Serotype Prevalence of Occult Pneumococcal Bacteremia

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ABSTRACT. Objective. The licensure and use of a pneumococcal conjugate vaccine that is immunogenic in children who are younger than 2 years may affect the epidemiology of occult bacteremia. This study was conducted to determine the serotype prevalence of *Streptococcus pneumoniae* isolates from children with occult bacteremia and to document the proportion that would be covered by the recently licensed heptavalent pneumococcal conjugate vaccine.

Methods. A cohort of 5901 children who were 2 to 24 months of age and had a temperature of ≥39.0°C evaluated with a blood culture at an urban tertiary care children’s hospital emergency department was studied to determine the prevalence of *S pneumoniae* serotypes. Patients were excluded if their immune system was suppressed, they had a diagnosis of a focal infection, they were evaluated by lumbar puncture, they were admitted to the hospital, or they died during initial evaluation. Blood cultures were inoculated into pediatric blood culture bottles and processed using an automated carbon dioxide monitoring system. All pneumococcal isolates were serotyped on the basis of capsular swelling with type-specific antisera (Quellung reaction).

Results. The study population consisted of 5901 patients. The overall rate of occult bacteremia was 1.9% (95% confidence interval [CI] 1.5–2.3). *S pneumoniae* accounted for 92 of 111 isolates (82.9%; 95% CI: 74.6–89.4) in children with occult bacteremia. Eight pneumococcal serotypes were represented: 6A (2%), 9V (6%), 19F (6%), 18C (8%), 4 (9%), 6B (13%), 23F (15%), and 14 (42%). Serotypes 14, 6B, and 23F accounted for 69.3% (95% CI: 58.6–78.7) of typed isolates. In the cohort, 97.7% (95% CI: 92–99.7) of isolated serotypes are represented in the newly licensed heptavalent pneumococcal conjugate vaccine. The single isolated serotype that would not have been covered by the currently licensed heptavalent pneumococcal conjugate vaccine was 6A.

Conclusions. *S pneumoniae* accounts for the vast majority of bacterial pathogens in children with occult bacteremia. As indicated by the results of this study, the heptavalent pneumococcal conjugate vaccine may prevent the majority of occult pneumococcal bacteremia episodes. The 2 cases of bacteremia with a serotype that would not have been included in the vaccine both were due to serotype 6A. It has been noted that there is potential nonvaccine serotype and subgroup cross-protection (6A from 6B) afforded to children who are immunized with the heptavalent vaccine. The high potential efficacy of the heptavalent pneumococcal conjugate vaccine for strains that cause occult bacteremia in our population may have a profound effect on the treatment of children with fever without a source. There has been an alarming and rapid emergence of antibiotic-resistant pneumococcal strains. Less pressure to use broad-spectrum antibiotics, which in turn causes further antibiotic resistance, should result. Laboratory testing and hospitalization also should be reduced. The prevalence rates determined by this study may be used as baseline data for comparison of serotype rates of occult pneumococcal bacteremia after widespread use of the heptavalent vaccine. Pediatrics 2001;108(2). URL: http://www.pediatrics.org/cgi/content/full/108/2/e23; bacteremia, pneumococcal vaccine, pediatrics.

**ABBREVIATIONS.** HIB, *Haemophilus influenzae* type b; PCV, pneumococcal conjugate vaccine; CI, confidence interval.

Identifying and managing occult bacteremia in children who are younger than 2 years is an important diagnostic dilemma for pediatricians and emergency medicine physicians. Recently, it was demonstrated that the epidemiology of the causative organisms of occult bacteremia has changed as a result of the *Haemophilus influenzae* type b (HIB) vaccine.1,2 With the elimination of HIB, *Streptococcus pneumoniae* accounts for the great majority of organisms that are isolated from blood cultures of children who are at risk for occult bacteremia. With the licensure of a pneumococcal conjugate vaccine (PCV) that is immunogenic in children who are younger than 2 years, the incidence of this organism in invasive disease, acute otitis media, and pneumonia also may change drastically.3,4 However, the currently licensed heptavalent PCV is expressly immunogenic for only 7 of the possible 90 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F).5,6 Previous studies of children of all ages, in inpatient and outpatient settings, and without regard to underlying medical conditions showed that serotypes included in the PCV account for 80% to 95% of all systemic pneumococcal infections.7,8 However, there has not been a previous report of the *S pneumoniae* serotype prevalence in a population specifically at risk for occult bacteremia. We report the serotype prevalence of *S pneumoniae* isolates from 5901 children who were at risk for occult bacteremia and the proportion that would have been covered by the recently licensed heptavalent PCV.

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Methods
The methods for this retrospective cohort study, involving 5901 children who were 2 to 24 months of age and had a temperature of $\geq 39.0^\circ C$ evaluated with a blood culture at an urban tertiary care children’s hospital emergency department between February 1993 and June 1996, were described previously. Standard practice during the study period was to obtain blood cultures on children who were 2 to 24 months of age and had a temperature of $\geq 39.0^\circ C$. Patients were excluded if their immune system was suppressed, they had a diagnosis of a focal infection, they were evaluated by lumbar puncture, they were admitted to the hospital, or they died during initial evaluation. The institutional review board approved this study.

