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Invasive Pneumococcal Disease Among Children With and Without Sickle Cell Disease in the United States, 1998 to 2009

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Abstract

Background—Children with sickle cell disease (SCD) are at increased risk of illness and death from invasive pneumococcal disease (IPD). The introduction in 2000 of the 7-valent pneumococcal conjugate vaccine (PCV7) and penicillin prophylaxis for children with SCD has greatly reduced the incidence of IPD in this population. However, a recent report suggested an increase in cases of IPD in children with SCD.

Methods—Using data from Active Bacterial Core surveillance (ABCs), we analyzed trends in hospitalizations, mortality, and serotype among children with SCD compared with other children. We used neonatal screening data to estimate SCD population denominators for each ABCs site.

Results—From 1998–2009, 3,069 cases of IPD occurred among African-American children less than 18 years of age in the ABCs catchment area. Of these, 127 (4.1%) had SCD identified by medical chart review and 185 (6.0%) had one or more IPD risk factors, excluding SCD. Rates of IPD among children with SCD declined by 53% (1,118 versus 530 per 100,000) while the overall rates among African-American children declined by 74% (54 to 14 per 100,000). For all time periods, children with SCD and IPD were more likely to be hospitalized (84%–92% versus 31%–56%) and more likely to die (6%–17% versus 1%–2%) than children with no risk factors.

Conclusions—While the rate of IPD in children with SCD has dropped dramatically since PCV7 introduction, the rate of IPD in children with SCD remains higher than that of the general population of African-American children, pointing to the need for more effective prevention efforts to prevent IPD in children with SCD.

Introduction

Children with sickle cell disease (SCD) have higher rates of invasive bacterial infections, including bacteremia, pneumonia, and meningitis (1, 2). In particular, since children with

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SCD often become functionally asplenic, they are at increased risk of infections caused by encapsulated bacteria such as *Streptococcus pneumoniae* (3). Before licensure of the seven-valent pneumococcal conjugate vaccine (PCV7) in the United States in 2000, children with SCD were recommended to receive penicillin prophylaxis until 5 years of age and to receive one dose of the 23-valent pneumococcal polysaccharide vaccine (PPV23) at 2 years of age (4, 5). Despite these interventions, rates of invasive pneumococcal disease (IPD) in children with SCD remained significantly higher than in healthy children (4, 6, 7) and pneumococcal infection was a leading infectious cause of death in children with SCD (8).

In pre-licensure trials of PCV7, the vaccine was found, unlike PPV23, to be immunogenic in children <2 years old (6, 9). Therefore, in addition to receiving PCV7 as part of the routine schedule at 2, 4, 6, and 12–15 months of age, PCV7 was specifically recommended for children 24–59 months of age with SCD (7). In the 11 years since PCV7's introduction, cases of IPD caused by the seven serotypes included in the vaccine have all but disappeared in the general pediatric population as well as in children with SCD (2, 10, 11). However, a recent report suggests a possible increase in the rate of IPD in children with SCD, particularly in the number of cases caused by non-PCV7 serotypes(12). At the same time, rates of non-PCV7 serotypes, especially types 19A and 7F, have increased significantly in healthy children (10, 13, 14). We sought to estimate the rate of IPD in children with SCD before and after the introduction of PCV7 and to compare cases of IPD among children with and without SCD.

Materials and Methods

Cases of IPD in African-American children under 18 years of age were identified through the Active Bacterial Core surveillance (ABCs) system with *Streptococcus pneumoniae* isolated from a normally sterile site (e.g., blood, cerebrospinal fluid, etc.) from 1998–2009. ABCs is an active population- and laboratory-based surveillance system which is a collaborative effort between the Centers for Disease Control and Prevention (CDC), state and local health departments, and academic institutions(15). As of 2009, ABCs included 1.4 million African-American children less than 18 years of age (16). ABCs collects demographic, hospitalization, and outcome information, and relevant underlying conditions (including SCD) for all cases via medical chart review. Additionally, all available isolates are tested for antimicrobial resistance by the Clinical Laboratory and Standards Institute broth microdilution procedure and serotype using latex agglutination and confirmation by Quellung reaction (17). PCV7 serotypes include the seven serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F), as well as serotype 6A, which is cross-reactive with the serotype 6B antigen in PCV7 and thus declined after PCV7 introduction(18). Therefore, despite the inclusion of serotype 6A only in the newer version of the conjugate vaccine introduced in 2010 (PCV13), we considered serotype 6A to be a "PCV7" serotype. The other five serotypes unique to PCV13 (1, 3, 5, 7F, 19A) were considered PCV5 serotypes.

