Invasive Pneumococcal Disease in Infants Younger Than 90 Days Before and After Introduction of PCV7

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KEY WORDS

invasive pneumococcal disease, *Streptococcus pneumoniae*, infant, pneumococcal conjugate vaccine

ABBREVIATIONS

ABC—Active Bacterial Core

CI—confidence interval

EDW—Enterprise Data Warehouse

IPD—invasive pneumococcal disease

PCMC—Primary Children's Medical Center

PCV7—heptavalent pneumococcal conjugate vaccine

PCV13—13-valent pneumococcal conjugate vaccine

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WHAT'S KNOWN ON THIS SUBJECT: Introduction of the pneumococcal conjugate vaccine was associated with decreased invasive pneumococcal disease (IPD) in children. Few data exist on the impact in infants aged 1 to 90 days, who are too young to be fully immunized.

WHAT THIS STUDY ADDS: The incidence and proportion of IPD in Utah infants aged 1–90 days remained stable after vaccine introduction. IPD caused by PCV7 serotypes decreased significantly in the post-vaccine period. Serotype 7F emerged as the predominant serotype and commonly resulted in meningitis.

abstract

NIH

BACKGROUND: Introduction of the heptavalent pneumococcal conjugate vaccine (PCV7) changed the epidemiology of invasive pneumococcal disease (IPD). We evaluated the changes that occurred after PCV7 introduction among Utah infants aged 1 to 90 days, too young to be fully immunized.

METHODS: We identified children <18 years with culture-confirmed IPD from 1997–2010. We analyzed demographic, clinical, and serotype data for infants aged 1–90 days. The pre- and post-vaccine introduction periods spanned 1997–2000 and 2001–2010, respectively.

RESULTS: Of 513 children with IPD, 36 were 1 to 90 days and accounted for 7% of IPD cases in both the pre- and post-vaccine introduction period. The pre-vaccine IPD incidence rate was 5.0 per 100 000 live births, and was unchanged in the post-vaccine introduction period. IPD caused by PCV7 serotypes decreased by 74% (from 2.2 to 0.58 per 100 000), whereas non-vaccine serotype IPD increased by 57% (from 2.8 to 4.4 per 100 000). Sixteen infants (44%) required intensive care, and 3 (8%) died. Bacteremia without focus (56%) and meningitis (44%) were the predominant syndromes in the pre- and post-vaccine introduction periods, respectively. In the post-vaccine introduction period, serotype 7F was the most common serotype among infants and was responsible for 50% of meningitis.

CONCLUSIONS: The incidence of IPD in Utah infants aged 1 to 90 days caused by PCV7 serotypes decreased after PCV7 introduction, but overall incidence was unchanged. In the post-vaccine introduction period, serotype 7F predominated in this age group and was associated with meningitis. *Pediatrics* 2013;132:e17–e24

Streptococcus pneumoniae is a leading cause of morbidity and mortality worldwide, particularly among children younger than 2 years.¹ The introduction of heptavalent pneumococcal conjugate vaccine (PCV7) in the United States in 2000, recommended for all children aged 2 to 23 months and for older children aged 24 to 59 months with a history of incomplete immunization or at increased risk of invasive pneumococcal disease (IPD),² has been associated with a decrease in the incidence of IPD caused by vaccine serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) in children younger than 5 years in the United States.^{3–6} The rate of IPD has also declined among unvaccinated older children and adults.^{3,7,8} However, data regarding the effects of PCV7 among infants who are too young to be fully immunized are limited.^{9,10}

Neonates and young infants are particularly vulnerable to serious bacterial infections, which may result from either vertical or horizontal transmission. Young infants may benefit from indirect protection from immunization of other populations. For example, after the introduction of *Haemophilus influenzae* type B vaccines for infants and children, the incidence of neonatal disease decreased.¹¹ Also, introduction of the meningococcal C conjugate vaccine in the United Kingdom was associated with beneficial indirect effects in infants younger than 3 months.¹² Poehling et al⁹ and Ladhani et al¹⁰ documented a substantial decrease in IPD in young infants in 8 US surveillance sites and in England and Wales in the 3 and 4 years after introduction of PCV7, respectively. The extent to which the epidemiology, clinical syndromes, and serotypes associated with IPD among neonates and young infants in the United States may have changed with prolonged use of PCV7 remains unknown.

