Racial and Regional Differences in Rates of Invasive Pneumococcal Disease

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abstract

BACKGROUND AND OBJECTIVES: Invasive pneumococcal disease (IPD) remains an important cause of illness in US children. We assessed the impact of introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) on pediatric IPD rates, as well as changes in racial and regional differences in IPD, in Tennessee.

METHODS: Data from active laboratory and population-based surveillance of IPD were used to compare IPD rates in the early-PCV7 (2001–2004), late-PCV7 (2005–2009), and post-PCV13 (2011–2012) eras. IPD rates were further stratified according to age, race, and region (east and middle-west TN).

RESULTS: Among children aged <2 years, IPD rates declined by 70% from 67 to 19 per 100 000 person-years in the early-PCV7 era and post-PCV13 era, respectively. Similar decreasing trends in IPD rates were observed in older children aged 2 to 4 years and 5 to 17 years. In the late-PCV7 era, IPD rates in children aged <2 years were higher in black children compared with white children (70 vs 43 per 100 000 person-years); however, these racial differences in IPD rates were no longer significant after PCV13 introduction. Before PCV13, IPD rates in children aged <2 years were also higher in east Tennessee compared with middle-west Tennessee (91 vs 45 per 100 000 person-years), but these differences were no longer significant in the post-PCV13 era.

CONCLUSIONS: PCV13 introduction led to substantial declines in childhood IPD rates and was associated with reduced regional and racial differences in IPD rates in Tennessee.

WHAT'S KNOWN ON THIS SUBJECT: Previous studies have shown racial differences in invasive pneumococcal disease (IPD) rates. Recent studies demonstrated a national decline in IPD rates after 13-valent pneumococcal conjugate vaccine (PCV13) introduction. The impact of PCV13 on racial and regional differences in IPD rates among Tennessee children is unknown.

WHAT THIS STUDY ADDS: After introduction of PCV13, pediatric IPD rates, including disease due to antibiotic-resistant strains, declined substantially. Racial and regional differences in IPD rates were no longer significant. Our study illustrates the impact of PCV13 and the importance of continued IPD surveillance.

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Dr de St Maurice conceptualized the study, assisted with data analysis, and drafted the initial manuscript; Dr Grijalva assisted with the data analysis and study design, and critically reviewed and revised the manuscript; Dr Fonnesbeck assisted with statistical support and reviewed the manuscript; Dr Schaffner led the research team that collected the initial data, assisted with the study design, and reviewed and revised the manuscript; and Dr Halasa assisted with study design and data analysis, and critically reviewed the manuscript. All authors approved the final manuscript as submitted.

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Streptococcus pneumoniae is a leading cause of bacterial meningitis, bacteremia, and community-acquired pneumonia in US children.[1,2] After introduction of the heptavalent pneumococcal conjugate vaccine (PCV7) in 2000, the incidence of pneumococcal diseases declined significantly.[1–4] While overall invasive pneumococcal disease (IPD) rates declined after the introduction of PCV7,[5–7] rates of residual IPD caused by non-PCV7 serotypes (particularly 19A) increased.[3,8] In February 2010, a 13-valent pneumococcal conjugate vaccine (PCV13) replaced PCV7 in the US routine infant vaccination schedule.[9] PCV13 contains the same PCV7 serotypes plus 6 additional serotypes, including 19A.

The Centers for Disease Control and Prevention (CDC) Active Bacterial Core surveillance (ABCs) network monitors IPD by using population-based observation across 10 US sites, including Tennessee.[10] Tennessee is the third most populous surveillance site in the network and encompasses a diverse population with distinct surveillance regions across the state. In addition, Tennessee experienced a sustained increase in IPD rates caused by non-PCV7 serotypes from 2004 to 2008 among subjects aged ≥15 years, suggesting intense serotype replacement after the introduction of PCV7.[11] By 2009, Tennessee had the highest overall IPD rates and the highest rate of IPD due to non-PCV7 serotypes among all ABCs sites.[12]

Before PCV7, IPD rates were higher among black children than among white children. Although these racial disparities decreased in the early years after PCV7 introduction,[13,14] residual disparities persisted during the PCV7 years because serotype replacement by non-PCV7 serotypes was greater among black subjects than among white subjects.[15]

Although several studies have shown a decrease in IPD in the United States after the introduction of PCV13, the impact of PCV13 on racial disparities is unknown.[16–19]

