) have increased susceptibility to invasive pneumococcal disease (IPD) [1] and are 30–600 times more likely to develop IPD than are individuals of comparable age and race without SCD [2–6]. Penicillin prophylaxis and pneumococcal polysaccharide vaccine (PPV) have decreased the rate of IPD among this high-risk population [5, 7–9], but breakthrough disease still occurs—most commonly in children aged <3 years [10–13]. Despite advancements in medical care, IPD continues to be a leading cause of death in children with SCD [14–18].

In February 2000, a 7-valent pneumococcal conjugate vaccine (PCV) was licensed and recommended for all children aged <2 years and for selected children aged 2–4 years with certain high-risk conditions, including SCD [19, 20]. Since the introduction of PCV, there has been a significant decrease in the incidence of IPD among all age groups and a decrease in the disparity of IPD rates between black and white children [21–24].
The incidence of IPD among individuals with SCD after the introduction of PCV, however, has not been previously reported and is the subject of this study.

**METHODS**

**Identification of individuals with SCD in the Tennessee Medicaid database.** Tennessee Medicaid (TennCare) administrative claims and encounter data files were used to identify individuals with SCD. In 1994, TennCare replaced the previous federal Medicaid program in the state. TennCare is a state-based, capitated, managed health care program covering state residents who are eligible for Medicaid benefits and those who are uninsured or uninsurable. The study population included individuals enrolled in TennCare from 1 January 1995 through 31 December 2004. We identified subjects as having SCD if they fulfilled 1 of the following conditions at any time during their enrollment in the Medicaid program during 1975–2004: (1) 1 hospitalization with a discharge diagnosis of SCD or (2) 2 outpatient (emergency department, office, or 23-h) visits that were at least 30 days apart with diagnoses of SCD. The following *International Classification of Diseases, Ninth Revision, Clinical Modification* codes for the diagnosis of SCD were used: 282.6, 282.60, 282.61, 282.62, 282.63, and 282.69 [25, 26]. A cohort of 2102 persons with SCD who were enrolled in TennCare during the study period (1995–2002) had previously been evaluated [27]. During 2 additional study years (2003–2004), 372 additional persons were identified, resulting in a total of 2474 persons with SCD. Persons entered the cohort at the time of their first enrollment in Medicaid and exited at the time of development of IPD, death, or loss of enrollment.

To validate our methods for identifying individuals with SCD, we linked children in the TennCare cohort with statewide, newborn SCD screen results. Newborn screen results were available for 363 cohort children born during 1996–2003. Of the 363 children, 312 (86%) had 1 of the 4 conditions (hemoglobin SC, hemoglobin SS, sickle-β-thalassemia, or sickle hemoglobin) and an unidentified variant indicating the diagnosis of SCD. The remaining children who were identified as having SCD through TennCare claims had a screen result indicating sickle cell trait (in 26 children) or hemoglobin C disease and/or trait (in 3 children), or 22 children had normal screen results. There were 32 individuals with a newborn screen result positive for SCD who were eligible for our cohort but did not meet our SCD definition. More than 100,000 children enrolled in TennCare had a newborn screen result during the 8 study years when screening was performed. Using the screen results as the gold standard, our definition of SCD had a sensitivity of >91%, a positive predictive value of 86%, and a specificity of >99%.

**Penicillin prophylaxis and pneumococcal vaccine use.**

Penicillin prophylaxis is recommended for children with SCD who are aged <5 years, and macrolides are used for those with a penicillin allergy [12]. Claim and encounter records for all prescriptions filled in the TennCare system for penicillin or macrolide drug classes for children with SCD who were aged <5 years were reviewed for the year prior to the IPD episode for children aged ≥1 year and from birth to the age of IPD onset for children aged <1 year.

PPV is recommended for children with SCD who are aged ≥2 years [28]. PCV is recommended for children with SCD who are aged <5 years [20]. TennCare records were reviewed for the following vaccine codes: pneumococcal vaccination (G0009 or V03.82), vaccination with PPV (J6065 or 90732), and vaccination with PCV (90069).

**Identification of IPD in Tennessee.** IPD was defined as the isolation of *Streptococcus pneumoniae* from ≥1 normally sterile body fluid, including blood, CSF, pleural fluids, peritoneal fluids, pericardial fluids, surgical aspirate, or bone or joint fluids [29]. Since 1 January 1995, prospective laboratory-based surveillance for episodes of IPD has been conducted at all of the hospitals in 5 urban counties in Tennessee, as part of the Active Bacterial Core surveillance (ABCs) network of the US Centers for Disease Control and Prevention [30]. In August 1999, 6 additional counties were added to the Tennessee ABCs network, increasing the surveillance population to >2.9 million persons, ~50% of the state’s population (according to the US Census Bureau [31]). Regular audits of laboratory records have been conducted to assess completeness of reporting. In addition, the collection of these data has not changed over the study period.