Cases were grouped into three time periods: 1) Pre-PCV7 (1998–99); 2) Early-PCV7 (2000–2004); and 3) Late-PCV7 (2005–2009). These time periods were chosen based on availability of data and to allow analysis of key demographics, risk factors, and outcomes both immediately after PCV7's introduction and in the years immediately before PCV13

was introduced (a potential baseline for future analyses). Analyses compared children with SCD (regardless of the presence of other underlying conditions), children without SCD who had one or more other risk factor for IPD (e.g., diabetes, HIV/AIDS, congenital heart disease, cancer, etc.), and children without these risk factors. Comparisons were made using chi-squared, Fisher's exact, and t-tests and differences were considered statistically significant at $p < .05$. Analyses were conducted using SAS, version 9.2 (SAS Institute Inc., Cary, NC).

Prevalence of SCD within the ABCs catchment area was estimated using a method similar to that of Hassel(19) (see Figure, Supplemental Digital Content 1). Briefly, incidence of SCD in African-American newborns in each of the ABCs states was estimated by dividing the total number of African-American newborn births(20) in each state with genotypes SS, SC, and Sβ Thalassemia, as reported in the National Newborn Screening Information System(21) or by the state's department of health via personal communication, in 2005, 2006, and 2007 by the total number of African-American newborn births(20) in each state over those year. When state-specific and/or race-specific data for newborns with SCD were not available, a national incidence rate was used. SCD newborn incidence estimates were then applied to birth cohorts(20) that would be under 18 during the relevant year of ABCs surveillance (e.g. 1981–1998 for surveillance year 1998); this calculation provided an estimate of the number of newborns with SCD in each birth cohort. The total number of SCD patients during each ABCs calendar year was estimated by adjusting each birth cohort population by estimated mortality rates published by Quinn et al(22) and summing over all birth cohorts included in that surveillance year. The pediatric prevalence of SCD in the ABCs states during each year was estimated by dividing the estimated number of SCD patients by the total number of African-American children less than 18 at that year (23). These prevalence estimates were then applied to the ABCs catchment area for that state in order to estimate the number of SCD patients covered in the catchment area. Rates of IPD in African-American children with SCD were estimated by dividing the number of cases of IPD in children with SCD reported to ABCs in a given time period by the estimated number of children with SCD in the ABCs catchment area during that time period.

Results

A total of 3,069 cases of IPD occurred in African-American children less than 18 years of age in the catchment area during 1998–2009 (Table 1). Of these, 127 (4.1%) had SCD identified during their medical chart review. An additional 185 (6.0%) had one or more IPD risk factors other than SCD, such as leukemia, immunosuppressive therapy, or diabetes.

Demographics

Children with SCD and those with other risk factors were significantly older at the time of culture than children without IPD risk factors (median range across time periods: 45–63 months for SCD; 42–76 months for children with other risk factors; 15–20 months for children without risk factors), consistent with the observation that rates of IPD in the general population decline markedly after age 5 years(10). There was a significant ($p<0.0001$) upward trend in age at the time of culture from 1998 to 2009 among children without risk

factors, but no significant trend in either children with SCD or children with other underlying conditions.

Clinical Presentation and Outcomes

Children with SCD were significantly more likely than either of the other groups to have pneumococcal meningitis in the early-PCV7 period; however, this outcome did not differ significantly in the other time periods. Children with SCD and those with other risk factors were significantly more likely to be hospitalized during their IPD episode in all time periods compared with children without IPD risk factors, and children with SCD were more likely to die from IPD than children without SCD. However, children with SCD had shorter average length of hospitalizations than children without SCD after vaccine introduction.