Although regional differences in IPD were reported before the introduction of pneumococcal conjugate vaccines, it is unclear if those differences in IPD rates remain. Specifically, differences between east and middle-west Tennessee have been previously described for IPD caused by antibiotic-resistant strains; in addition, previous regional differences in influenza vaccine use, antibiotic-prescribing patterns, respiratory syncytial virus circulation, and medical utilization have been documented.[20–24] Interestingly, the demographic composition of the pediatric population in east and middle-west Tennessee is different. The pediatric population in the eastern section is mostly white (82%), whereas the population is more diverse in the middle-west section, with black children comprising ∼37% of the pediatric population.[25]

The goal of the present study was to determine the effect of PCV13 introduction on IPD rates, including disease due to antibiotic-resistant strains, and to examine racial and regional differences in IPD rates in Tennessee children before and after PCV13 introduction.

METHODS

Study Population

During the study period 2001 to 2012, eleven counties in Tennessee were under continuous active laboratory and population-based surveillance in the ABCs network.[26] The combined population under surveillance represented 53% of the state's pediatric population in 2012. Tennessee's pediatric population under surveillance was 62% white and 31% black compared with the state's pediatric population, which was 74% white and 20% black.[25]

Based on geography, Tennessee counties were classified into 2 regions, east (Knox and Hamilton) and middle-west (Cheatham, Davidson, Dickson, Robertson, Rutherford, Shelby, Sumner, Williamson, and Wilson). The pediatric population under surveillance in east Tennessee consisted of 171 782 children, 12% of the state's total pediatric population (76% white, 17% black). In middle-west Tennessee, the surveillance population encompassed 789 852 children, 41% of the state's total pediatric population (59% white, 34% black).[25]

IPD Case Definition

IPD surveillance is conducted through a standardized process to identify laboratory-confirmed IPD cases at all participating sites.[26] IPD cases were defined as the isolation of *S pneumoniae* from a normally sterile body site (eg, blood, cerebrospinal fluid, joint, pleural or pericardial fluid) from a resident of a surveillance county. Trained surveillance officers systematically extracted clinical and laboratory data from the medical records of each case. Clinical syndromes, including isolated bacteremia, meningitis, and bacteremic pneumonia, were assigned based on chart review. The Vanderbilt University institutional review board approved the study.

Serotyping and Antibiotic Susceptibility Testing

Isolates were sent for serotyping to the University of Texas Health Science Center at San Antonio or the CDC laboratory in Atlanta, where the Quellung reaction was performed.[26] Isolates were categorized into the following vaccine serotype groups: PCV7 (4, 6B, 9V, 14, 18C, 19F, and 23F), PCV13 (includes only serotypes

exclusively included in PCV13 but not in PCV7: 1, 3, 5, 6A, 7F, and 19A), or non-PCV (other, including nontypeable serotypes). Antibiotic susceptibility testing was performed at the CDC laboratory by using broth microdilution. Strains were categorized as susceptible or resistant according to the Clinical and Laboratory Standards Institute criteria.[27] For penicillin, a minimum inhibitory concentration ≤2 was used to categorize an isolate as susceptible; this level represents the nonmeningitis breakpoint, and most cases were nonmeningitis cases.[27,28]

Statistical Analyses

IPD rates were calculated by using annual US census data and expressed per 100 000 person-years; they were calculated according to age group (<2, 2–4, and 5–17 years), vaccine serotype (PCV7, PCV13, and non-PCV), race (white and black [other groups <10% were excluded]), and region (east and middle-west). Annual IPD rates were grouped into 3 vaccine eras: early-PCV7 (2001–2004), late-PCV7 (2005–2009), and post-PCV13 (2011–2012). The 2 time periods in the PCV7 era were separated because in the early-PCV7 era, IPD rates decreased rapidly; however, starting in 2005, an increase in non-PCV7 serotypes was noted.[11] Because PCV13 was introduced in 2010, this year was considered a transitional year and was excluded from analyses.

IPD rates were compared by calculating incidence rate ratios (IRRs), and their test-based 95% confidence intervals (CIs) were obtained.[29] We considered that rates were significantly different if the 95% CI of the estimated rate ratio excluded 1. All analyses were conducted in Stata version 13.0 (Stata Corp, College Station, TX).

