Emergence of Vaccine-Related Pneumococcal Serotypes as a Cause of Bacteremia

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Background. The heptavalent pneumococcal conjugate vaccine (PCV7) has decreased the incidence of invasive pneumococcal disease among children in the United States. In the postlicensure period, the impact of non-PCV7 serotypes against pediatric pneumococcal bacteremia is unknown.

Methods. Episodes of bacteremia due to Streptococcus pneumoniae and other respiratory pathogens (ORP), namely Neisseria meningitidis, Haemophilus influenzae, and Moraxella catarrhalis, were identified in children <18 years old at the Children’s Hospital of Philadelphia from January 1999 to May 2005. For pneumococci, serotype distribution and antibiotic resistance were compared.

Results. A total of 188 episodes of pneumococcal bacteremia and 55 episodes of ORP bacteremia were identified. By comparing data from 1999–2000 with data from 2001 to May 2005, we found that the incidence of pneumococcal bacteremia decreased by 57%. The incidence of bacteremia caused by ORPs was unchanged; 1.43 episodes (95% confidence interval [CI], 0.84–2.29 episodes) to 1.25 (95% CI, 0.88–1.71) per 10,000 emergency department visits. Vaccine serotypes caused 85% of episodes of bacteremia in 1999–2000, compared with 34% of episodes of bacteremia in 2001 to May 2005 (P < .01). The percentage of isolates nonsusceptible to penicillin increased from 25% to 39% (P < .05). The percentage of episodes of pneumococcal bacteremia caused by vaccine-related serotypes—those of the same serogroup but not of the same serotype as PCV7—increased from 6% of episodes in the prelicensure period to 35% of episodes in the postlicensure period (P < .01). Rates of serotype pneumococcal bacteremia caused by nonvaccine serotypes were not statistically different between the 2 periods.

Conclusions. The overall incidence of pneumococcal bacteremia decreased by 57% after the introduction of PCV7. During the postlicensure period, there were significant decreases in the incidence of pneumococcal bacteremia caused by vaccine serotypes; however, rates of penicillin resistance and bacteremia due to vaccine-related serotypes increased.

The heptavalent Streptococcus pneumoniae protein conjugate vaccine (PCV7) contains polysaccharide conjugates of serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. These serotypes accounted for 80%–95% of pediatric invasive pneumococcal infections in the United States in the prelicensure era, but they represent only 7 of the 90 known immunologically distinct pneumococcal serotypes [1–4]. PCV7 was licensed for use in the United States in February 2000 and was added to the routine childhood immunization schedule in October 2000 [5].

Postlicensure surveillance revealed substantial regional decreases in the incidence of invasive pneumococcal disease caused by vaccine serotypes [2, 6–11]. This success has been tempered by concerns regarding potential reduced PCV7 effectiveness in the context of reports documenting increases in colonization and infection by nonvaccine serotypes [6, 12]. The impact of conjugate pneumococcal vaccines on invasive disease caused by vaccine-related and nonvaccine serotypes remains to be determined.

The concept of cross protection derives from the antigenic similarity of the pneumococcal polysaccharide capsules of isolates from the same serogroup. The capsules of serotypes 6B and 6A, for example, differ by only 1 bond [13]. Therefore, immunization with serotype 6B may confer protection against serotype 6A.
The degree of immunity afforded to patients in the clinical setting is unknown [14].

PCV7 targets the most-commonly drug-resistant pneumococcal serotypes, which account for 78% of all penicillin-resistant strains from the prelicensure era. Studies have demonstrated a decrease in the prevalence of penicillin-resistant isolates in the postlicensure period, up to the year 2003 [6, 8, 15]. However, reports of increases in antibiotic resistance among the more prevalent nonvaccine serogroups in the postlicensure era have begun to emerge [7, 16]. The objectives of this study were to compare incidences of pneumococcal bacteremia, serotypes causing bacteremia, and antimicrobial susceptibility patterns in the periods before and after PCV7 licensure.

