Invasive Pneumococcal Disease Among Infants Before and After Introduction of Pneumococcal Conjugate Vaccine

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Context *Streptococcus pneumoniae* is a serious infection in young infants. A heptavalent pneumococcal conjugate vaccine (PCV7) was licensed in 2000 and recommended for all children aged 2 to 23 months.

Objective To determine the rates of invasive pneumococcal disease (IPD) in young infants before and after PCV7 was incorporated into the childhood immunization schedule in June 2000.

Design, Setting, and Participants A prospective, population-based study of infants aged 0 to 90 days who resided in areas in 8 US states with active laboratory surveillance for invasive *S pneumoniae* infections from July 1, 1997, to June 30, 2004.

Main Outcome Measures Rates of laboratory-confirmed IPD before (July 1, 1997-June 30, 2000) and after (July 1, 2001-June 30, 2004) PCV7 introduction, excluding a transition year (July 1, 2000-June 30, 2001).

Results There were 146 cases of IPD, 89 before and 57 after PCV7 introduction. Isolated bacteremia occurred in 94 cases (64%), pneumonia in 27 (18%), meningitis in 22 (15%), and septic arthritis and/or osteomyelitis in 3 (2%). Mean rates of IPD for infants aged 0 to 90 days decreased 40% from 11.8 (95% confidence interval [CI], 9.6-14.5) to 7.2 (95% CI, 5.6-9.4; *P* = .004) per 100 000 live births following PCV7 introduction. Among black infants, mean rates of IPD decreased significantly from 17.1 (95% CI, 11.9-24.6) to 5.3 (95% CI, 2.8-10.1; *P* = .001) per 100 000 live births, with a nonsignificant decrease from 9.6 (95% CI, 7.3-12.7) to 6.8 (95% CI, 4.9-9.4) per 100 000 live births for white infants. Rates of PCV7-serotype isolates decreased significantly from 7.3 (95% CI, 5.3-10.1) to 2.4 (95% CI, 1.6-3.8; *P* < .001) per 100 000 live births, while rates of non-PCV7 serotypes remained stable (*P* = .55).

Conclusions Since PCV7 introduction, rates of IPD in young infants have decreased significantly, providing evidence that vaccinating children aged 2 to 23 months has led to changes in pneumococcal carriage in infants too young to receive PCV7. With a significant decrease in rates of IPD among black infants, the previous racial difference has been eliminated.

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Neonates (0 to 30 days) and young infants (31 to 90 days) are at high risk for certain bacterial infections, most often due to group B Streptococcus, Escherichia coli, and Listeria monocytogenes. Although S pneumoniae causes invasive disease in young infants, the incidence has not been clearly defined. Clinical manifestations of S pneumoniae infections in neonates and young infants are serious and include meningitis, sepsis, bacteremia, pneumonia, otitis media, abscesses, and bone and joint infections. Whether PCV7 vaccination of children aged 2 months or older would protect neonates and young infants by changing pneumococcal carriage in those too young to receive PCV7, similar to that reported after Haemophilus influenzae type b vaccination, is unknown. We sought to determine the rates of IPDs among neonates and young infants in 8 states performing active, population-based laboratory surveillance. We hypothesized that the rates of IPD would decline from 1997-1999 to 2001-2004 and coincide temporally with the introduction of PCV7 in 2000; racial differences in rates would exist in the pre-PCV7 years and decline in the post-PCV7 years; and the decline would be more pronounced for serotypes included in PCV7 than non-PCV7 serotypes.

**METHODS**

**Ascertainment of IPD**

An active, prospective, laboratory-based surveillance for IPD was performed in portions of 8 US states (San Francisco county, California; the state of Connecticut; 20 counties of Georgia, including the Atlanta metropolitan area; 6 jurisdictions encompassing the Baltimore metropolitan area of Maryland; 7 counties surrounding Minneapolis/St Paul, Minnesota; 7 counties surrounding Rochester, New York; 3 counties surrounding Portland, Oregon; and 5 urban counties of Tennessee). Continuous surveillance has been performed in each state since at least July 1997 as a part of the Centers for Disease Control and Prevention’s (CDC’s) Active Bacterial Core surveillance of the Emerging Infections Program Network. Invasive pneumococcal disease was defined as the isolation of S pneumoniae from a normally sterile site (blood, cerebrospinal fluid, pleural fluid, surgical aspirate, and bone or joint fluid). For individuals from whom S pneumoniae was isolated concurrently from multiple sites, the episode was counted as a single case of invasive disease. The clinical presentation of IPD was classified by clinical diagnosis and sterile-site isolation in the following hierarchical order: meningitis, pneumonia (with bacteremia or isolation from other sterile site but without requiring radiographic confirmation), bone or joint infection, and isolated bacteremia.