RESULTS

Patient Characteristics

From 2001 to 2012, a total of 974 cases of pediatric IPD were detected in the Tennessee surveillance areas, with an annual median IPD rate of 17 per 100 000 person-years. The median age of cases was 1.9 years (range: 1 day–17.9 years), with 53% aged <2 years, 24% aged 2 to 4 years, and 23% aged 5 to 17 years. The distribution of co-morbidities was similar among cases in both regions, other than HIV/AIDS and sickle cell, which were present in 1% and 2% of cases in middle-west Tennessee, respectively, and in no cases in east Tennessee. Table 1 presents the racial and clinical syndrome distributions stratified according to region. In east Tennessee, there were more cases detected in the outpatient setting (56%) and more cases of isolated bacteremia (51%) compared with middle-west Tennessee, where only 34% of cases were detected as outpatients and only 37% of cases were due to isolated bacteremia.

Changes in IPD Rates After PCV13 Introduction

Annual IPD rates in Tennessee declined over the study period in all age groups. IPD rates were highest in children aged <2 years throughout the study period compared with the other age groups (Fig 1). Among these children, IPD rates decreased by 72% during the study years. Similarly, overall IPD rates in children aged 2 to 4 years decreased by 60% during the study period. IPD rates in children aged 5 to 17 years remained low throughout the study period, with a median of 3 cases per 100 000 person-years.

Changes in IPD Serotype Distribution According to Vaccine Era

Of the 974 patients with IPD, 821 (84%) had isolates serotyped. Nonserotyped isolates were excluded from further serotype analyses. Both the proportion and rate of IPD due to PCV7 serotypes declined steadily from the early-PCV7 era to the post-PCV13 era (Table 2). In contrast, PCV13 serotypes represented a fraction of IPD in the early-PCV7 era but caused 56% of IPD in the late-PCV7 era. By the post-

TABLE 1 Demographic Characteristics of Cases of Pediatric IPD, Tennessee Surveillance Areas, 2001 through 2012

Characteristic	All (*N* = 974)	Middle-West (*n* = 666)	East (*n* = 308)
Total population under surveillance in 2012	789 852	618 070	171 782
Age, median, y	1.9	2.0	1.7
Male, %	58	59	56
Race, 5			
White	52	44	69
Black	40	47	24
Other	8	9	7
Comorbidity, %			
Sickle cell	1	2	0.3
Asthma	5	6	4
HIV/AIDS	1	2	0
Clinical syndrome, %			
Isolated bacteremia	41	37	51
Meningitis	8	9	6
Bacteremic pneumonia	32	36	22
Other (eg, septic arthritis)	19	18	21
Setting, %			
Inpatient	42	49	28
Outpatient	41	34	56
Unknown	17	17	16

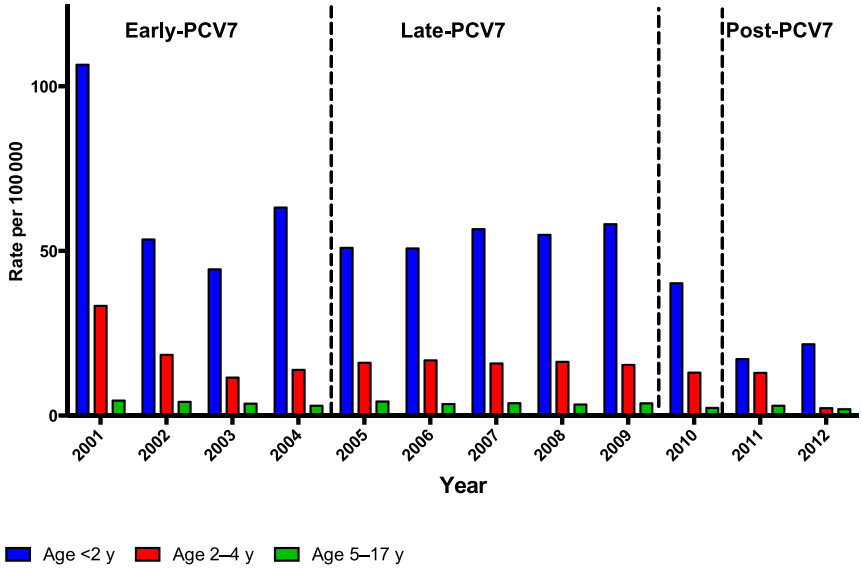

FIGURE 1

Annual IPD rates per 100 000 person-years in Tennessee during the early-PCV7 (2001–2004), late-PCV7 (2005–2009), and post-PCV13 (2011–2012) eras stratified according to age groups: age <2 years, age 2 to 4 years, and age 5 to 17 years.