METHODS

Study setting and design. This study was conducted at the Children’s Hospital of Philadelphia (CHOP), a large, urban, tertiary-care children’s hospital. This was a quasi-experimental study of a cohort of children who were 2.5 months to 17 years old who had a blood culture at CHOP between 1 January 1999 and 31 May 2005. We used a 1-group pretest-posttest study design with a nonequivalent dependent variable [17]. The primary variable was bacteremia caused by *S. pneumoniae*. The nonequivalent dependent variable—bacteremia caused by other respiratory pathogens (ORPs)—was chosen because these bacteria are presumed to have similar potential causal and confounding variables, except for the effect of PCV7. Incidences of bacteremia were calculated per 10,000 emergency department visits, because bacteremia caused by *S. pneumoniae* and by ORPs are typically of community rather than of nosocomial origin. The study received institutional review board approval.

Study definitions. Patients were defined as having bacteremia caused by an ORP if *Neisseria meningitidis*, *Haemophilus influenzae*, or *Moraxella catarrhalis* was isolated from a blood culture. For *S. pneumoniae*, vaccine (VT) serotypes were defined as serotypes found in PCV7 (i.e., 4, 6B, 9V, 14, 18C, 19F, and 23F). VT-related serotypes were defined as isolates of the same serogroup but not of the same serotype as those in PCV7 (i.e., 6A, 9 non-V, 18 non-C, 19 non-F, and 23 non-F). Non-VT serotypes were defined as all other serotypes. The prelicensure period was defined as 1 January 1999 to 31 December 2000, a period before and during implementation of PCV7 immunization. The postlicensure period was defined as 1 January 2001 to 31 May 2005.

Study protocol and data collection. Patients were identified using microbiology laboratory records. Patients with growth of *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, or *M. catarrhalis* in blood cultures performed during the study period were included. Multiple positive culture results from the same patient were counted as a single episode if the results were obtained within 7 days of each other.

All patients, including patients transferred from other institutions, had blood culture results obtained in the emergency department, and these results were processed as described elsewhere [18]. The criteria used by clinicians to perform blood cultures in the emergency department did not change during the study period, although the exact frequency with which they were performed for febrile children was unknown.

Pneumococcal serotypes were determined on the basis of capsular swelling with type-specific antisera (Statens Serumin-stitut) and were reported using the Danish nomenclature. Antimicrobial susceptibility testing was performed in accordance with procedures recommended by the 2005 Clinical and Laboratory Standards Institute [19]. MICs were determined for isolates with E-test strips (AB BioDisk) for penicillin, meropenem, cefotaxime, ceftriaxone, trimethoprim-sulfamethoxazole, and vancomycin.

For all patients, the following information was collected: sex; patient age at time of blood culture; blood culture result; and serotype and antibiotic susceptibility profile of *S. pneumoniae* for patients from whom the organism was isolated. We did not collect information regarding vaccination status from emergency department records, because parental reporting of children’s vaccination status has poor sensitivity and specificity [20].

Statistical analysis. Data were analyzed with STATA software, version 8.0 (Stata). Continuous demographic and outcome variables were summarized using mean and range values if the data were normally distributed and by median and interquartile range (IQR) values if the data were not normally distributed. Binary variables were summarized by proportions and corresponding binomial exact 95% CIs. Age for infected patients was compared in the prelicensure period versus the postlicensure period using the Wilcoxon rank-sum test. Sex was compared using the χ² test.

We initially evaluated annual incidences of *S. pneumoniae* bacteremia using a χ² test for trend, which is similar to other studies [6, 7]. The χ² test assumes that the annual incidences follow a linear pattern, and it allowed us to determine whether the annual incidences generally increased or decreased over the study period. We also fit log-linear models to examine nonlinear annual fluctuations in the incidences of bacteremia [21]. This model does not assume that the changes in bacteremia over time are linear; thus, it permits more-robust interpretation of annual fluctuations.

In other analyses, the Pearson χ² test was used to compare the proportion of bacteremia episodes in the prelicensure and postlicensure periods, by VT, VT-related, and non-VT serotypes. Similar tests were used to compare the proportion of infected patients in the 2 groups who had non-antibiotic-sus-
Table 1. Comparison of incidences of pneumococcal bacteremia caused by a vaccine serotype, a vaccine-related serotype, and nonvaccine serotype before and after the introduction of heptavalent pneumococcal conjugate vaccine (PCV7).