Blood cultures were obtained by ED nurses using sterile techniques and inoculated into pediatric blood culture bottles (Pediacult, Organon Teknika Corporation, Durham, NC). A single bottle containing supplemented brain-heart infusion broth with 0.02% sodium polyanethol sulfonate was inoculated for each blood culture ordered. A minimum of 0.5 mL and a maximum of 4 mL are recommended by the manufacturer (Organon Teknika Corporation, Durham, NC). Standard procedure in the ED was to inoculate 0.5 to 1.0 mL. The microbiology laboratory used the BacT/Alert Microbial Detection System to process all blood cultures. Bottles that were identified as positive were removed immediately from the instrument and, an aliquot was taken for Gram stain and subculture. Bacterial isolates were identified by conventional procedures. All pneumococcal isolates were serotyped on the basis of capsular swelling with type-specific antisera (Quellung reaction). The antisera were purchased from Statens Seruminstitut (Copenhagen, Denmark), and serotypes were reported with the use of the Danish nomenclature. Pneumococcal isolates were susceptibility tested according to the procedures recommended by the National Committee for Clinical Laboratory Standards. Minimum inhibitory concentrations end points were determined for the isolates with the use of commercially available E-Test strips (AB Biolabs, Solna, Sweden) for penicillin, meropenem, cefotaxime, ceftriaxone, trimethoprim-sulfamethoxazole, and vancomycin. The minimum inhibitory concentrations end points were determined, and results were interpreted following the national committee’s guidelines.

Statistical Methods
Discrete variables were described using counts and percentages, with binomial exact 95% confidence intervals (CIs).

Results
The study population consisted of 5901 patients. The rate of occult bacteremia was 1.9% (95% CI: 1.5–2.3). Of the 111 cultures that were positive for pathogenic bacteria, 92 grew S pneumoniae. Other pathogenic bacteria isolated included Salmonella species (5.4%), Group A streptococci (4.5%), Enterococcus species (1.8%), Moraxella catarrhalis (1.8%), Escherichia coli (0.9%), and Campylobacter species (0.9%). Serotypes were determined for 96% (88 of 92) of all S pneumoniae isolates. The remaining 4 isolates did not have serotype testing performed.

Table 1 presents the serotype distribution of S pneumoniae organisms that were isolated in this cohort that was at risk for occult bacteremia. The majority (69.3%) of S pneumoniae isolates were 1 of 3 serotypes (14, 6B, 23F). In the overall study cohort, 97.7% (95% CI: 92.0–99.7) had serotypes that are included in the currently licensed heptavalent PCV.

The single isolated pneumococcal serotype that would not have been covered by the heptavalent PCV was serotype 6A. The 2 cultures of this serotype became positive in <15 hours with the automated carbon dioxide monitoring blood culture system. Each 6A isolate was pan-sensitive on antibiotic resistance testing. Both patients were well on follow-up examination.

Discussion
After widespread HIB vaccination, the pneumococcus has become the most common cause of invasive bacterial disease in children in the United States. The prevalence of bacteremia in children who are 2 to 24 months of age and have a fever without a source is documented to be in the range of 2%, with pneumococcus accounting for the vast majority of bacterial pathogens (83%–92%). The magnitude of invasive pneumococcal disease in the United States is a significant public health issue. Among children who are younger than 5 years, pneumococcal infections cause an estimated 17 000 cases of bacteremia and 1400 cases of meningitis annually.

Licensure of the heptavalent pneumococcal conjugate vaccine (Prevnar; Wyeth Lederle Vaccines, Pearl River, NY) by the Food and Drug Administration this year should significantly reduce the extent of pneumococcal disease in children. The importance of prevention of invasive pneumococcal disease via vaccination is underscored by factors other than the frequency of the disease. There has been an alarming and rapid emergence of antibiotic-resistant pneumococcal strains. A recent multicenter surveillance study revealed nearly a doubling of S pneumoniae organisms that are not susceptible to penicillin and ceftriaxone over 3 years. Currently, approximately 25% of all pneumococci and 75% of nasopharyngeal isolates from children in some communities are penicillin resistant. The heptavalent PCV also may result in herd immunity by reducing carriage of vaccine serotypes, thus reducing spread of the organism. However, there have been concerns expressed over a potential increase in carriage rates of non-vaccine pneumococcal serotypes in an immunized population. A recent study of the efficacy of the PCV demonstrated a 33% increase (95% CI: −1–80) in the rate of acute otitis media attributed to non-vaccine serotypes. Therefore, ongoing surveillance after introduction of the heptavalent vaccine is prudent. Hopes for prevention of pneumococcal disease are encouraged by the success of the HIB vaccine. A 98% reduction in cases of H influenzae disease has occurred since licensure of the HIB protein conjugate vaccine. However, H influenzae invasive disease is caused principally by 1 bacterial serotype as compared with the multiple pathogenic S pneumoniae