We have conducted surveillance for pediatric IPD in Utah through Primary

Children's Medical Center (PCMC; Salt Lake City, UT) since 1996 and archived all isolates from children with IPD since 1997.^{13,14} The marked decreases in IPD due to PCV7 strains have been offset to varying degrees by an increased incidence of IPD due to nonvaccine replacement strains. Given that in Utah emergence of replacement strains was earlier and more complete than in some other regions, our objectives were to examine the effect of PCV7 on the epidemiology, serotype distribution, clinical presentation, and outcomes of IPD in infants aged 1 to 90 days before and after the introduction of PCV7 in the childhood immunization schedule.

METHODS

Human Subjects Protection

The institutional review boards of the University of Utah and Intermountain Healthcare approved this study. Informed consent was waived.

Setting and Study Design

PCMC is the only children's hospital in the Intermountain West region of the United States. The facility is owned and operated by Intermountain Healthcare, a large, vertically integrated, health care system. Over the study period, PCMC grew from a 234-bed to a 289-bed children's hospital. It serves both as a community pediatric hospital for Salt Lake County, Utah, and as a tertiary referral center for 5 states in the Intermountain West (Utah, Idaho, Wyoming, Nevada, and Montana). Throughout the study period, >90% of hospital admissions for infants ≤90 days of age in the state of Utah occurred at PCMC (E. Donnelly, Strategic Planning-Intermountain Healthcare, personal communication, 2013).

The study period included January 1997 through December 2010. We defined the pre-vaccine introduction period as

January 1997 through December 2000 (48 months). We defined the post-vaccine introduction period as January 2001 through December 2010 (120 months), when vaccine use progressively increased in the United States and in Utah.¹⁵ PCV7 and 13-valent pneumococcal conjugate vaccine (PCV13) were licensed in the United States in February 2000 and 2010, overlapping the endmost part of the pre- and post-vaccine introduction periods, respectively.^{2,16}

Identification of IPD

IPD was defined as isolation of *S pneumoniae* from a normally sterile site (ie, blood, cerebrospinal fluid, joint, pleural or peritoneal fluid, or abscess) in a child <18 years of age. The PCMC microbiology laboratory information system is linked to the Intermountain Enterprise Data Warehouse (EDW). The EDW captures all clinical, laboratory, pharmacy, and radiographic data for all Intermountain Health facilities. Data including age at the time of *S pneumoniae* isolation, diagnosis, and demographic and clinical information were extracted from the EDW. Clinical syndromes were assigned by clinical diagnosis and sterile site isolation.

S pneumoniae isolates were typed annually by means of the capsular swelling method with the use of commercially available type-specific anti-serum samples at Baylor College of Medicine. The investigator performing the analyses (E.O.M.) was blinded to the source (ie, blood, pleural fluid) and clinical information associated with the bacterial isolates.

Incidence of IPD in Infants

We restricted the analysis of incidence rates to the subset of infants who were residents of Utah at the time of admission for IPD. To estimate the age-specific incidence of IPD we used Utah residents with IPD cared for at

Intermountain Healthcare facilities as the numerator and annual intercensus population estimates for Utah as the denominator.¹⁷

Statistical Analyses

Descriptive statistics were used to characterize the study population. The χ^2 test and Fisher's exact test were used to compare the characteristics of infants with IPD before and after introduction of PCV7. We compared associations between individual serotypes and age groups by using an extended $2 \times n$ form of the χ^2 test.¹⁸ Ninety-five percent confidence intervals (CIs) were calculated on the basis of a Poisson distribution. P values ≤ 0.05 were considered statistically significant. Statistical analyses were performed by using Stata 11.2 (StataCorp, College Station, TX).

RESULTS

Identification of Children With IPD and Demographic Characteristics

During the study period, 513 children younger than 18 years were diagnosed with culture-confirmed IPD and were cared for at PCMC, 128 in the pre-vaccine introduction period and 385 in the post-vaccine introduction period. Of these, 36 of 513 (7%) were infants aged 1 to 90 days: 9 of 128 (7%) infants in the pre-vaccine introduction period and 27 of 385 (7%) infants in the post-vaccine introduction period. There were no recurrent cases.