Trends in IPD

Rates of IPD among children with SCD less than 18 years of age declined by 53% (Figure 1), from an average of 1,118 cases per 100,000 children (CI: 814/100,000–1,1537/100,000) before PCV7 introduction to an average of 530 cases per 100,000 children (CI: 424/100,000–664/100,000) after vaccine introduction. The rate of IPD among children with SCD has remained relatively stable since vaccine introduction, with rates ranging from a low of 290 cases per 100,000 children in 2004 to a high of 510 cases per 100,000 children in 2006. Rates of IPD among children with SCD <18 year of age remain higher than the overall rate among African-American children. The incidence rate ratio comparing the rate of IPD among children with SCD to the overall rate among African-American children was 5 (4–7) in the pre-PCV7 period, 29 (23–37) in the early-PCV7 period, and 44 (35–56) in the late-PCV7 period. The decline in incidence of IPD among children with SCD post vaccine introduction but remaining disparity compared to children without SCD was observed in children younger and older than 5 years of age (Table 2).

Significant declines in PCV7-type IPD, as well as increases in PCV5-type disease were seen amongst all three groups (Table 3). PCV5 serotypes are those primarily responsible for the phenomenon known as ‘serotype replacement’ in the general population(24). During the pre-PCV7 period, the distribution of serotypes causing disease in children with and without SCD was similar, with the vast majority of cases caused by one of the PCV7 serotypes. In the late-PCV7 period, however, children with SCD had fewer cases of IPD caused by the PCV5 types (SCD 24%, other risk factors 41%, no risk factors 57%). In contrast, 45% of IPD in children with SCD was caused by one of four serotypes: 6C (19% of cases), 15A (12% of cases), and 15B/C (14% of cases). These same four serotypes accounted for only 11% of cases among children with other underlying conditions and only 9% of cases among children without these conditions.

In the pre-PCV7 period, IPD isolates obtained from children with SCD were significantly more likely than the other two groups to be nonsusceptible to one or more classes of antibiotics (77% of isolates in children with SCD vs. 44% in the other-risk-factors group and 45% in the no-risk-factors group). Among SCD cases, 77% were nonsusceptible in the pre-PCV7 period compared to 45% in the late-PCV7 period.

Discussion

Our estimates indicate the rate of IPD in children with SCD has dropped 53% since vaccine introduction. This trend has been previously reported(2, 4, 11, 25) and explains the observations of reduced mortality(8) and hospitalizations(11) due to IPD in children with SCD that have also been previously reported. The results of this study support the fact that the introduction of PCV7 has effectively reduced the burden of IPD in children with SCD.

While the rate of IPD in children with SCD has declined significantly since PCV7 introduction, we found the rate is still dramatically higher than the overall rate in African-American children. Our analyses also indicate children with SCD still have significantly higher mortality due to IPD than children with other underlying conditions and healthy children, implying children with SCD are still disproportionately affected by IPD. This is likely due to the inherently increased susceptibility to disease among children with SCD(26).

Because children with SCD are at increased risk for infection, the American Academy of Pediatrics (AAP) recommends all children with sickle cell disease receive penicillin prophylaxis at least until their fifth birthday(27). Furthermore, the AAP recommends timely administration of the pneumococcal conjugate and 23-valent pneumococcal polysaccharide vaccines (PPV23), defined as administration of the conjugate vaccine at 2, 4, 6 and 12–15 months of age and administration of the 23-valent vaccine in high-risk children at the earliest opportunity to expand serotype coverage(28). These prevention strategies have served to drastically reduce the rate of IPD in children with SCD, as shown by this and other analyses (11). However, the increased incidence rate of IPD among children with SCD compared with the overall population of African-American children remains, pointing to a need for further examination of prevention strategies. Importantly, the Advisory Committee on Immunization Practices recently (29) voted to recommend routine administration of one dose of PCV13 to children 6 through 18 years of age with immunocompromising conditions, including SCD, who have not previously received PCV13, regardless of whether they have previously received PCV7or PPV23. Future evaluations of the impact of this new recommendation are needed. Conjugate vaccines with broader serotype coverage or vaccines that target a broader diversity of pneumococci are urgently needed.

McCavit et al describe a trend of increasing mean age of onset of IPD in children with SCD in a large sample of hospitalized pediatric patients before and after PCV7 introduction(11). Although not statistically significant, we also report this trend. In their report, McCavit et al suggest reconsideration of cessation of penicillin prophylaxis at age 5 and immunization schedules for children with SCD. Our results indicate more research in this area is warranted.