PCV13 era, IPD rates and the proportion of IPD due to PCV13 serotypes declined.

In the early-PCV7 era, serotype 19A caused only 12% of IPD cases, increasing to 32% in the late-PCV7 era. However, in the post-PCV13 era, serotype 19A caused 15% of IPD. In the post-PCV13 era, no single serotype dominated the residual IPD burden. However, 4 non-PCV serotypes were most prominent: 22F (11%), 33F (10%), 12F (8%), and 38 (7%).

Changes in IPD Caused by Serotype Vaccine Groups Among Children Aged <2 Years

IPD rates due to PCV7 serotypes were highest during the early-PCV7 era in children aged <2 years (Table 2). By the late-PCV7 era, IPD rates due to PCV7 serotypes declined by 95%, with no PCV7 serotypes identified during the post-PCV13 era (Fig 2A). Although rates of IPD due to the 6 additional serotypes in PCV13 increased from the early-PCV7 era to the late-PCV7 era, rates of IPD due to the 6 additional serotypes then decreased by 86% in the post-PCV13 era.

TABLE 2 Overall IPD Rates in Tennessee According to Age Group and Serotype, 2001 to 2012

Age Group	Early-PCV7 Rate per 100 000 Person-Years (% Total Cases)	Late-PCV7 Rate per 100 000 Person-Years (% Total Cases)	Post-PCV13 Rate per 100 000 Person-Years (% Total Cases)
<18 y			
PCV7 serotype	4.2 (36)	0.68 (2)	0.06 (2)
PCV13 serotype	3.4 (30)	10.3 (56)	1.3 (27)
Non-PCV serotype	3.8 (34)	7.7 (42)	3.3 (71)
<2 y			
PCV7 serotype	18 (32)	0.94 (2)	0
PCV13 serotype	17 (30)	25 (56)	3.4 (19)
Non-PCV serotype	22 (38)	19 (42)	14 (81)
2–4 y			
PCV7 serotype	7.5 (45)	0.47 (4)	0
PCV13 serotype	4.4 (26)	6.9 (54)	1.9 (29)
Non-PCV serotype	4.8 (29)	5.5 (43)	4.6 (71)
5–17 y			
PCV7 serotype	1.3 (38)	0.22 (7)	0.09 (4)
PCV13 serotype	1.1 (32)	1.8 (56)	0.79 (36)
Non-PCV serotype	0.99 (30)	1.2 (38)	1.3 (60)

Changes in IPD Caused by Serotype Vaccine Groups Among Children Aged ≥2 Years

Overall IPD rates in children aged 2 to 4 years and those aged 5 to 17 years declined during the study period. Specifically in children 2 to 4 years of age, PCV7 IPD rates decreased by 94% from the early-PCV7 era to the late-PCV7 era, with no documented cases due to PCV7 serotypes in the post-PCV13 era (Fig 2B). In children aged 5 to 17 years, PCV7 IPD rates decreased by 85% from the early-PCV7 era to the late-PCV7 era, with only 1 case of IPD due to a PCV7 serotype in the post-PCV13 era. In children aged 2 to 4 years and those aged 5 to 17 years, PCV13 IPD rates increased during the late-PCV7 era but declined in the post-PCV13 era (Table 2).

Changes in Racial Differences in IPD After PCV13 Introduction

Disease severity did not differ according to race. However, IPD rates in black children aged <2 years were significantly higher than in white children aged <2 years during both the early-PCV7 era and the late-PCV7 era (92 vs 54 and 70 compared with 43 per 100 000 person-years; IRR of 1.7 [95% CI 1.3–2.2], then IRR of 1.6 [95% CI: 1.2–2.1], respectively). These racial disparities between black and white children aged <2 were essentially eliminated in the post-PCV13 era (IRR: 1.5 [95% CI: 0.7–3.2]) (Fig 3). Although non-PCV rates were higher among black children in the post-PCV13 era, these differences were not statistically significant.