Fifty-eight percent of the infants aged 1 to 90 days were male and 67% were white. Thirty-three infants (92%) were born full term (>37 weeks' gestation). The 3 preterm infants were born at 30, 32, and 36 weeks' gestation. One infant had Pierre-Robin syndrome, and no other chronic medical conditions were identified. PCV7 vaccine records were available for 25 (93%) of 27 infants in the post-vaccine introduction period.

Three (12%) infants had received the first dose of PCV7, and all others were unimmunized.

The age distribution of infants with IPD in the pre- and post-vaccine introduction period is shown in Table 1. The median age was 42 (range: 6–89) days. The majority of IPD cases overall occurred in infants older than 30 days (83%). In the pre-vaccine introduction period, however, a greater proportion of infants were younger than 30 days (3 of 9 vs 3 of 27 infants); however, this proportion did not reach statistical significance ($P = .15$). Two infants were younger than 7 days old, 1 of 9 (11%) infants in the pre-vaccine introduction period and 1 of 27 (4%) infants in the post-vaccine introduction period.

IPD Incidence Rate

There were 181 711 and 519 215 live births in Utah during the pre- and post-vaccine introduction periods, respectively. One infant aged 1 to 90 days was not a Utah resident at the time of admission. This infant presented during the late post-vaccine introduction period, and his isolate was identified as a non-PCV7 serotype. Therefore, we used 9 and 26 Utah infants for the analysis of the prevaccine and post-

vaccine IPD incidence rates, respectively. The IPD incidence rate during the pre-vaccine years was 5.0 (95% CI: 2.3–9.4) per 100 000 live births and 5.0 (95% CI: 3.3–7.3) per 100 000 live births during the post-vaccine introduction period. The IPD incidence rate decreased from 5.0 per 100 000 live births to 4.1 (95% CI: 1.8–8.0) per 100 000 live births in the early post-vaccine introduction period (2001–2004; 197 542 Utah live births) (-18% ; $P = .8$) and then increased by 37% to 5.6 (95% CI: 3.3–8.8) per 100 000 live births in the late post-vaccine introduction period (2005–2010; 321 673 Utah live births) ($P = .5$).

Clinical Syndromes of IPD

Clinical syndromes and outcomes associated with *S pneumoniae* infection in infants are shown in Table 2. There was no difference in the proportion of infants admitted to intensive care in the pre- and post-vaccine introduction periods; 3 (33%) were admitted to intensive care in the pre-vaccine introduction period versus 13 (48%) admitted in the post-vaccine introduction period ($P = .7$). Three infants (8%) died: 1 (11%) in the pre-vaccine introduction period and 2 (7%) during the post-vaccine introduction period.

TABLE 1 Age Distribution of IPD in Infants Aged 1 to 90 Days

Age	Prevaccine (n = 9)	Postvaccine (n = 27)	Total (n = 36)	P
≤ 30 days	3 (33)	3 (11)	6 (17)	.15
31–60 days	6 (67)	15 (56)	21 (58)	.56
61–90 days	0	9 (33)	9 (25)	.08

Data are presented as n (%). Pre-vaccine introduction period, 1997–2000; post-vaccine introduction period, 2001–2010.

TABLE 2 IPD Clinical Syndromes in Infants Aged 1 to 90 Days

Syndrome	Prevaccine (n = 9)	Postvaccine (n = 27)	P
Bacteremia without focus	5 (56)	6 (22)	.10
Meningitis	1 (11)	12 (44)	.11
Pneumonia $\pm$ empyema	1 (11)	4 (15)	1.00
Abscess/cellulitis/myositis	2 (22)	2 (7)	.26
Mastoiditis	—	2 (7)	1.00
Septic arthritis/osteomyelitis	—	1 (4)	1.00
Peritonitis	1 (11)	—	.25

Data are presented as n (%). Pre-vaccine introduction period, 1997–2000; post-vaccine introduction period, 2001–2010. —, indicates zero cases.

All deaths occurred in neonates: 2 in infants younger than 7 days and 1 in a 30-day-old infant born preterm at 36 weeks' gestation. Two of the fatal cases were caused by serotype 1 and 1 by serotype 8.

In the pre-vaccine introduction period, bacteremia without focus was the most common clinical syndrome among infants, accounting for 56% of cases. During the post-vaccine introduction period, meningitis was the most common syndrome, accounting for 44% of cases.