**Data Abstraction**

Trained Active Bacterial Core surveillance program personnel and infection control practitioners used standardized definitions to abstract data from clinical records of each case of IPD. The abstracted information included demographics (age, race, sex), birth weight for neonates, comorbid conditions, source of pneumococcal isolate, outcome of illness, and length of hospitalization. Race and ethnicity were determined by a review of medical records.

**Study Populations**

The total and race-specific numbers of live births per calendar year were obtained from each surveillance area using vital records from each state. Live births served as a surrogate for living infants; no correction for deaths in the first 90 days of life was used.

**Study Period**

The study period extended from July 1, 1997, to June 30, 2004. The PCV7 was licensed in the United States in February 2000. However, PCV7 was not covered by most health insurance companies or routinely incorporated into the childhood immunization schedule until mid-2000, when the American Academy of Pediatrics and the CDC issued recommendations and the Vaccines for Children Program included PCV7. Thus, we defined a pre-PCV7 study period (July 1, 1997, to June 30, 2000), a 1-year transition period (July 1, 2000, to June 30, 2001) to allow for vaccine uptake, and a post-PCV7 study period (July 1, 2001, to June 30, 2004).

**Serotype and Antibiotic Sensitivity Testing**

Beginning in 1998, pneumococcal serotype determination was performed on all available isolates by the quellung reaction. Isolates from Minnesota were tested at the Minnesota Department of Health, and isolates from all other states were tested at the CDC. The PCV7 serotypes included all vaccine-specific strains (4, 6B, 9V, 14, 18C, 19F, and 23F). All other serotypes, including vaccine-related strains, were considered non-PCV7 serotypes.

Throughout the study period, the CDC, the Minnesota Department of Health, and the University of Texas Health Science Center at San Antonio performed antibiotic susceptibility testing on all available isolates using broth microdilution. Using the 2002 National Committee for Clinical Laboratory Standards, isolates were defined as nonsusceptible if they were intermediate or resistant to penicillin, erythromycin, or cefotaxime.

**Statistical Analysis**

Demographic characteristics of infants with IPD for the period before PCV7 introduction (July 1, 1997, to June 30, 2000) were compared with those after PCV7 introduction (July 1, 2001, to June 30, 2004) using the χ² or Fisher exact tests. Rates of IPD were determined by the number of laboratory-confirmed cases divided by the number of live births in the surveillance areas. Calendar year denominators were used to estimate live births for the subsequent study years, July through June. For example, we used the 1997 live births as the denominator for the 1997-1998 study year. Rates for the period before and after PCV7 introduction.
were compared. Although the rates reflect comprehensive, laboratory-based surveillance within the surveillance areas, 95% confidence intervals (CIs) were computed to project national rates using the binomial distribution. The most conservative method to determine statistical significance is nonoverlapping 95% CIs. However, another valid, yet less conservative method is to compare the number of cases and noncases in the surveillance population using \( \chi^2 \) or Fisher exact tests. A 2-sided \( P < .05 \) was considered significant.

Cases from the transition year were excluded from all analyses to allow time for vaccine uptake; the primary result, change in rates of IPD for all infants aged 0 to 90 days, remained statistically significant with and without the inclusion of the transition year. The rates and 95% CIs of all isolates that were PCV7 or non-PCV7 serotypes were analyzed beginning in July 1998, the first study year after routine serotype testing began. With 17% of the isolates missing serotype data both before and after PCV7 introduction, the calculations were performed assuming that all the missing values were either PCV7 or non-PCV7 isolates. With statistically significant results using both extreme assumptions, we chose to report the results without imputation. Rates and 95% CIs of isolates that were nonsusceptible to penicillin, erythromycin, or cefotaxime were compared during the period before and after PCV7 introduction. All statistical analyses were calculated using STATA version 8.1 (Stata Corp, College Station, Tex). This study was approved by the Vanderbilt University Medical Center institutional review board and exempt from requiring review by the CDC institutional review board.