Among children aged 2 to 4 years, IPD rates were higher in black

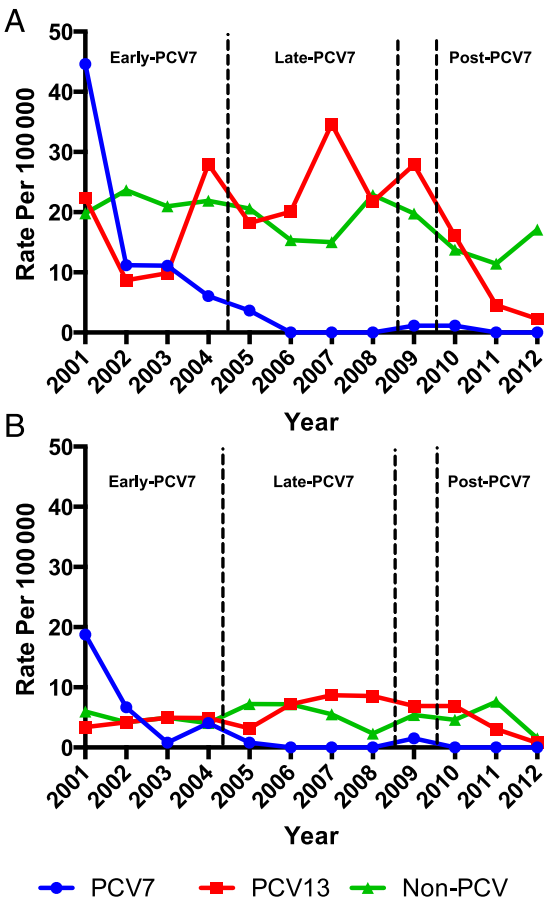

FIGURE 2

Annual IPD rates per 100 000 person-years in Tennessee according to vaccine serotypes: PCV7, PCV13, and non-PCV in (A) children aged <2 years and (B) children aged 2 to 4 years during the early-PCV7 (2001–2004), late-PCV7 (2005–2009), and post-PCV13 (2011–2012) vaccine eras.

children in the early-PCV7 era compared with white children (30 vs 13 cases per 100 000 person-years; IRR: 2.2 [95% CI: 1.5–3.4]). However, in the late-PCV7 and post-PCV13 eras, these differences were no longer significant (IRR of 1.2 [95% CI: 0.7–1.8] and 1.0 [95% CI: 0.3–2.9], respectively). IPD rates among children aged 5 to 17 years were low throughout the study period in both races but were significantly higher among black children in the early-PCV7 era only (IRR: 2.0 [95% CI: 1.2–3.1]). In the late-PCV7 and post-PCV13 eras, these differences were no longer significant (IRR: 1.4 [95% CI: 0.9–2.0]; IRR: 0.7 [95% CI: 0.3–1.7]).

Changes in Regional Differences in IPD After PCV13 Introduction

The distribution of grouped vaccine serotypes among IPD cases over the 3 vaccine eras for all children according to region is shown in Fig 4. In children aged <2 years, IPD rates were ~2-fold higher in east Tennessee compared with middle-west Tennessee during the early-PCV7 era (IRR: 1.9 [95% CI: 1.4–2.5]). IPD rates declined in both regions during the late-PCV7 era but remained 2-fold higher in east Tennessee compared with middle-west Tennessee. However, during the post-PCV13 era, IPD rates declined further in both regions, and IPD rates differences were no longer statistically significant between the 2 regions (Table 3).

Outpatient and inpatient IPD rates were also compared according to region. During all 3 vaccine eras, outpatient IPD rates were significantly higher in east Tennessee than in middle-west Tennessee in children aged <2 years. However, inpatient IPD rates in children <2 years of age did not differ significantly between the 2 regions, suggesting that overall regional rate differences in children aged <2 years were substantially driven by differences in regional outpatient IPD rates.

Overall IPD rates in children aged 2 to 4 years were also higher in east Tennessee compared with middle-west Tennessee in the early-PCV7 and late-PCV7 eras (Table 3). However, this difference was no longer statistically significant in the post-PCV13 era. During the early-PCV7 and late-PCV7 eras, outpatient IPD rates were higher in children aged 2 to 4 years in east Tennessee compared with middle-west Tennessee, but this difference was not significant in the post-PCV13 era. In children aged 5 to 17 years, IPD rates were low throughout the study period and were similar in both regions.

