Epidemiology of Invasive Pneumococcal Disease in Southern California: Implications for the Design and Conduct of a Pneumococcal Conjugate Vaccine Efficacy Trial

Kenneth M. Zangwill, Constance M. Vadheim, Ann M. Vannier, Leslie S. Hemenway, David P. Greenberg, and Joel I. Ward

Population-based prospective surveillance of invasive pneumococcal disease was done in Southern California from 31 March 1992 to 1 April 1995; 814 cases were identified, for an incidence of 12.5/100,000 persons/year. The incidence among persons ≤2, ≤5, and ≥65 years of age was 145, 72, and 32/100,000, respectively. More than 95% of cases included bacteremia; incidence of meningitis was 0.8/100,000. Among children ≤2 years of age, 79% of isolates were obtained in the outpatient setting, compared with 16% of isolates among persons ≥15 years of age. Eighty percent of isolates were serotypes included in heptavalent pneumococcal conjugate vaccines currently being evaluated. Children ≤2 years of age were at highest risk of having an isolate resistant to penicillin. Among resistant isolates, high-level resistance increased from 4% to 21% over a 3-year period. Prospective epidemiologic data are needed to perform a protective efficacy trial of pneumococcal conjugate vaccines in infants, among whom most invasive pneumococcal disease is vaccine-preventable.

In both children and adults, Streptococcus pneumoniae is an important cause of serious bacterial infections, and such disease is potentially vaccine-preventable. S. pneumoniae causes a variety of serious infections, including meningitis, bacteremia, and pneumonia as well as several less serious but very common illnesses, such as otitis media and sinusitis. In the United States, S. pneumoniae causes an estimated 10%–25% of all pneumonia and 40,000 deaths annually [1].

The currently licensed pneumococcal polysaccharide vaccine is recommended for use in adults and children ≤2 years of age who are at high risk for invasive pneumococcal disease (IPD) and for adults ≥65 years of age [2]. However, these vaccines are not immunogenic among children <2 years of age and do not provide long-term immunity, presumably because of the T cell–independent nature of the immune response to polysaccharide antigens [3]. Haemophilus influenzae type b (Hib) conjugate vaccines are the prototype for T cell–dependent polysaccharide-protein conjugate vaccines. They are immunogenic and efficacious in infants and elicit booster responses with repeat dosing, thus providing a theoretical basis for the use of pneumococcal conjugate vaccines. The dramatic reduction of invasive Hib disease in vaccinated children [4, 5] further underscores the potential usefulness of pneumococcal conjugate vaccine (PCV). Safety and immunogenicity trials with these vaccines are underway [6, 7], and soon large-scale efficacy trials will be conducted to evaluate protection against disease.

Over the past 5 years, there has been an increasing number of reports of pneumococci with high-level resistance to penicillin and cephalosporins as well as multidrug resistance [8, 9]. In some areas of the United States, >50% of pneumococcal nasopharyngeal isolates [10] and 25% of invasive isolates [11] exhibit intermediate or high-level resistance to penicillin. These data have led to revised guidelines regarding appropriate empiric treatment of presumed pneumococcal infections [12] and highlight the importance of disease prevention by vaccination.

A clearer understanding of the epidemiology of pneumococcal disease will have direct impact on the development and evaluation of PCVs. Few prospective, population-based studies of the epidemiology of all invasive pneumococcal disease have been reported in the United States. Here we describe results of an epidemiologic investigation in a large health maintenance organization population intended to characterize the incidence and other epidemiologic features of IPD in all age groups, determine the serotype distribution of IPD, determine the antimicrobial susceptibility patterns of S. pneumoniae, and assess the feasibility of conducting a PCV efficacy trial designed to evaluate protection against invasive disease.

Methods

Epidemiology. We did prospective, laboratory-based surveillance for IPD in the Kaiser Permanente Southern California Region.
(KPSCR) from 1 April 1992 through 31 March 1995. The KPSCR serves >2.2 million persons in eight contiguous Southern California counties (Los Angeles, San Diego, San Bernardino, Imperial, Kern, Ventura, Riverside, and Orange) with ~29,000 newborns per year. All microbiologic specimens are processed through a single centralized microbiology laboratory. We defined a case of IPD as a positive culture from a normally sterile body site (blood, cerebrospinal fluid, other tissue aspirates). We did not include cases of pneumonia or positive sputum cultures unless there was concomitant bacteremia or a positive culture from the pleural fluid. Complete reviews on all available inpatient and outpatient charts using a standardized questionnaire were completed by trained reviewers. In addition, the presence of underlying conditions was evaluated with the use of discharge codes from the International Classification of Disease, Ninth Revision. Total, age-specific, and disease-specific population denominators (for specific underlying conditions) were provided by the KPSCR.