**RESULTS**

Of 170 cases of IPD identified among infants aged 0 to 90 days from July 1, 1997, to June 30, 2004, 24 cases (14%) occurred during the transition year. The study population comprised the remaining 146 cases from the 3 pre-PCV7 years (n=89) and 3 post-PCV7 years (n=57). All infants had a single episode of IPD with the median age of onset at 46 days (range, 0-88 days). The age group, racial distribution, sex, and state from which IPD cases were identified were statistically similar during the 2 periods (TABLE 1); however, the proportion that was black in the post-PCV7 years was half that of the pre-PCV7 years. The annual number of IPD cases during the pre-PCV7 years ranged from 26 to 35 and during the post-PCV7 years from 14 to 24. Isolated bacteremia occurred in 94 cases (64%), and pneumonia was found in 27 infants (18%), meningitis in 22 (15%), and septic arthritis and/or osteomyelitis in 3 (2%). The respective proportions were 66%, 18%, 15%, and 1% during the pre-PCV7 years, and 62%, 19%, 16%, and 4% during the post-PCV7 years (\( P = .76 \)).

Two of 7 infant deaths (29%) from IPD occurred during the post-PCV7 years, whereas 1 (14%) and 4 (57%) deaths occurred during the transition and pre-PCV7 years, respectively. Two premature neonates died of IPD within the first week of life (1 developed pneumonia on the day of birth and 1 developed meningitis at 4 days old). Two infants, one of whom had congenital heart disease, developed meningitis at almost 2 months, and 4 infants developed bacteraemia between 1 and 3 months.

One hundred nineteen infants (82%) with IPD were hospitalized, and only 2 (7%) of 27 infants not hospitalized were neonates. For the 115 hospitalizations with admission and discharge dates, the median length of stay was 6 days (range, 0-159 days). The median length of stay was 10 days for meningitis (range, 0-55 days), 5.5 days for pneumonia (range, 1-65 days), and 5 days for bacteraemia (range, 0-159 days).

**Neonatal IPD**

Of the 44 neonates aged 0 to 30 days with IPD, 30 (68%) occurred at 0 to 6
days. Thirty-nine neonates (89%) had gestational ages and birth weights recorded. Of these, 9 (23%) were born premature (<37 weeks' gestation), with a median gestational age of 34 weeks and a median birth weight of 1982 g.

The clinical presentation of neonatal IPD was similar both before and after PCV7 introduction. The median day of presentation for early onset neonatal IPD (0 to 6 days) was 0 days. Late-onset neonatal IPD (7 to 30 days) had a median onset of 21 days. The clinical manifestations of neonatal early onset and late-onset IPD were similar (9% had meningitis, 25% had pneumonia, and 66% had bacteremia). Furthermore, the antimicrobial susceptibility patterns were similar in both age groups with 75% of the isolates sensitive to penicillin, cefotaxime, and erythromycin.

**IPD Rates**

The 8 surveillance areas had 759 739 live births during the 3 pre-PCV7 years and 794 106 live births during the 3 post-PCV7 years, with a mean of 258 974 live births per year. Among all the infants aged 0 to 90 days, the mean rate of IPD decreased significantly from 11.8 (95% CI, 9.6-14.5) per 100 000 live births in the pre-PCV7 years to 7.2 (95% CI, 5.6-9.4; P=.004) per 100 000 live births in the post-PCV7 years (FIGURE 1). The mean rate of IPD decreased by 39%, 45%, and 32% for infants aged 0 to 30 days, 31 to 60 days, and 61 to 90 days, respectively. Notably, the rate of IPD among infants aged 0 to 60 days decreased from 7.3 (95% CI, 5.6-9.5) per 100 000 live births in the pre-PCV7 years to 4.2 (95% CI, 3.0-5.9; P=.01) per 100 000 live births in the post-PCV7 years, although PCV7 is not recommended until infants reach 2 months of age.

Among black infants, mean IPD rates decreased significantly from 17.1 (95% CI, 11.9-24.6) per 100 000 live births during the pre-PCV7 years to 5.3 (95% CI, 2.8-10.1; P=.001) per 100 000 live births during the post-PCV7 years (FIGURE 2). Among white infants, mean IPD rates decreased, albeit not significantly, from 9.6 (95% CI, 7.3-12.7) to 6.8 (95% CI, 4.9-9.4; P=.11) per 100 000 live births, respectively. With the significant decrease in rates among black infants, the racial difference in IPD rates for black and white infants in the pre-PCV7 years (P=.01) was eliminated in the post-PCV7 years (P=.47).