Changes in IPD Caused by Antibiotic-Resistant Strains After PCV13 Introduction

Over the study period, IPD rates due to penicillin-resistant strains in children aged <2 years were stable at 10 and 9 per 100 000 person years in the early-PCV7 and late-PCV7 eras, respectively but then decreased to 2 per 100 000 person-years (IRR: 0.3 [95% CI: 0.1–0.7]) in the post-PCV13 era. A similar decrease in penicillin-resistant IPD rates was noted in the post-PCV13 era in children aged 2 to 4 years. Rates of penicillin-resistant IPD in children aged 5 to 17 years were low throughout the study period.

In children aged <2 years, IPD rates due to penicillin-resistant strains

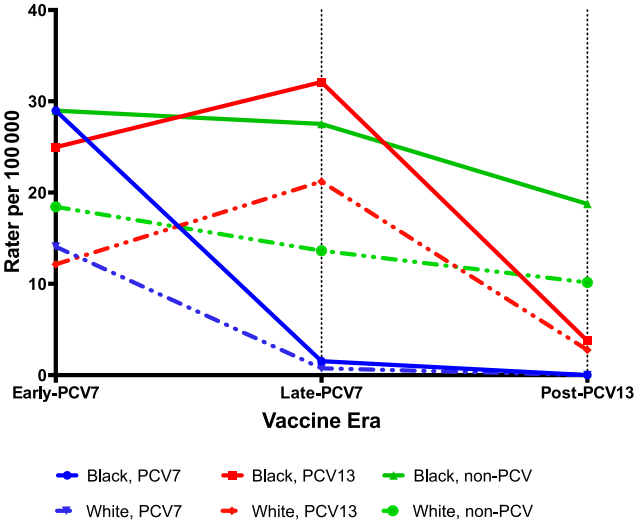

FIGURE 3

Annual IPD rates per 100 000 person-years in Tennessee according to vaccine serotypes: PCV7, PCV13, and non-PCV in children aged <2 years according to race, black and white race, during the early-PCV7 (2001–2004), late-PCV7 (2005–2009), and post-PCV13 eras (2011–2012).

were significantly higher in east Tennessee compared with middle-west Tennessee during the early-PCV7 and late-PCV7 vaccine eras, but the difference in IPD rates due to penicillin-resistant strains was no longer significant in the post-PCV13 era (Table 4). This pattern in children aged 2 to 4 years and 5 to 17 years was less consistent, although the proportion of penicillin-resistant isolates was generally higher in east than in middle-west Tennessee.

DISCUSSION

Since the introduction of the routine vaccination of young children with PCV13, IPD rates in children aged <2 years in Tennessee have declined to the lowest incidence ever recorded, with a >90% decline from a historical IPD rate of 230 in 1999 to 19 per 100 000 person-years in 2012.[11,14] Pediatric IPD due to PCV7 serotypes was virtually eliminated during the study period, with no cases noted in children aged <5 years after 2011.

After the introduction of PCV7, rapid increases in IPD caused by non-PCV7 serotypes, especially 19A, were detected in Tennessee and elsewhere.[11,30] Despite the overall reductions in IPD a few years after PCV7 introduction, IPD rates remained steady during subsequent years, and serotype 19A accounted for most residual IPD in the late-PCV7 era.[30] In our cohort, 19A represented 32% of IPD cases in the late-PCV7 era but rapidly decreased in the post-PCV13 era, causing only 7% of IPD cases in 2012. Unlike the post-PCV7 introduction years, during which 19A emerged as a distinct replacement serotype, no single serotype seems to dominate the residual burden of IPD in the post-PCV13 era. The most frequent non-PCV serotypes in the post-PCV13 era were 22F, 33, 12F, and 38. In other studies, serotypes 12F and 22F have also been reported as common residual serotypes after the introduction of PCV13.[16,31] Decreases in penicillin-resistant IPD rates are likely secondary to decreases in overall IPD rates.