<table>
<thead>
<tr>
<th>Organism</th>
<th>Incidence of pneumococcal bacteremia (95% CI)</th>
<th>Relative risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before introduction of PCV7</td>
<td>After introduction of PCV7</td>
<td></td>
</tr>
<tr>
<td>Other respiratory pathogens</td>
<td>1.43 (0.84–2.29)</td>
<td>1.25 (0.88–1.71)</td>
<td>0.96 (0.80–1.14)</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine serotype</td>
<td>6.33 (4.98–7.93)</td>
<td>1.15 (0.80–1.59)</td>
<td>0.44 (0.34–0.58)</td>
</tr>
<tr>
<td>Vaccine-related serotype</td>
<td>0.42 (0.14–0.98)</td>
<td>1.15 (0.80–1.59)</td>
<td>1.21 (1.08–1.37)</td>
</tr>
<tr>
<td>Non-vaccine serotype</td>
<td>0.76 (0.35–1.44)</td>
<td>0.92 (0.61–1.32)</td>
<td>1.05 (0.87–1.26)</td>
</tr>
<tr>
<td>All serotypes</td>
<td>7.51 (6.03–9.24)</td>
<td>3.25 (2.64–3.95)</td>
<td>0.73 (0.64–0.84)</td>
</tr>
</tbody>
</table>

**NOTE.** Incidences presented as rate per 10,000 emergency department visits.

* One isolate in this group was untypeable.

** Relative risk of bacteremia during the postvaccine period compared with the prevaccine period.

* By the χ² test.

RESULTS

**Demographic characteristics.** A total of 188 children with pneumococcal bacteremia were identified, with 89 episodes occurring in the prelicensure period and 99 episodes occurring in the postlicensure period. Fifty-five children (29%) were white, and 108 children (58%) were black. There were 95 male subjects (51%). The median age was 24 months (range, 2.5 months–17 years). The age difference between patients in the prelicensure group (median age, 24.0 months; IQR, 12.0–62.0 months) and patients in the postlicensure group (median age, 26.0 months; IQR, 12.0–62.0 months) was not statistically significant (P = .93). The numbers of age-specific episodes of pneumococcal bacteremia in the prelicensure period versus the postlicensure period were as follows: patients who were ≤12 months old, 27 episodes versus 25 episodes; patients who were >12 months to ≤24 months old, 13 episodes versus 18 episodes; and patients who were >24 months old, 49 episodes versus 52 episodes.

**Overall rates of bacteremia.** There was a statistically significant decrease in the incidence of pneumococcal bacteremia between the prelicensure and postlicensure periods (table 1). A total of 55 episodes of bacteremia caused by ORPs occurred; however, the rate of ORP bacteremia did not change. We explored the trend in incidences of pneumococcal bacteremia during 1999–2005 in 3 ways. First, annual pneumococcal bacteremia incidences were calculated per 10,000 emergency department visits (figure 1). The incidence decreased from 7.24 episodes (95% CI, 5.22–9.78 episodes) per 10,000 emergency department visits in 1999 to a low of 2.23 episodes (95% CI, 1.27–3.62 episodes) per 10,000 emergency department visits in 2003. Rates subsequently increased to 2.88 episodes (95% CI, 1.76–4.44 episodes) per 10,000 emergency department visits in 2004 and to 3.64 episodes (95% CI, 1.88–6.35) per 10,000 emergency department visits in 2005. Second, analysis of linear trends revealed that the relative risk of pneumococcal bacteremia decreased by 0.81 (95% CI, 0.75–0.88) per year on average from 1999 to 2005, whereas the risk was unchanged for ORP bacteremia (relative risk, 0.98; 95% CI, 0.85–1.29). Third, annual relative risks of bacteremia were calculated by comparing the overall risk of *S. pneumoniae* bacteremia for each year with the risk of bacteremia for 2000 (figure 2).

**Serotype-specific rates of bacteremia.** In the postlicensure...
period, there was a statistically significant decrease in the incidence of VT bacteremia and an increase in the incidence of VT-related bacteremia (table 1). Changes in the incidence of non-VT bacteremia were not statistically significant. Annual incidences of bacteremia related to PCV7 were explored in 2 ways (figure 3). First, the overall linear trend revealed that the relative risk of VT bacteremia decreased on average by 0.60 (95% CI, 0.53–0.68; P < .001) per year from 1999 to 2005. The relative risk of VT-related bacteremia increased by 1.19 (95% CI, 1.001–1.413; P = .048) on average per year from 1999–2005. For non-VT bacteremia, the relative risk remained the same at 1.05 (95% CI, 0.88–1.25; P = .586).