Table 1. Distribution of Streptococcus pneumoniae Serotypes in Children 2 to 24 Months of Age With Fever $\geq 39.0^\circ C$ ($n = 88$)

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Frequency</th>
<th>Percentage (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6A</td>
<td>2</td>
<td>2.3–8.0</td>
</tr>
<tr>
<td>9V*</td>
<td>5</td>
<td>2.9–13.6</td>
</tr>
<tr>
<td>19F*</td>
<td>5</td>
<td>2.9–13.6</td>
</tr>
<tr>
<td>18C*</td>
<td>7</td>
<td>5.3–16.3</td>
</tr>
<tr>
<td>14*</td>
<td>8</td>
<td>5.4–14.2</td>
</tr>
<tr>
<td>6B*</td>
<td>11</td>
<td>6.6–21.3</td>
</tr>
<tr>
<td>23F*</td>
<td>13</td>
<td>8.4–24.3</td>
</tr>
<tr>
<td>14*</td>
<td>27</td>
<td>17.3–53.3</td>
</tr>
</tbody>
</table>

* Serotypes included in the heptavalent pneumococcal conjugate vaccine.
serotypes. The prevalence rates determined by this study may be used as baseline data for comparison of serotype rates of occult pneumococcal bacteremia after widespread use of the heptavalent vaccine.

Epidemiologic data suggest that a vaccine that includes 7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) will prevent 86% of bacteremia and 83% of meningitis caused by \textit{S pneumoniae} in children who are younger than 6 years in the US. Additionally, these 7 serotypes include 80% to 90% of penicillin-nonsusceptible and multidrug-resistant \textit{S pneumoniae}. In our study population, 98% of \textit{S pneumoniae} serotypes that cause occult bacteremia were included in the heptavalent vaccine. Serotype 14 caused the largest number of cases (42%). The 2 cases of bacteremia whose serotype would not have been included in the vaccine both were attributable to serotype 6A and both were pan-sensitive on antibiotic-resistance testing. It is interesting that it has been suggested that there is potential nonvaccine serotype and subgroup cross-protection afforded to children who are immunized with the heptavalent vaccine.\textsuperscript{3,10} Eskola et al\textsuperscript{12} noted a 57% reduction (95% CI: 24–76) in acute otitis media episodes attributed to cross-reactive serotype 6A in an immunized population.

Two studies of California Kaiser Permanente patients described the serotype etiology of pneumococci that cause invasive bacterial disease but were not limited to patients with occult bacteremia. The first study, a 1992 to 1995 prospective laboratory-based surveillance of invasive pneumococcal disease, serotyped a proportion of their positive cultures.\textsuperscript{8} The most common pneumococcal serotype for patients who were younger than 2 years in this study was type 14, which caused 26% of invasive disease. However, 22% of pneumococcal strains were not included in the proposed heptavalent vaccine, with the most common also being 6A (8%). A 1995 to 1999 investigation of the efficacy, safety, and immunogenicity of heptavalent pneumococcal conjugate vaccine in children also reported the serotypes of pneumococci that cause invasive bacterial disease.\textsuperscript{3} In this study group, 19F was the most common organism (29%), followed by type 14 (21%).

Black et al\textsuperscript{3} reported an effectiveness against invasive disease for the heptavalent PCV of 93.9% (95% CI: 79.6–98.5) in children who were randomized to receive the immunization. As suggested by our results, this overall efficacy may approximate or prove to be even greater for patients who are at risk for occult bacteremia. Serotype-specific efficacy in Black’s study ranged from 84.6% for type 19F to 100% for types 14, 18C, 23F, and 9V. These strains for which the vaccine has 100% serotype-specific efficacy in Black’s trial accounted for 71% of the cases of occult bacteremia in our report. Only 6% of cases of occult pneumococcal bacteremia were caused by type 19F, the serotype with the lowest reported serotype-specific efficacy.

Our study is limited by representing information from only 1 geographic area, as distributions of serotype prevalence and resistance patterns may vary by region of the country. However, the high potential efficacy of the heptavalent PCV for strains that cause occult bacteremia in our population may have a profound effect on the treatment of children who have fever without a source. Laboratory testing, presumptive antibiotic therapy, and hospitalization all should be reduced. Less pressure to use broad-spectrum antibiotics, which in turn causes further antibiotic resistance, should result. Although each child must be evaluated individually for immunization status, the extremely high penetrance of this vaccine since its licensure, with 5.3 million doses shipped by mid-October 2000 (personal communication with B. L. Rogers, MS, MD, Wyeth Ayerst Pharmaceuticals, October 2000), certainly will improve the outcome of children who are at risk for occult pneumococcal bacteremia and other invasive diseases caused by \textit{S pneumoniae}.

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