In children with SCD we found a significant increase over time in IPD caused by serotypes unique to PCV13, a phenomenon known as serotype replacement. A similar increase has been seen in healthy children since the introduction of PCV7. Of concern, while serotypes accounting for 60% of IPD among children with no risk factors in the late-PCV7 era are covered by PCV13, only 26% of IPD in children with SCD is represented by PCV13 serotypes. The remaining disease (74%) in that time period was due to serotypes not

included in PCV13, leaving children with SCD more likely to be unprotected by the conjugate vaccine. Of note, the most common non-PCV13 serotype causing IPD in children with SCD in the late-PCV7 era was serotype 6C, which may be cross-reactive with the serotype 6A antigen in PCV13 (30). If PCV13 does provide cross-protection against serotype 6C, an additional 19% of IPD in children with SCD may be preventable.

Our study has certain limitations. Because the number of children living with SCD was not known, we estimated rates of SCD in the ABCs catchment area to define the SCD population. These estimates were derived from data reported to the National Newborn Screening Information System. Reporting of these data has been shown to be variable for some states. These estimates also do not account for immigration and emigration into and out of the catchment area. However, because we applied the same method to all ABCs sites and all years, any under- or over-estimation of the rate of SCD would not affect the overall trends observed. Also, we did not estimate PCV7 or PPV23 vaccine coverage in children with SCD. Thus, we were unable to determine if the disparity in rates of IPD among African-American children with and without SCD is due to differences in vaccine coverage and/or vaccine effectiveness. We were also unable to determine if the disparity in rates of IPD among African-American children with and without SCD is due to ascertainment differences. It has been reported that total blood cultures drawn in children with no IPD risk factors has decreased since vaccine introduction(31). However, treatment guidelines(32) published by the National Heart, Lung, and Blood Institute recommend febrile patients with SCD be evaluated rapidly and intensively for possible *Streptococcus pneumoniae* infection, making it more likely cases of IPD would be detected in children with SCD compared to children without SCD.

Conclusion

This report demonstrates the effectiveness of the PCV7 vaccine to dramatically reduce the rate of IPD in children with SCD. However, our analyses show children with SCD are still at much greater risk of IPD infection than healthy children and are more likely to die as a result of infection. This indicates better prevention strategies are warranted to reduce the overall morbidity and mortality due to IPD in children with SCD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Abbreviations

AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core surveillance
CDC	Centers for Disease Control and Prevention
IPD	invasive pneumococcal disease
PCV7	7-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PPV23	23-valent pneumococcal polysaccharide vaccine
SCD	sickle cell disease
PCV5	5-valent serotypes unique to PCV13