**Linkage of ABCs and the TennCare database.** ABCs data from the period 1 January 1995–31 December 2004 were linked to TennCare enrollment data by patient-specific identifiers to capture all persons with SCD and IPD.

**Susceptibility testing and serotyping.** All available pneumococcal isolates from patients with IPD were sent to the reference laboratory at the University of Texas Health Science Center at San Antonio for susceptibility testing. Nonsusceptibility was defined, according to standards set by the Clinical and Laboratory Standards Institute, as the presence of intermediate- or high-level resistance to the specific antimicrobial tested [32]. Pneumococcal isolates were sent to reference laboratories for serotyping by Quellung reaction [32]. The PCV serotypes were those serotypes included in the 7-valent conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F), and the PPV serotypes included 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23 F, and 33F.

**Statistical analysis.** We determined rates of IPD for the periods 1995–1999 (pre-PCV introduction) and 2001–2004 (post-PCV introduction). Because 2000 was a transitional year corresponding with PCV introduction, it was not included in
the analyses. To calculate the rates of IPD among individuals with SCD who lived in the surveillance counties and who were enrolled in TennCare, we divided the number of cases of IPD by the number of person-years in that time period. Rates were expressed as cases per 100,000 person-years.

Because of the small numbers of IPD cases per year, we could not assess secular trends for the pre-PCV and post-PCV periods. Therefore, to describe the change in IPD rates between the pre-PCV and post-PCV time periods, we computed rate differences and 95% CIs. Among children with SCD and without IPD who were aged ≥1 but <2 years, we had sufficient numbers to assess secular trends of use of penicillin prophylaxis for the pre-PCV and post-PCV periods, and among those aged ≥2 but <5 years, we assessed the trends of both penicillin and PPV use; we used Poisson regression to assess these trends for both age groups. All statistical tests were 2-sided, and we used Stata software, version 9.0 (Stata), to perform the analyses. The Institutional Review Board of Vanderbilt University (Nashville, TN) approved this study.

RESULTS

SCD Population
Of the 2474 individuals with SCD who were enrolled in TennCare during 1995–2004, 2026 (82%) lived in the counties in which there was active surveillance for IPD. This study cohort contributed 13,687 person-years of follow-up, including 1811 person-years for all children aged <5 years (of which 723 person-years were for children aged <2 years) and 11,876 person-years for persons aged ≥5 years. During the study period, 37 individuals with SCD had IPD (age range, 0.6–44 years). No individuals with SCD had an episode of IPD during the study period. Of the individuals with SCD and IPD, 21 (56%) were aged <5 years, and 54% were male.

Rates of IPD among Individuals with SCD Before and After Introduction of PCV
The incidence rates of IPD among individuals with SCD decreased after the introduction of PCV (figure 1). In a comparison of the pre-PCV period (1995–1999) with the post-PCV period (2001–2004), the IPD rate decreased by 90.8% among children aged <2 years (from 3630 to 335 cases per 100,000 person-years; P < .001) and by 93.4% among children aged ≥5 years (from 2044 to 335 cases per 100,000 person-years; P < .001) (table 1). These reductions corresponded to rate differences of −3295 cases per 100,000 person-years for children aged <2 years (95% CI, 1216–5375 cases per 100,000 person-years) and −1910 cases per 100,000 person-years for children aged ≥5 years (95% CI, 929–2889 cases per 100,000 person-years) (table 1). There was a nonsignificant 38% reduction in the rate of IPD among individuals with SCD who were aged ≥5 years (from 161 to 99 cases per 100,000 person-years; P = .36) (table 1).

Serotypes and Resistance Patterns
Serotyping was available for 12 of 37 isolates, with 67% of the serotypes represented in the PCV and 83% represented in the PPV. Three of the 6 cases of IPD that occurred during the post-PCV era (2001–2004) involved serotypes 12F, 35B, and 15C—serotypes not included in PCV. Two (5.4%) of the 37 patients with SCD and IPD died in 2000; one child was aged 14.7 years, and the other was aged 1.4 years. Both children were infected with IPD serotype 23F—a serotype included in PCV. Twenty-three isolates were tested for penicillin susceptibility, and 6 (26%) of them were resistant to penicillin, including 4 resistant isolates in the pre-PCV era, 1 in 2000, and 2 in the post-PCV era.