**Laboratory.** *S. pneumoniae* were identified at the KPSCR Regional Laboratories according to the standards of the National Committee for Clinical Laboratory Standards (NCCLS) using colony morphology, ethylhydrocuprein (optochin) susceptibility, and bile solubility. We serotyped invasive clinical isolates for children <10 years of age by the Quellung method and report results here with the Danish system of nomenclature. Antimicrobial susceptibility testing was done at the KPSCR according to the methods recommended by the NCCLS. Beginning in April 1993, all pneumococcal isolates noted to be resistant by 1-μg oxacillin disk testing (zone of inhibition <20 mm) were evaluated for penicillin MICs, and beginning July 1993, isolates were also tested for susceptibility to cefotaxime and vancomycin by the broth microdilution method. Antimicrobial resistance to each drug was defined using the proposed NCCLS break points [13] as follows (MIC in μg/mL): penicillin ≥0.12 (≥2 highly resistant), cefotaxime ≥0.5 (≥2 highly resistant), vancomycin >1. After August 1994, we determined penicillin, cefotaxime, and vancomycin MICs using the Epsilometer test (E test) [14].

**Data analysis.** Annualized, age-specific incidence rates are reported as number of cases per 100,000 population or 1000 live births, as appropriate. Relative risks and means were evaluated using SAS statistical software [15].

**Results**

**Descriptive epidemiology.** During the surveillance period, we identified 814 cases of IPD, an annual incidence of 12.5/100,000 population. The incidence among persons ≤2, ≤5, and ≥65 years of age was 145, 72, and 32/100,000 population, respectively (figure 1). The incidence of IPD increased 12% between the first and second years of the surveillance period, primarily among children 7–12 months of age (37% increase) and adults ≥65 years old (77% increase). Between the second and third years of the surveillance period, children ≤5 years of age had a 35% increase in incidence of IPD; there was a slight decline among adults ≥65 years of age. Neonates (infants ≤30 days of age) accounted for only 3 cases (0.4%), an annualized incidence of 0.04/1000 live births/year.

Among 511 patients for whom data were available, 267 (52%) were white, 139 (27%) were black, and 71 (14%) were Hispanic. This differs substantially from the racial/ethnic distribution among the general KPSCR membership (~35% white, 13% black, 45% Hispanic). The incidence of disease was similar among males (13.3/100,000) and females (11.9/100,000; relative risk [RR] = 1.1, 95% confidence interval [CI] = 0.9–1.4). Neither the sex nor the racial/ethnic distribution differed substantially by age. A seasonal distribution was evident; cases clustered from November to April and peaked during December to February.

In all age groups, the incidence of nonmeningeal disease (bacteremia) was substantially higher than for meningitis alone. The annualized overall incidence of meningitis was 0.8/100,000 population (figure 1); the highest incidence was among children ≤6 months of age (21/100,000 population). The incidence of meningitis among children ≤2 years of age was significantly higher than among adults ≥65 years old (10.3 vs. 0.9/100,000 population; RR = 13.1, 95% CI = 2.8–62). The incidence of pneumonia with bacteremia was 6/100,000 population. Children ≤2 years of age and adults ≥65 years of age were significantly more likely to be diagnosed with bacteremic pneumonia than were persons 2–65 years of age (RR = 4.7, CI = 2.4–9.0 and RR = 7.0, CI = 4.8–10, respectively).

Of 741 cases for which outcome information was available, 59 (8.0%) resulted in death, an annualized incidence of death due to IPD of 0.9/100,000 population. Among infants ≤2 years of age and adults ≥65 years of age, 1.4% and 15.6% died of IPD, respectively. Forty-seven percent of all deaths occurred in adults ≥65 years of age, and death was more likely to occur in this age group than in those ≤2 years of age (RR = 11.4, 95% CI = 3.5–37). Overall, the presence of pneumonia substantially increased the likelihood of death, but the majority of these deaths were among older adults. The presence or absence of meningitis did not increase the likelihood of death. There was no difference in mortality rate by sex or race.

Overall, 359 (44%) of 814 patients were identified as outpatients. Among children ≤2 years of age, 199 (79%) of 253 isolates were from outpatients. In contrast, only 72 (16%) of 449 isolates from patients ≥15 years of age were obtained in the outpatient setting.

**Clinical presentation.** A wide range of clinical diagnoses were noted among patients with IPD. Of 814 cases identified, 796 (98%) were bacteremic. Fifty-three patients (6.5%) had meningitis, 44 (83%) of whom were also bacteremic (table 1). Other diagnoses included pneumonia (47%), otitis media (6.8%), arthritis (2.5%), and cellulitis (2.7%). The distribution of clinical presentations did not differ by year or sex. We identified 3 neonatal cases; all patients were bacteremic, 2 had pneumonia, 0 had meningitis, and 1 died.