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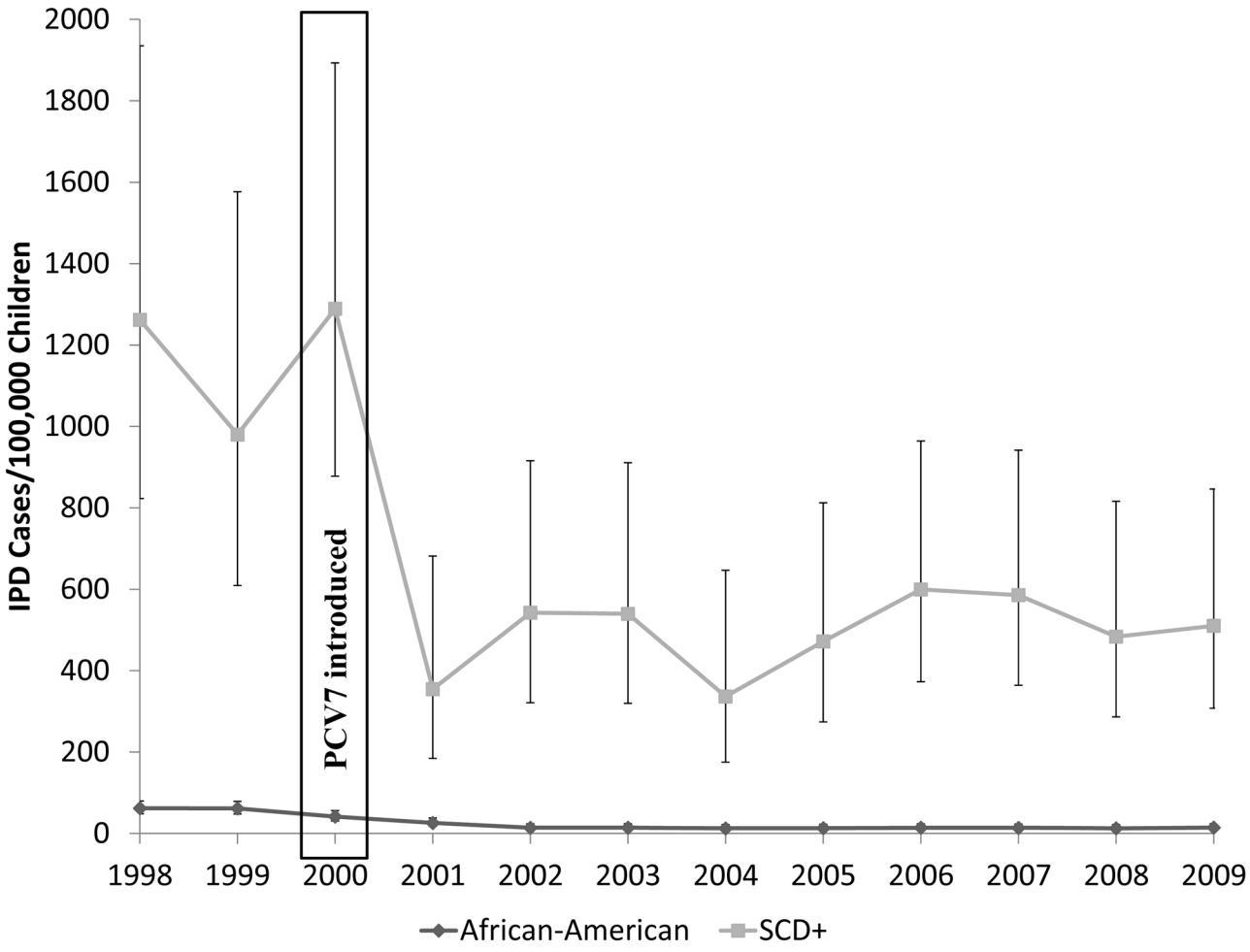

Figure 1.

Rates of IPD in children under 18 with SCD compared to overall rate of IPD in African-American children under 18 in ABCs (1998–2009)

Table 1

Characteristics of African-American children younger than 18 years with IPD by time period, 1998–2009

	Pre-PCV7 (1998–1999) number (%)			Early-PCV7 (2000–2004) number (%)			Late-PCV7 (2005–2009) number (%)		
	SCD+	**Other IPD risk factors**	**No IPD risk factors**	**SCD+**	**Other IPD risk factors**	**No IPD risk factors**	**SCD+**	**Other IPD risk factors**	**No IPD risk factors**
Total cases	31	29	914	47	91	1083	49	65	760
Average cases/year	15.5	5.8	182.8	9.4	18.2	216.6	9.8	13	152
Total ABCs population <18 years		8,476,777			29,430,937			35,573,664	
Average population/year		4,238,389			5,886,187			7,114,733	
Age in months, median (IQR)	**45.0 (17–58)**	**76.0 (33–116)**	**15.0 (9–23)**	**63.0 (18–106)**	**73.0 (31–137)**	**17.0 (10–32)**	**53.0 (23–76)**	**42.0 (22–112)**	**20.0 (11–46)**
Clinical									
Meningitis	0	3 (10)	36 (4)	**8 (17)**	**5 (5)**	**80 (7)**	2 (4)	3(5)	49 (6)
Bacteremic pneumonia	8 (26)	7 (24)	161 (18)	**15 (32)**	**41 (45)**	**346 (32)**	14 (29)	22 (34)	307 (40)
Other	23 (74)	19 (66)	717 (78)	**24 (51)**	**45 (49)**	**657 (61)**	33 (67)	40 (62)	404 (53)
Hospitalized [a]	**26 (84)**	**19 (66)**	**287 (31)**	**39 (83)**	**66 (73)**	**432 (40)**	**45 (92)**	**56 (86)**	**424 (56)**
Length of hospitalization in days, median	**5**	**6**	**3**	3	4	4	**4**	**7**	**5**
Died	2 (6)	0	7 (1)	**8 (17)**	**5 (5)**	**22 (2)**	**4 (8)**	**1 (2)**	**7 (1)**

[a] Some race, ethnicity, and hospitalization data were missing

Bold indicates statistically significant differences (p<0.05) between children with SCD, children without SCD but with other risk factors for IPD, and children with no risk factors for IPD within a given time period.