Second, annual incidences of bacteremia were compared year to year. For VT-related serotypes, the incidence of bacteremia increased from 0.17 episodes (95% CI, 0–0.92 episodes) in 2000 to an incidence of 1.30 (95% CI, 0.59–2.46) in 2004. The relative risk of pneumococcal bacteremia caused by VT-related serotypes was greater in 2003 and 2004, compared with the risk in 2000 (table 2). Compared with the risk in 2000, the risk of VT bacteremia was significantly lower each year from 2001 to 2005. The risk for non-VT bacteremia was unchanged across all years, when compared with the risk in 2000 (table 2).

Specific serotypes accounting for bacteremia are shown in table 3. Numbers of all VT serotypes decreased in the postlicensure period, except for 19F, which increased in number, and 18C, which contributed equally to both groups. For VT-related serotypes, 19A showed the greatest increase in number (1 isolate in the prelicensure period vs. 20 isolates in the postlicensure period), followed by 6A and 23B. Serotype 15B (2 isolates) was the most common non-VT serotype in the prelicensure period. In the postlicensure period, 7F and 22F were the most common non-VT serotypes, with 4 isolates of each serotype, followed by serotypes 3 and 33F, with 3 isolates each.

**Antibiotic resistance patterns.** Overall, 60 (32%) of 187 isolates were not susceptible to penicillin, and susceptibilities for 1 isolate were not known. Thirty-six (19%) of 187 isolates were not susceptible to penicillin and cefotaxime, and 19 (10%) were not susceptible to cefotaxime and meropenem. The relative risk of antibiotic nonsusceptibility for penicillin and trimethoprim-sulfamethoxazole was higher in the postlicensure period than in the prelicensure period (table 4). There was an increase in the proportion of penicillin-resistant isolates between 1999–2005 (P = .019, by 1-tailed Cochran-Armitage test for trend) (figure 4A and 4B). The proportion of cefotaxime-resistant isolates did not change significantly over time (P = .22, by 1-tailed Cochran-Armitage test for trend). There were no vancomycin-resistant organisms.

**DISCUSSION**

We documented a significant decrease in the incidence of pneumococcal bacteremia after the introduction of PCV7 among children presenting to an emergency department serving the
Table 2. Comparison of 95% CIs and relative risks (RRs) associated with pneumococcal bacteremia caused by heptavalent pneumococcal conjugate vaccine serotype, a vaccine-related serotype, and a nonvaccine serotype, by year.

<table>
<thead>
<tr>
<th>Year</th>
<th>Vaccine serotype</th>
<th>Vaccine-related serotype</th>
<th>Nonvaccine serotype</th>
<th>Cause of pneumococcal bacteremia, RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>0.78 (0.49–1.23)</td>
<td>4.17 (0.47–37.32)</td>
<td>2.09 (0.52–8.34)</td>
<td></td>
</tr>
<tr>
<td>2000a</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>0.38 (0.22–0.67)</td>
<td>5.82 (0.70–48.24)</td>
<td>1.94 (0.49–7.76)</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>0.19 (0.09–0.38)</td>
<td>6.23 (0.77–50.67)</td>
<td>1.78 (0.45–7.12)</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>0.02 (&lt;0.01 to 0.14)</td>
<td>7.58 (0.96–59.86)</td>
<td>1.69 (0.42–6.74)</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>0.12 (0.05–0.29)</td>
<td>7.84 (0.99–61.86)</td>
<td>1.16 (0.26–5.19)</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>0.09 (0.02–0.35)</td>
<td>7.33 (0.82–65.62)</td>
<td>3.67 (0.92–14.66)</td>
<td></td>
</tr>
</tbody>
</table>

* Reference.

Philadelphia area. This decrease was a result of a reduced incidence of VT bacteremia during the postlicensure period. Despite the overall reduction in the incidence of *S. pneumoniae* bacteremia, both the incidence of VT-related bacteremia and the proportion of penicillin-resistant isolates increased in the postlicensure period.