**Changes in Serotypes and Antibiotic Susceptibility**

Of the 120 cases of IPD occurring after July 1, 1998, the first study year when routine serotype analysis was performed, 99 cases (83%) were available for serotype determination; the proportion of IPD cases with serotype determination was identical in the pre-PCV7 and post-PCV7 years. Demographic characteristics of infants with serotypes reported did not differ from those without serotype determination. Most PCV7 serotypes decreased with the exception of 18C and 19F (TABLE 2). Mean rates of IPD caused by PCV7 serotypes decreased significantly from 7.3 (95% CI, 5.3-10.1) per 100 000 live births in the pre-PCV7 years to 2.4 (95% CI, 1.6-3.8; P<.001) per 100 000 live births in the post-PCV7 years (FIGURE 3). In contrast, rates of non-PCV7 serotypes remained stable (P=.55). Although rates of PCV7 isolates were significantly higher than rates of non-PCV7 iso-

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lates during the pre-PCV7 years \((P = .002)\), the 2 rates were similar during the post-PCV7 years \((P = .19)\).

Of the 146 cases of IPD, 116 (79%) had antibiotic sensitivity analyses performed. Rates of disease due to PCV7 serotypes that were nonsusceptible to penicillin, cefotaxime, or erythromycin decreased 73% from 2.30 (95% CI, 1.44-3.68) per 100 000 live births during the pre-PCV7 years to 0.57 (95% CI, 0.22-1.43; \(P < .001\)) per 100 000 live births during the post-PCV7 years; whereas, susceptible PCV7 serotypes had a modest decrease from 4.0 (95% CI, 2.6-6.1) to 1.9 (95% CI, 1.2-3.2; \(P = .03\)) per 100 000 live births. No significant changes in rates for susceptible or nonsusceptible non-PCV7 serotypes were observed.

**COMMENT**

Among infants aged 0 to 90 days, IPD rates decreased significantly after PCV7 introduction. The change was attributable to a decrease in the rate of disease caused by PCV7 serotypes. Although we did not observe an increased rate of non-PCV7 serotypes, we had limited power to detect such an increase. The 42% decrease in IPD rates among infants aged 0 to 60 days is similar to decreases reported for children older than 5 years and adults, who are not specific targets of PCV vaccinations. These data are the first to suggest that neonates and infants too young to receive PCV7 are benefiting from herd immunity. Herd immunity occurs when vaccinated persons in a population indirectly protect unvaccinated members by impeding the transmission of the infectious agent in the population. Although the exact mechanism of herd immunity is uncertain, one hypothesis is that vaccinated children are less likely to have nasal carriage of pneumococcus and hence have less pneumococcal transmission to their contacts.²⁷

Other potential explanations for the decrease in IPD should be considered. Changes in the diagnosis or treatment of infectious diseases in infants are unlikely to account for the change in IPD rates. Although rates of early onset group B streptococcal infections have decreased with the incorporation of intrapartum antimicrobial prophylaxis into routine practice in the 1990s, rates of neonatal infections due to *E coli* and *Enterococcus* have remained stable, rather than declining, as would be expected if the diagnosis or treatment of infectious diseases accounted for the change in IPD.²⁸ Although guidelines for the evaluation of infants who are febrile have not changed, physician awareness of the decrease in IPD with PCV7 introduction may have influenced practice patterns, such as obtaining blood cultures. However, if fewer blood cultures explained this difference, we would expect a much greater decrease in isolated bacteremia compared with meningitis, which we did not observe. It is also possible that the decrease in the incidence of IPD after the peak in 1999-2000 might reflect regression to the mean; however, the similar decreases in rates of IPD among adults and persons older than 2 years since the introduction of PCV7 make this explanation less likely.²⁹ Finally, secular trends may have contributed, but this is unlikely given that PCV7 serotypes had been increasing over the past decades.³⁰

Several studies have demonstrated that black individuals have historically had higher rates of IPD than white individuals, but the reason for this difference is unclear.³¹,³² Recently, disparate rates in IPD have been reported to have narrowed between black and white individuals since PCV7 licensure in 2000 for children aged 2 to 23 months.³⁶,³³ Similarly, we found that the racial differences in the rates of IPD between white and black infants

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**Table 2. Number of Cases of Invasive Pneumococcal Disease by PCV7 and Non-PCV7 Serotype Before and After PCV7 Introduction, Beginning in July 1998**

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<tr>
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Abbreviation: PCV7, heptavalent pneumococcal conjugate vaccine.