Penicillin Prophylaxis
Prescription data for the year prior to the episode of IPD were available for 20 of 21 children with IPD who were aged <5 years. For the 4 children aged <1 year, the proportion of time with a current penicillin prescription prior to their IPD episode ranged from 0% to 57%, but 2 children had a current penicillin prescription at the time of their diagnosis. Of the 16 children aged ≥1 year at the time of their IPD diagnosis, 2 children had no penicillin prescriptions during the prior year, 9 had <270 days of supply, and 5 had ≥270 days of supply. At the time of diagnosis of IPD, 8 (50%) of 16 children had a current penicillin prescription filled.
Comparison of pre- and post-PCV periods

Prior to the introduction of PCV, children aged <2 years were not eligible to receive PPV. The 3 children aged <2 years who developed IPD during the period 2000–2001 had no record of receipt of any doses of PCV prior to their IPD episode. No children with SCD who were aged <2 years were identified as having IPD after 2001. The remaining 21 individuals aged ≥2 years at the time of their diagnosis of IPD had no record of receipt of PPV or PCV prior to their episode.

Individuals with SCD and without IPD. Evidence of pneumococcal vaccination during the prior year for children with SCD but without IPD was obtained from TennCare claims. Prior to the introduction of PCV, children aged <2 years were not eligible to receive PPV, and a mean of 11% of children aged ≥2 but <5 years had a claim for receipt of PPV, which was recorded during the prior year in the pre-PCV era. In the post-PCV era, a mean of 13% of children aged ≥2 but <5 years had a claim for receipt of PPV, and a mean of 19% had ≥1 claim for receipt of PCV. No secular trend of PPV use in children aged ≥2 but <5 years was observed. In the post-PCV era, a mean of 69% of children aged <2 years had evidence of receipt of ≥1 dose of PCV during the prior year.

Vaccine Coverage

Individuals with SCD and IPD. In the pre-PCV era (1995–1999), 13 children with IPD and SCD were aged <2 years and, thus, not eligible to receive PPV. The 3 children aged <2 years who developed IPD during the period 2000–2001 had no record of receipt of any doses of PCV prior to their IPD episode. No children with SCD who were aged <2 years were identified as having IPD after 2001. The remaining 21 individuals aged ≥2 years at the time of their diagnosis of IPD had no record of receipt of PPV or PCV prior to their episode.

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DISCUSSION

Our study clearly demonstrates that the incidence of IPD in individuals with SCD dramatically decreased after the introduction of PCV into the routine childhood immunization schedule. Among children with SCD who were aged <5 years, the incidence of IPD decreased by 93%. This reduction in IPD rates was consistent with earlier reports of decreases in IPD rates among the general population after the introduction of PCV [22, 24, 32] but was greater in magnitude. To our knowledge, this is the first report that specifically evaluated rates of IPD among patients with SCD after the introduction of PCV.

Individuals with SCD have a higher incidence of IPD than age- and race-matched children without SCD [33, 34]. Prior to the availability of pneumococcal capsular polysaccharide vaccines or routine penicillin prophylaxis, reported rates of IPD among individuals with SCD ranged from 4600 to 27,300 cases per 100,000 person-years, with the highest rates among children aged <2 years [4, 35–37]. In the era of PPV, prior to the licensure of PCV and prior to penicillin prophylaxis, the rate of IPD among children with SCD who were aged <5 years was 4400 cases per 100,000 patient-years [38]. In our study, as well, children aged <2 years had the highest rate of IPD.

A landmark, multicenter, clinical study published in 1986 revealed that penicillin prophylaxis produced a remarkable 84% reduction in the rate of IPD among children with SCD [5]. In our cohort, however, only 25%–30.5% of the children with SCD who were aged <5 years had their penicillin prescriptions filled for ≥270 days of a 1-year period. Similarly, in an earlier study about penicillin prophylaxis for children with SCD who were aged <4 years and who were enrolled in either the Tennessee or Washington State Medicaid programs during the period 1995–1999 [26], 10.3% of the patients received no prophylaxis, and only 21.5% received prophylaxis for >270 days. Thus, because ongoing penicillin prophylaxis is difficult to sustain [11, 39, 40], the effectiveness of this approach in practice appears to be less than that demonstrated in the randomized, clinical trial [5].

A recent study of children with SCD who were aged <5 years reported an IPD rate of 2400 cases per 100,000 person-years during the period 1992–1998, when both PPV and penicillin vaccine were recommended [41]. This rate is nearly identical to the IPD rate from the pre-PCV era among children aged <5 years in our cohort (2044 cases per 100,000 person-years), yet the rate is 10–100 times higher than that among individuals without SCD [39]. In the post-PCV era in our study, the rate of IPD among children with SCD who were aged <5 years decreased to 132 cases per 100,000 person-years, only 6.5 times