IPD Serotype Distribution

All 36 isolates were viable. Seventeen pneumococcal serotypes were identified in infants with IPD. The distribution of serotypes is shown in Table 3. PCV7 serotypes decreased from 44% of isolates in the pre-vaccine introduction period to 11% in the post-vaccine introduction period (-75% ; $P = .05$). The incidence of IPD due to PCV7 serotypes decreased from 2.2 (95% CI: 0.6–5.6) to

0.58 (95% CI: 0.1–1.7) per 100 000 (-74%), whereas the incidence of disease due to non-PCV7 serotypes increased from 2.8 (95% CI: 0.9–6.4) to 4.4 (95% CI: 2.8–6.7) per 100 000 ($+57\%$) (Fig 1). In the post-PCV7 era, 70% of IPD cases were due to serotypes included in PCV13.

No single serotype predominated in the pre-vaccine introduction period. However, serotype 7F was the most common serotype identified in the post-vaccine introduction period, and was responsible for 44% of all IPD in this age group. In the post-vaccine introduction period, serotype 7F was associated with a significantly higher proportion of IPD in infants younger than 90 days compared with older infants and children (44% of infants aged 1–90 days, 16% of children aged 91 days to <5 years, and 22% of children aged 5–17 years; $P = .001$). Six of 12 cases of meningitis in infants aged 1 to 90 days were due to serotype 7F in the post-vaccine introduction period.

DISCUSSION

Our study revealed significant changes in the epidemiology of IPD in infants aged 1 to 90 days over 10 years after the introduction of PCV7. Although we did not observe an overall decrease in the incidence of IPD among infants after the introduction of PCV7, IPD caused by

PCV7 serotypes decreased by 74%, revealing indirect protection for this population from immunization of older children. The clinical spectrum of IPD changed among infants after the introduction of PCV7, with a decrease in bacteremia without focus and an increase in meningitis. Serotype 7F emerged as the predominant serotype causing IPD in young infants.

Since the introduction of PCV7 in 2000, rates of pediatric IPD have declined significantly.^{5,9,19,20} By using surveillance data from the Active Bacterial Core (ABC) surveillance sites, Pilishvili et al⁵ reported a 45% decrease in the incidence of IPD (from 24.4 to 13.5 cases per 100 000 population) in all age groups in 2007. The largest decrease was among children younger than 5 years, the target group for vaccine. However, the impact of vaccine on young infants is more complex, because they are too young to be directly protected by vaccine, and may acquire infection through horizontal or vertical transmission.

A small proportion of IPD occurs in young infants.^{5,21–23} Hoffman et al²¹ reported that among 3200 children with IPD in the pre-vaccine introduction period, 0.65% of cases were in infants aged 1 to 30 days. In a study in 8172 children with IPD from Germany, only 88 (1%) were infants

TABLE 3 IPD Serotypes in Infants Aged 1 to 90 Days

Serotype	Prevaccine (n = 9)	Postvaccine (n = 27)	P
PCV7			
4 ^{a,b}	2 (22)	—	.06
18C ^{a,b}	1 (11)	1 (3.7)	.44
19F ^{a,b}	1 (11)	2 (7.4)	1.00
Non-PCV7			
7F ^b	—	12 (44)	.016
6A ^b	1 (11)	—	.25
1 ^b	1 (11)	1 (3.7)	.44
19A ^b	—	2 (7.4)	1.00
3 ^b	—	1 (3.7)	1.00
16	1 (11)	—	.25
11	1 (11)	—	.25
22F	1 (11)	1 (3.7)	.44
23A	—	1 (3.7)	1.00
35	—	1 (3.7)	1.00
20	—	1 (3.7)	1.00
23B	—	1 (3.7)	1.00
8	—	1 (3.7)	1.00
Pool G	—	1 (3.7)	1.00
Nontypeable	—	1 (3.7)	1.00

Data are presented as n (%). Pre-vaccine introduction period, 1997–2000; post-vaccine introduction period, 2001–2010. —, indicates zero cases.

^a PCV7 (4, 6B, 9V, 14, 18C, 19F, 23F).

^b PCV13 (PCV7 + 1, 3, 5, 6A, 7F, 19A).

FIGURE 1
Number of IPD cases per year.