Table 2

Incidence rates of IPD among children with SCD compared to children without SCD by age group and time period, 1998–2009

	Pre-PCV7 (1998–1999)			Early-PCV7 (2000–2004)			Late-PCV7 (2005–2009)		
	Cases per 100,000 (95% CI)			Cases per 100,000 (95% CI)			Cases per 100,000 (95% CI)		
	SCD+	SCD-	Rate Ratio[a] (95% CI)	SCD+	SCD-	Rate Ratio[a] (95% CI)	SCD+	SCD-	Rate Ratio[a] (95% CI)
0–4 Years	2,266 (1,519–3,381)	825 (799–853)	3 (2–4)	587 (393–875)	58 (54–61)	10 (7–15)	537 (368–782)	33 (30–35)	16 (11–24)
5–17 Years	299 (142–627)	7 (6–9)	42 (19–90)	287 (193–429)	5 (4–5)	63 (41–97)	224 (146–343)	3 (3–4)	72 (45–113)

[a]Comparison of rate of IPD in children with SCD compared to rate of IPD in children without SCD

Table 3

Characteristics of serotypes identified in African-American children younger than 18 years old with IPD by time period, 1998–2009

	Pre-PCV7 (1998–1999) number (%)			Early-PCV7 (2000–2004) number (%)			Late-PCV7 (2005–2009) number (%)		
	SCD+	Other IPD risk factors	No IPD risk factors	SCD+	Other IPD risk factors	No IPD risk factors	SCD+	Other IPD risk factors	No IPD risk factors
Serotype [a b d]									
PCV7	29 (94)	20 (80)	684 (89)	**26 (59)**	**51 (60)**	**627 (66)**	**1 (2)**	**9 (16)**	**25 (4)**
PCV5	0	2 (8)	31 (4)	**4 (9)**	**11 (13)**	**132 (14)**	**10 (24)**	**24 (41)**	**384 (57)**
Non-PCV13 Serotypes	2 (6)	3 (12)	55 (7)	**14 (32)**	**23 (27)**	**186 (20)**	**31 (74)**	**25 (43)**	**263 (39)**
15B/C[c]	0	0	5 (1)	**6 (14)**	**2 (2)**	**38 (4)**	**6 (14)**	**5 (9)**	**34 (5)**
6C[c]	0	0	0	**1 (2)**	**0**	**6 (1)**	**8 (19)**	**0**	**17 (3)**
15A[c]	0	0	1 (0)	**0**	**1 (1)**	**2 (0)**	**5 (12)**	**1 (2)**	**9 (1)**
Resistant to ≥ 1 classes of antibiotics	**24 (77)**	**11 (44)**	**344 (45)**	22 (50)	32 (38)	384 (41)	19 (45)	23 (40)	289 (43)
Resistant to penicillin									
Old breakpoints [d e]	**19 (61)**	**9 (36)**	**245 (32)**	15 (34)	26 (31)	288 (30)	23 (55)	22 (38)	270 (40)
New breakpoints [d e]	3 (10)	4 (16)	67 (9)	4 (9)	9 (11)	111 (12)	5 (12)	5 (9)	115 (17)

[a] Some serotype data were missing.

[b] PCV7 types include all serotypes in the 7-valent pneumococcal conjugate vaccine, plus serotype 6A due to cross-reactivity with vaccine type 6B. PCV5 types include the remaining serotypes in the 13-valent pneumococcal conjugate vaccine.

[c] Top three non-vaccine serotypes among children with SCD during the study period.

[d] Denominator includes only those cases with an isolate available for serotyping.

[e] The old/oral/meningitis breakpoints classify isolates as penicillin nonsusceptible at a minimum inhibitory concentration (MIC) ≥ 0.12 μg/mL. The new parenteral breakpoints classify isolates as penicillin nonsusceptible at an MIC ≥ 4 μg/mL for nonmeningitis disease and ≥ 0.12 μg/mL for meningitis 17.

Bold indicates statistically significant differences ($p<0.05$) between children with SCD, children without SCD but with other risk factors for IPD, and children with no risk factors for IPD within a given time period.