Our study noted racial differences in IPD rates in young children. Previously, Talbot et al[14] reported higher IPD rates in black children compared with white children in Tennessee but then documented a decrease in racial differences 2 years after PCV7 introduction. These same findings were consistent with national data.[14] After extending the study years, our data revealed that during the late-PCV7 era, black children reverted to higher IPD rates than white children, a phenomenon facilitated in part by intense serotype

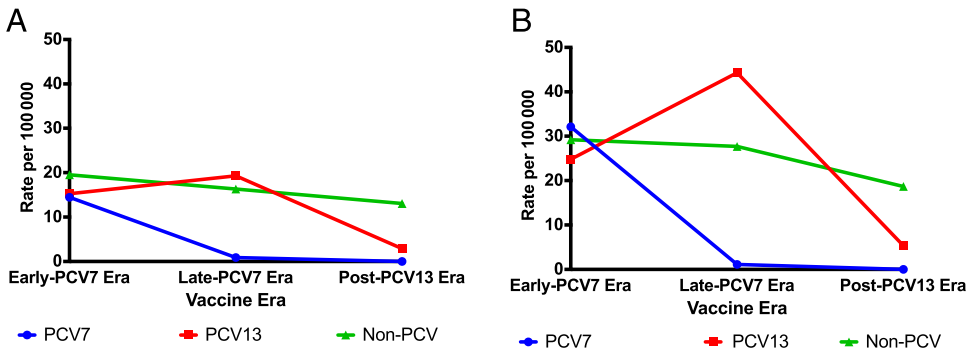

FIGURE 4

IPD rates in children aged <2 years in Tennessee according to vaccine serotype: PCV7, PCV13, and non-PCV during the early-PCV7 (2001–2004), late-PCV7 (2005–2009), and post-PCV13 eras (2011–2012) in (A) middle-west and (B) east Tennessee.

TABLE 3 Annual IPD Rates per 100 000 Person-Years in East and Middle-West TN, 2001 to 2012

IPD Rate	Age <2 y			Age 2–4 y			Age 5–17 y		
	MW TN	East TN	IRR (95% CI)	MW TN	East TN	IRR (95% CI)	MW TN	East TN	IRR (95% CI)
Early-PCV7									
Total	56.7	105.1	1.9 (1.4–2.5)*	15.8	31.5	1.9 (1.3–3.1)*	3.8	3.8	1.0 (0.6–1.7)
PCV7	14.5	32.1	2.2 (1.3–3.9)*	5.8	13.8	2.4 (1.1–4.9)*	1.3	1.1	0.8 (0.2–2.2)
PCV13	15.2	24.8	1.6 (0.9–2.9)	4.2	4.9	1.2 (0.3–3.3)	1.1	1.1	1.0 (0.3–2.7)
Non-PCV	19.5	29.2	1.5 (0.84–2.6)	4.7	4.9	1.0 (0.3–2.9)	1.0	1.1	1.1 (0.3–3.1)
Late-PCV7									
Total	44.5	90.8	2.0 (1.5–2.7)*	13.6	25.2	1.9 (1.2–2.8)*	3.8	3.5	0.9 (0.5–1.5)
PCV7	0.9	1.1	1.2 (0–15.5)	0	2.2	NA	0.2	0.3	1.8 (0.2–12.5)
PCV13	19.3	44.3	2.3 (1.5–3.5)*	6.2	9.6	0.5 (0.2–1.2)	2.0	1.0	0.5 (0.2–1.2)
Non-PCV	16.3	27.7	1.7 (1.0–2.8)*	4.8	8.1	1.7 (0.8–3.6)	1.2	1.0	0.8 (0.3–2.0)
Post-PCV13									
Total	16.7	29.4	1.8 (0.8–3.8)	7.7	7.1	0.9 (0.2–2.9)	2.4	2.8	1.2 (0.4–2.9)
PCV7	0	0	NA	0	0	NA	0	0.4	NA
PCV13	2.9	5.3	1.8 (0.2–12.9)	2.4	0	NA	0.6	1.6	2.9 (0.6–13.2)
Non-PCV	13.1	18.7	1.4 (0.5–3.6)	4.4	5.3	1.2 (0.2–4.9)	1.6	0.4	0.3 (0–1.7)

*Denotes significance (CI does not cross 1). MW, middle-west; NA, not available; TN, Tennessee.

replacement. After PCV13 introduction, these differences were largely reduced. Non-PCV rates were higher in black children during the post-PCV13 era; however, this finding did not reach significance due to the small number of cases. Inpatient and outpatient IPD rates were consistently higher in black children than in white children (Supplemental Figs 5 and 6). Continuous surveillance over time will be important to monitor the sustainability of these observations.