The only VT serotype that increased in frequency between the prelicensure and postlicensure periods was 19F. The reasons for this change are not clear, because the vaccination status of the patients in our study was not known. A recent study suggested that PCV7 provided poor protection against postvaccination nasal colonization with serotype 19F [12]. Vaccine failure against serotype 19F has also been reported [1].

A shift in the serogroups causing invasive pneumococcal disease has occurred since the introduction of PCV7 [7]. Data regarding serotype changes, however, remain to be determined. A study in northern California documented no change in the incidence of invasive disease caused by non-VT serotypes but showed a 69.7% reduction in the incidence of VT-related serotype invasive disease among children <5 years old when comparing data collected between April 2002 and March 2003 with data collected during the 4-year prelicensure period [8]. However, VT-related serotype 19A was responsible for 7 of 9 episodes of VT-related invasive disease in vaccinated children. More recently, Pai et al. [22] reported a ∼2.5-fold increase in the incidence of invasive pneumococcal disease caused by serotype 19A that began 3 years after licensure. In our study, serotype 19A caused many more infections during the postlicensure period than during the prelicensure period.

Replacement of serotypes may occur in 3 ways: (1) by replacement of previous PCV7 carriage with serotypes unaffected by vaccine immunity [23]; (2) by the unmasking of previous minority strains (standard culture methods of nasopharyngeal specimens detect only the majority strains; once PCV7 serotypes have been eradicated after vaccination, minority strains experience a selective advantage); and (3) by serotype switch, in which pneumococcal strains express a new capsular serotype, which may occur to evade host immunity [24]. The ability of *S. pneumoniae* to undergo genetic transformation has been demonstrated both in vitro and in vivo [25, 26]. Acquisition of a new serotype may provide the transformant with an advantage against the immune system of the host, potentially changing the clinical epidemiology of invasive pneumococcal disease [16].

The concept of cross protection allows for the prediction that PCV7 recipients possess immunity against VT-related serotypes. Murine and human data, however, have demonstrated variable changes in detectable antibody titers and opsonophagocytic activity for VT-related serotypes 6A and 19A after administration of conjugate vaccines containing 6B and 19F [27–29]. These cross-protective responses are more variable and, when present, less robust in experimental models than are responses to vaccine serotypes 6B and 19F. In clinical practice, the degree of cross protection against invasive disease is not completely understood. We report a significant increase in the incidence of VT-related serotype bacteremia in the period after the introduction of PCV7, with serotypes 19A and 6A accounting for 83% of episodes. Possible explanations include marginal cross protection, serotype replacement, and the acquisition of resistance against serotypes 6B and 19F.

Table 3. Serotypes of isolates collected from children with *Streptococcus pneumoniae* bacteremia at the Children’s Hospital of Philadelphia.

<table>
<thead>
<tr>
<th>Pneumococcal serotype</th>
<th>Year of isolate collection</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1999–2000 ( (n = 89) )</td>
<td>2001–2005a ( (n = 99) )</td>
</tr>
<tr>
<td>Vaccine serotype</td>
<td>14</td>
<td>6B</td>
</tr>
<tr>
<td></td>
<td>22 (25)</td>
<td>13 (15)</td>
</tr>
<tr>
<td></td>
<td>5 (5)</td>
<td>8 (8)</td>
</tr>
<tr>
<td></td>
<td>27 (14)</td>
<td>21 (11)</td>
</tr>
<tr>
<td>Vaccine-related serotype</td>
<td>19A</td>
<td>6A</td>
</tr>
<tr>
<td></td>
<td>1 (1)</td>
<td>3 (3)</td>
</tr>
<tr>
<td></td>
<td>20 (20)</td>
<td>11 (11)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of isolates.

a Through 31 May 2005.
b One isolate was nontypeable.
c Twenty-three non-F isolates were 23A \( (n = 1) \) and 23B \( (n = 2) \).
Table 4. Relative risk of antibiotic-nonsusceptible pneumococcal isolates before and after the introduction of heptavalent pneumococcal conjugate vaccine (PCV7).