### Table 1. Rates of invasive pneumococcal disease (IPD) among individuals with sickle cell disease (SCD).

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>No. of patients with IPD and SCD</th>
<th>Rates of IPD, cases per 100,000 person-years</th>
<th>Comparison of pre- and post-PCV periods</th>
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<td>Pre-PCV era</td>
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<td>&lt;5 years</td>
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<td>161</td>
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**NOTE.** The pre-pneumococcal conjugate vaccine (PCV) era was defined as the period 1995–1999, the transition year was 2000, and the post-PCV era was defined as the period 2001–2004.
higher than national IPD rates for white children (20.5 cases per 100,000 person-years in 2002) and only 4 times higher than the rates for black children (33 cases per 100,000 person-years in 2002) [21]. In our cohort, the proportion of children with penicillin prescriptions for ≥270 days per year did not significantly increase after the introduction of the PCV. In addition, PPV use did not increase significantly among children aged ≥2 but <5 years. These data and parallel trends for children without SCD suggest that PCV was responsible for the decrease in IPD rates, especially in children aged <2 years who did not receive PPV. Moreover, these results further support the value of PCV as a highly effective prevention strategy against IPD in children with SCD.

Historically, IPD associated with SCD has been associated with substantial mortality, especially among young children. Reported IPD-related case-fatality rates among individuals with SCD have been as high as 35% [5]. In our cohort, the mortality rate was 5.4%, and no deaths occurred in the post-PCV era. Many factors, such as the introduction of PPV, penicillin prophylaxis, newborn screening, and improved medical care with an emphasis on emergent treatment of fever in individuals with SCD, likely contributed to this reduction. The fact that no fatalities occurred in the post-PCV period in our cohort, however, suggests that PCV may also contribute to a reduction in mortality among individuals with SCD [42].

During a prelicensure clinical trial, the authors of this study gave 4 doses of PCV to children with SCD at ages 2, 4, 6, and 12 months. The immune responses were similar to those experienced by children without SCD [4]. Children in this trial also received the 23-valent polysaccharide vaccine at 24 months. A single dose of PPV resulted in dramatic increases in the antibody concentrations of all serotypes in PCV, supporting the evidence of memory response and providing encouragement that this would be an effective vaccine in young children. Our study also supports PCV as an effective prevention strategy against IPD in children with SCD.

Our study has several limitations. First, the overall number of individuals with SCD and IPD was small and consisted of patients who lived in surveillance counties in Tennessee and who were enrolled in the Tennessee Medicaid program. The pre-PCV era IPD rates in individuals with SCD in this study, however, were nearly identical to those reported from other locations, suggesting that these results are generalizable to others with SCD in the United States. Second, vaccination records, especially from the period prior to the introduction of PCV, may not have captured receipt of all pneumococcal vaccines by persons enrolled in TennCare. Published surveys indicate receipt of ≥3 doses of PCV by 73% of children aged 19–35 months nationally and by 71% (72% of white children and 67% of black children) of children in Tennessee in 2004 [43]. The 69% vaccination rate in our cohort in the post-PCV period is nearly identical to that reported for black children in Tennessee. Although other factors could have contributed to the decrease in the rate of IPD among children with SCD, the lack of secular trends for penicillin prophylaxis and PPV, the strong temporal relationship with the introduction of PCV, and the similar response among children without SCD strongly suggest that the decrease was an effect of PCV. The relative contributions of direct and herd immunity could not be determined from this study.

In summary, this study clearly demonstrates a significant reduction in the rate of IPD after the introduction of PCV for individuals with SCD. With the universal administration of PCV to all children, both with and without SCD, it is expected that the rates of IPD will continue to decrease among all children. However, ongoing monitoring of these rates and serotyping of all invasive pneumococcal isolates must remain an important priority to monitor whether serotype replacement will occur under continued vaccine pressure. Despite this caution, our data indicate that PCV is effective for reducing the rate of IPD, especially among vulnerable populations.

Acknowledgments

We thank Brenda G. Barnes and all of the members of the Tennessee Active Bacterial Core surveillance network. We are indebted to the Tennessee Bureau of Medicaid of the Department of Finance and Administration and the Tennessee Department of Health, which provided the data.

Financial support. Association of Prevention Teaching and Research/ Centers for Disease Control and Prevention (CDC) cooperative agreement (TS-0825), CDC Emerging Infections Program cooperative agreement (U50/CCU416123), National Institutes of Health Vanderbilt Mentored Clinical Research Scholar Program (K12 RR-017697 to N.B.H.), and National Center for Research Resources, National Institutes of Health (M01 RR-00095).

Potential conflicts of interest. N.B.H. receives grant support from MedImmune and Sanofi-Pasteur, M.R.G. receives grant support from MedImmune and Pfizer and consulting fees from MedImmune and Merck, T.R.T. receives grant support from Nabi and speaking fees from GlaxoSmithKline, and P.G.A. receives grant support from Pfizer. All other authors: no conflicts.

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