0 to 60 days old.²² A single-center study from Israel reported that 6% (24 of 412) of IPD cases were in infants 1 to 60 days old.²³ In a recent study from England and Wales, IPD in infants aged 0 to 90 days accounted for 1.1% (480 of 42 875) of all cases.¹⁰ In our study, 7% of IPD occurred in infants aged 1 to 90 days: 1.2% of cases in those aged 0 to 30 days and 5.8% of cases in those aged 31 to 90 days. These figures are somewhat higher than in other US and European studies but similar to the recent Israeli study. The incidence of IPD infants in our study in the pre-vaccine period was noticeably lower at 5.0 (95% CI: 2.3–9.4) per 100 000 live births than that reported in England and Wales¹⁰ (13.0 per 100 000; 95% CI: 12.0–14.0) and in the US ABC sites⁹ (11.8 per 100 000; 95% CI: 9.6–14.5). The low IPD incidence in the pre-vaccine introduction period in our study may be related to differences in surveillance methodology, population characteristics, clinical practice, and other environmental factors.

Early-onset IPD in the first week of life may represent acquisition from the maternal genital tract. Early-onset disease was uncommon in our population, representing 11% of IPD among infants in the pre-vaccine introduction period and 4% after vaccine introduction. In contrast, Ladhani et al¹⁰ and Poehling et al⁹ reported that 37.9% and 19% of IPD among infants in the United Kingdom and the United States after the introduction of PCV7 was early onset, respectively. In the UK study population and in the earlier US study, 23% of infants were premature, compared with 8% in our study. Utah has been reported to have a lower rate of preterm births than the average for the United States.²⁴ Our study included 8 years after the release of the Centers for Disease Control and Prevention guidelines for group B *Streptococcus*.²⁵ The resulting increase in intrapartum

antibiotic use²⁶ may have contributed to the lower rate of early-onset IPD because the majority of non-PCV7 serotypes isolated in Utah are penicillin susceptible. Finally, low IPD rates in the neonatal period may also be related to the presence of maternal antibodies. Maternal pneumococcal antibodies have been detected in infants aged <36 days but were reported to wane rapidly.²⁷ An estimated half-life of maternal pneumococcal antibodies of 35 days has been reported.²⁸

The incidence rate of IPD in infants remained stable over the study period. However, the IPD incidence initially decreased by 18% during the early vaccine period (2001–2004) and then increased by 37% in the late vaccine period (2005–2010). Our results differ from other multicenter studies that documented more substantial declines in IPD rates in infants younger than 3 months after the introduction of PCV7, but these studies focused on the early period after vaccine introduction.^{5,9} Poehling et al⁹ reported an overall decrease of 40% in IPD cases in infants aged 1 to 90 days, from 11.8 to 7.2 cases per 100 000 live births from 1997 to 2004; and Pilishvili et al⁵ reported a 50% decrease in the overall incidence of IPD among infants younger than 2 months from 1998 to 2007. Ladhani et al¹⁰ reported a 25% decrease in the overall IPD incidence in infants aged 0 to 90 days in the 4 years after vaccine introduction in the United Kingdom. The unchanged incidence of IPD in our study could be related to several factors. First, the serotype distribution of IPD in Utah differed from other US locations before the introduction of PCV7, and may have allowed more rapid emergence of replacement disease.^{13,14,29} Our study did not consider a transitional year after the introduction of PCV7. Moreover, our study period included a longer period of observation than most studies,^{5,10} 10

years after vaccine introduction, and likely represents a greater impact of strain replacement over this period. Second, Utah has the largest households and greatest number of children per household in the United States.^{17,30} Household crowding and greater numbers of children may facilitate early pneumococcal colonization of young infants, which may result in IPD.³⁰ Day care attendance and young children in the household have been described as risk factors for pneumococcal colonization in American children younger than 2 years.^{31,32} Studies in neonates in Africa and Asia also revealed that infants with at least 2 siblings or siblings in child care are at increased risk of earlier colonization with *S pneumoniae*.^{21,33–35}