*There are 2 pre-PCV7 years and 3 post-PCV7 years.

**Figure 3. Rates of Invasive Pneumococcal Disease Caused by PCV7 and Non-PCV7 Serotypes in Neonates and Young Infants Aged 0 to 90 Days by Study Year**

PCV7 indicates heptavalent pneumococcal conjugate vaccine. Error bars indicate SE. The pre-PCV7, post-PCV7, and transition study years extend from July 1 of the first year to June 30 of the last year.
aged 0 to 90 days have been eliminated following PCV7 introduction. One possible explanation for the greater decrease in rates among black infants is that their higher rates of disease during the pre-PCV7 years may have been due to higher rates of transmission, perhaps due to environmental or genetic factors. The impact of herd immunity would be expected to be largest in settings and among groups with the highest potential for transmission.

We found that rates of IPD from PCV7 serotypes decreased, which is consistent with that reported for other age groups. Because of small numbers, we cannot exclude the possibility that this decrease could be limited to that observed in black infants. The reason for the lack of decline in IPD caused by serotypes 18C and 19F is not known. The antibody response to these 2 serotypes may be less vigorous than to the other PCV7 serotypes, which would be compatible with pneumococcal colonization data from Massachusetts. Furthermore, the isolation of a few non-PCV7 serotypes, particularly 11A, 33F, and 35B, in the post-PCV7 years but not pre-PCV7 years raises the possibility of serotype replacement.

The decrease in rates of disease was greater for nonsusceptible vs susceptible PCV7 serotypes. Although other studies have also reported a decrease in nonsusceptible IPD, we analyzed susceptible and nonsusceptible isolates by PCV7 and non-PCV7 serotypes. This discrepant reduction for susceptible and non-susceptible PCV7 serotypes may reflect limited power or a possibility of serotype replacement. The decrease in rates of disease was an important cause of IPD in neonates and young infants.

Our findings should be interpreted in light of some potential limitations. The PCV7 immunization history for infants, particularly those aged 2 months who were recommended to receive 1 dose of PCV7 as of 2000, was not obtained in our study. According to the National Immunization Survey, the estimated PCV7 coverage for infants up to 3 months increased more than 10-fold from 5.7% (95% CI, 5.2%-6.2%) in 2001-2002 to 61.0% (95% CI, 59.9%-62.1%) nationwide in 2003-2004. Because 17% of IPD cases during the pre-PCV7 and post-PCV7 years did not have serotype determination, we may have underestimated the true change in rates for PCV7 and non-PCV7 serotypes. However, it is unlikely that there was differential selection of missing isolates because characteristics of those infants with serotype determination were similar to characteristics of the total study population. Laboratory-based surveillance may underestimate the rate of IPD if cultures are not obtained or obtained after antibiotics are administered or if infants die from IPD before receiving medical care. Such events should be uncommon and are unlikely to have changed dramatically during the study period.

Our data provide further evidence that PCV7 has resulted in herd immunity because neonates and young infants have had a significant decrease in IPD rates, although they are too young to receive a full series of PCV7. Continued surveillance of IPD in this and other age groups is important to determine if this trend continues or if serotypes not included in PCV7 will emerge as an important cause of IPD in neonates and young infants.

Author Contributions: Dr Poehling had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Poehling, Griffin, Whitney, Reingold, Farley, Schaffner. Acquisition of data: Poehling, Griffin, Craig, Whitney, Lexton, Thomas, Harrison, Hadler, Farley, Anderson, Schaffner. Analysis and interpretation of data: Poehling, Talbot, Griffin, Whitney, Zell, Reingold, Schaffner. Drafting of the manuscript: Poehling, Talbot, Reingold, Schaffner. Critical revision of the manuscript: Poehling, Talbot, Griffin, Craig, Whitney, Zell, Thomas, Harrison, Reingold, Hadler, Farley, Anderson. Statistical analysis: Poehling, Zell. Obtained funding: Whitney, Reingold, Farley, Schaffner. Administrative, technical, or material support: Griffin, Craig, Whitney, Thomas, Reingold, Farley, Anderson, Schaffner. Study supervision: Talbot, Griffin, Reingold, Schaffner. Financial Disclosures: Ms Zell reports that she owns stock in Merck and Pfizer. No other authors reported financial disclosures.

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References

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