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Before the introduction of PCV7 (n = 89)</th>
<th>After the introduction of PCV7 (n = 99)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>25</td>
<td>39</td>
<td>1.34 (1.03–1.75)</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>18</td>
<td>29</td>
<td>1.31 (1.00–1.73)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>9</td>
<td>17</td>
<td>1.35 (0.99–1.84)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>12</td>
<td>13</td>
<td>1.04 (0.70–1.54)</td>
</tr>
</tbody>
</table>

NOTE. Data are % of isolates. TMP-SMX, trimethoprim-sulfamethoxazole.

virulence factors by VT-related serotypes. In 2005, the incidence of non-VT bacteremia also increased in our study. In the postlicensure period, serotypes 7F and 22F accounted for 29% of non-VT serotypes and, with the addition of serotypes 3 and 33F, these 4 serotypes accounted for 50% of episodes of non-VT serotype bacteremia. Additional surveillance of serotypes causing invasive pneumococcal disease may assist in understanding the importance of these changes.

Changes in antibiotic susceptibility patterns are also a concern for the postlicensure period. In Tennessee, the percentage of non–penicillin-susceptible isolates decreased from 59.8% to 30.4% between 1999 and 2002 in children <2 years old [15]. In the intermountain west, the percentage of isolates resistant to penicillin decreased from 34% in 1997–2000 to 22% in 2001–2003 [6]. In northern California, the percentage of isolates with high-level resistance to penicillin decreased from 15% to 5% between 2000 and 2003 [8]. By contrast, no change in penicillin nonsusceptibility was observed in Arkansas, when data from 1998–2000 was compared with data from 2001–2003 [10]. Eight children’s hospitals in the United States demonstrated that penicillin nonsusceptible isolates increased slightly among non-VT serotypes in the years 2001 and 2002, compared with 1994–2000 [7]. In our study, through May 2005, the prevalence of both penicillin and trimethoprim-sulfamethoxazole nonsusceptibility increased.

This study has several limitations. There are no data regarding the vaccine status of our patients. Therefore, we cannot be certain that factors other than the introduction of PCV7 were not responsible for our findings. Other studies have reported rates of invasive pneumococcal disease and vaccination status without addressing the issue of confounders, which is inherent in any cross-sectional study. Confounding cannot be underestimated, because a cross-sectional study cannot attribute causality. Using a quasi-experimental study design, we found no change in bacteremia due to ORPs, suggesting that the decrease in the incidence of pneumococcal bacteremia was unlikely to be caused by factors other than PCV7. Although it is a useful approach, designating ORP as the nonequivalent dependent variable does have its own limitations. For example, functionally asplenic patients, such as patients with sickle-cell disease, are more likely to experience bacteremia caused by *S. pneumoniae* than bacteremia caused by an ORP. Interventions other than PCV7 that disproportionately affected asplenic patients could also account for the decreased incidence of *S. pneumoniae* bacteremia and the unchanged incidence of ORP bacteremia. However, such an intervention would not necessarily explain the serotype changes observed in our study. Immunization rates were also affected during the study period. From December 2001 to early 2003, there was a national shortage of PCV7 that necessitated vaccine rationing [30, 31]. During this time period, the percentage of 19–35-month-old children who received ≥3 vaccinations decreased from 59.8% to 30.4% (95% CI: 1.03–1.75).
doses of PCV7 in Philadelphia was above the national average: 50% vs. 41% in 2002, 77% vs. 68% in 2003, and 86% vs. 73% in 2004 [32].

Misclassification bias would occur if blood culturing practices changed during the study period. If a blood culture was performed less frequently for febrile children after the introduction of PCV7, children with occult bacteremia may not have been identified as having bacteremia, unless they developed a suppurative complication. Such bias would cause us to underestimate the rates of S. pneumoniae bacteremia after vaccine administration. However, the incidence of occult bacteremia decreased prior to the introduction of PCV7, resulting in blood cultures being performed less frequently at our institution, even before PCV7 was introduced [18]. Hence, we assume that the year-to-year variation was negligible. The generalizability of a single center’s experience warrants cautious interpretation, because rates of invasive pneumococcal disease and serotype frequency vary geographically [33].

In summary, we document a decrease in the incidence of pediatric pneumococcal bacteremia in the Philadelphia area after the introduction of PCV7. However, the incidence of bacteremia caused by VT-related S. pneumoniae and the prevalence of penicillin resistance increased during the same period. Continued surveillance of invasive pneumococcal serotypes is important to fully understand the impact of PCV7 and to define whether such changes merit alteration of the composition of the conjugate vaccine. The magnitude of cross protection against invasive disease caused by VT-related serotypes warrants additional study.

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