Although we did not observe changes in the overall incidence of IPD in young infants, we observed a substantial decrease of 74% in IPD caused by PCV7 serotypes after vaccine introduction. Our results are similar to those of Poehling et al⁹ and Ladhani et al¹⁰ who reported decreases of 67% and 83%, respectively, in IPD caused by PCV7 serotypes in infants aged 1 to 90 days in the United States and the United Kingdom. With the use of the same ABC surveillance system, Pilishvili et al⁵ reported that, by 2007, PCV7-type IPD in infants younger than 2 months had decreased by 94% compared with 1997. Associated with the overall decrease in IPD among US children, infections by non-PCV7 serotype have increased. In the ABC surveillance sites, IPD due to non-PCV7 serotypes increased by 22% by 2004 among children aged younger than 5 years.³⁶ In Utah, the incidence of IPD due to non-PCV7 serotypes in this age group increased by 67% during 2007–2010.¹³ In the current study, IPD due to non-PCV7 serotypes in young infants increased by 57% in the post-vaccine introduction period, with the resultant effect being no change in the

overall incidence of IPD in infants aged 1 to 90 days.

Bacteremia without focus and meningitis were the most common clinical syndromes of IPD in infants aged 1 to 90 days. The proportion of IPD due to bacteremia without focus decreased from 56% to 22% in young infants. Although this decrease was not significant, we previously reported an overall decrease in bacteremia without focus from 14% of IPD to 5% ($P = .02$) in Utah children younger than 18 and an overall decreased incidence of the syndrome.^{14,29} Studies from the United States, Spain, and Italy have reported similar findings even in settings with moderate PCV7 coverage.^{37–41} We also observed a trend toward an increase in the proportion of meningitis in infants with IPD after the introduction of PCV7. Poehling et al⁹ reported a 15% proportion of meningitis in young infants; however, Ladhani et al¹⁰ reported a higher proportion of meningitis (37%), which is similar to our study.

Meningitis in young infants in our study was associated with serotype 7F, which was the most common serotype causing IPD in infants in the post-vaccine introduction period. In Utah, serotype 7F has emerged as one of the most common causes of IPD in all children.¹³ Our findings are similar to recent studies from Germany where serotype 7F was the most common serotype among children younger than 60 days, and more common in infants than among older children.^{22,42} The recent study from the United Kingdom also

noted the emergence of serotype 7F in infants aged 0 to 90 days during 2008–2010.¹⁰ Similarly, a study in Denmark, where PCV7 was introduced in 2007, revealed that the proportion of serotypes 1, 3, 5, and 7F was higher for IPD in children aged <6 months than in those aged 6 months to <2 years.⁴³ Our findings, however, contrast with those from other sites in the United States, where serotype 19A has been the most common emerging serotype.^{5,16,36,41,44}

Serotype 7F has been reported to be associated with a higher risk of severe and fatal outcomes than other serotypes.⁴⁵ Increased susceptibility of newborns to infection from serotype 7F might be related to significantly lower concentrations of specific antibodies to type 7F pneumococcal capsular polysaccharide in cord serum than in maternal serum.⁴⁶

There are a number of limitations to this study. First, the study was conducted in a single geographic area, and geographic variation in serotype distribution is well described. Second, the reported incidence may underestimate the true incidence of IPD in Utah infants because the IPD incidence was determined by culture-confirmed surveillance and the incidence rate was not adjusted for PCMC's market share of statewide hospital admissions. Third, the sample size was small, which limited the statistical power of comparisons of pre- and post-vaccine introduction data. Last, information regarding family size, number, age and immunization

status of children in the household, and child care attendance was not available. These variables may influence infant pneumococcal colonization and risk of invasive disease.

CONCLUSIONS

Our study provides evidence of important changes in the epidemiology of IPD in infants aged 1 to 90 days over a 10-year period after the introduction of PCV7. We revealed a substantial decrease of IPD cases caused by PCV7 serotypes in infants, which provides evidence of indirect protection for this vulnerable population. However, the overall IPD incidence remained stable due to an increase in disease associated with nonvaccine serotypes. Serotype 7F emerged as the most common serotype in the post-vaccine introduction period, and was frequently isolated from infants with meningitis. Serotype 7F and the majority of the emerging serotypes isolated from infants aged 1 to 90 days in our study are included in PCV13. Therefore, it is likely that widespread use of PCV13 will indirectly protect infants. Ongoing surveillance is warranted to evaluate the incidence and serotype distribution of IPD among infants in the PCV13 era. Vaccine strategies to protect the youngest infants should be considered.

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