Our study also noted regional IPD differences across the state of Tennessee before the introduction of PCV13, with higher IPD rates in the eastern section compared with the middle-west section. These differences cannot be explained by disparities in vaccine uptake because the proportion of children receiving at least 3 doses of PCV vaccine in both areas was similar throughout the study period, with the most recently reported uptake in 2013 (94.8% to 97.4% in middle-west Tennessee vs 94.6% to 95.4% in east Tennessee).[32] Furthermore, the proportion of black children is higher in middle-west Tennessee relative to east Tennessee, which suggests that racial differences could not explain the observed differences in IPD incidence. A possible explanation for these regional variations in IPD rates is detection bias due to differences in clinical practices between the 2 regions. Differences in blood culture practices may account for variations in IPD rates among various institutions.[33] Outpatient IPD rates, particularly due to isolated bacteremia, were higher in children aged <2 years in east Tennessee compared with middle-west Tennessee and accounted for most of the difference in rates (Supplemental Figs 5 and 6). Personal communication with institutions in both regions suggest that there may be important differences in the frequency of obtaining blood cultures in febrile children aged <2 years. Nevertheless, whether this difference in outpatient blood culture practices could fully account for the observed regional differences in IPD remains unclear. After the introduction of *Haemophilus influenzae* type B and pneumococcal conjugate vaccination, occult bacteremia in children aged 2 to 36 months became infrequent.[34] Subsequently, some physicians argue that obtaining blood cultures in otherwise well-appearing febrile children is not cost-effective.[34–36] In future analyses, blood culture practices should be considered when determining and interpreting IPD rates.

TABLE 4 Proportion of Penicillin-Resistant Isolates and Penicillin Resistance Rates in IPD in Children Aged <2 Years According to Region in Tennessee

Era	Middle-West		East	
	Proportion	Rate (per 100 000 PY)	Proportion	Rate (per 100 000 PY)
Early-PCV7	11% (14/126)	5.5	30% (18/59)	26.3
Late-PCV	16% (20/123)	5.9	26% (17/66)	18.8
Post-PCV13	9% (2/22)	1.5	22% (2/9)	5.3

PYA, person-years.

The proportion of antibiotic-resistant isolates was highest in east Tennessee, suggesting that antibiotic utilization may also be different in the 2 regions. The correlation of increased antibiotic utilization and increased antibiotic resistance is well documented and could explain the higher IPD rates due to penicillin-resistant strains observed in east Tennessee.[37] In addition, because the rates of meningitis and hospitalization were similar in east and middle-west Tennessee, we do not believe that the increase in

antibiotic-resistance IPD rates in east Tennessee indicate more severe disease (Table 1, Supplemental Fig 6).

Strengths of our study included the use of established population-based and active, laboratory-based surveillance, which facilitated a detailed characterization of serotypes associated with IPD. Furthermore, the Tennessee surveillance areas encompass a large population (>960 000 children). However, several limitations must be also acknowledged. The population under surveillance in Tennessee overrepresented black children relative to the general Tennessee population; our overall IPD rates may therefore be an overestimate, and extrapolation of our findings to other settings must carefully consider this difference. Some isolates could not be serotyped and thus were not included in some assessments. IPD cases could have been missed because of variations in culturing practices. Low current numbers of IPD cases precluded a comparison of racial differences in IPD rates between regions. Finally, continuous monitoring will be needed to evaluate the sustainability of our observed post-PCV13 changes.

CONCLUSIONS

The introduction of PCV13 led to substantial reductions in pediatric IPD rates in Tennessee and elimination of regional differences. Although racial differences in IPD rates initially diminished after introduction of PCV7, these differences reappeared during the late-PCV7 era but were not significant after the introduction of PCV13. Our study highlights the need for continued active surveillance to comprehensively evaluate the impact of this powerful vaccination program.

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ABBREVIATIONS

ABCs: Active Bacterial Core surveillance
CDC: Centers for Disease Control and Prevention
CI: confidence interval
IPD: invasive pneumococcal disease
IRR: incidence rate ratio
PCV7: 7-valent pneumococcal conjugate vaccine
PCV13: 13-valent pneumococcal conjugate vaccine

FINANCIAL DISCLOSURE: Drs de St Maurice, Fonnesbeck, and Halasa received funding from Pfizer, which manufactures the 13-valent pneumococcal conjugate vaccine; Dr Halasa receives or has received grant funding within the past 2 years from Sanofi Pasteur, AstraZeneca, and Gilead; Dr Grijalva has served as a consultant for Pfizer; and Dr Schaffner is a member of Data Safety Monitoring Boards for both Merck and Pfizer.

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