We identified 10 persons with more than one episode of IPD during the surveillance period. Nine had two episodes and 1
had four episodes; all survived. The latter child was an 11-year-old boy with recurrent meningitis, who had no known risk factors for IPD. The demographic and clinical characteristics and distribution of underlying conditions among these patients did not differ from the rest of the cohort. Forty-six percent of cases had at least one underlying condition before development of IPD, particularly among older adults (table 2). The most common conditions included chronic respiratory and cardiac diseases, immunosuppressive drug use, and diabetes mellitus. The incidence of IPD among human

**Table 1.** Invasive pneumococcal disease: clinical presentation, by age.

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Incidence* (no. of cases) in age group</th>
<th>Mortality* in age group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All ages</td>
<td>≤2 years</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>13 (796)</td>
<td>143 (249)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6 (385)</td>
<td>17 (29)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>0.8 (53)</td>
<td>10 (18)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>0.9 (55)</td>
<td>20 (34)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>&lt;1 (20)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>&lt;1 (22)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>&lt;1 (5)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>&lt;1 (10)</td>
<td>&lt;1 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>13 (814)</td>
<td>145 (253)</td>
</tr>
</tbody>
</table>

* Per 100,000 population per year.

* Several cases had >1 clinical diagnosis.
Table 2. Frequency of underlying conditions before development of invasive pneumococcal disease.

<table>
<thead>
<tr>
<th>Condition*</th>
<th>≤2 years (n = 210)</th>
<th>3–14 years (n = 102)</th>
<th>15–64 years (n = 234)</th>
<th>≥65 years (n = 174)</th>
<th>All ages (n = 720)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td>&lt;1</td>
<td>3</td>
<td>9</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Endocrine/metabolic</td>
<td>2</td>
<td>3</td>
<td>7</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>HIV infection/AIDS</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other immunosuppression†</td>
<td>&lt;1</td>
<td>7</td>
<td>13</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Neurologic‡</td>
<td>&lt;1</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Chronic cardiac conditions§</td>
<td>&lt;1</td>
<td>0</td>
<td>4</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>Chronic lung conditions§</td>
<td>2</td>
<td>2</td>
<td>14</td>
<td>29</td>
<td>13</td>
</tr>
<tr>
<td>Acute/chronic liver disease</td>
<td>0</td>
<td>1</td>
<td>9</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Skin/collagen-vascular</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Physical anomaly</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Injury/burn</td>
<td>&lt;1</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>At least 1 of the above</td>
<td>11</td>
<td>24</td>
<td>62</td>
<td>81</td>
<td>46</td>
</tr>
</tbody>
</table>

NOTE. Data are %. HIV = human immunodeficiency virus.

* Several cases had >1 concurrent condition.
† 720 of 814 charts were available for review.
‡ Includes conditions or medications associated with immunosuppression (including sickle cell disease).
§ Includes dementia, neuromuscular disease, seizure disorder, intracranial vascular disease.
¶ Includes chronic valvular disease or rheumatic disease, arteriosclerosis, cardiomyopathy, congestive heart failure, congenital heart disease.
‖ Includes asthma, chronic obstructive pulmonary disease, pneumoconioses, pulmonary hypertension, smoking, emphysema.

immunodeficiency virus (HIV)-infected persons was 176/100,000, significantly greater than that seen in the non–HIV-infected population (OR = 6.6, CI = 3.9–11). Eighty-two percent of HIV-infected persons were 25–44 years of age, reflecting the age distribution of HIV infection at KPSR. The youngest person with IPD and HIV infection was 17 years old. The incidence of disease among children ≤5 years of age with sickle cell disease was 1.5/100 patient-years, 22-fold higher than unaffected children in this age group. The clinical presentation and case-fatality of IPD among HIV-infected and sickle cell disease cases were not different compared to the respective unaffected groups.

Overall, 10 case-patients (1%) received pneumococcal polysaccharide vaccine before development of IPD (range, 22 days–12.7 years). It is not known if these cases were due to serotypes contained in the pneumococcal vaccine. Forty-five percent of case-patients were included in target groups currently recommended to receive pneumococcal vaccine [1].

Serotype distribution. We serotyped 79 (22%) of 360 isolates among case-patients <10 years of age including the range of clinical presentations. Serotype 14 (19/79 [24%]) was the most common (table 3). Sixty-three (80%) of 79 isolates were included among the serotypes included in PCVs currently in development (6B, 19F, 23F, 18C, 4, 14, 9V, and 1 or 5). Eighty-six percent of isolates were included in the 23-valent polysaccharide vaccine.

Antimicrobial susceptibilities. From 1 April 1993 through 31 March 1996, 780 sterile site pneumococcal isolates were identified (patients with >1 isolate were only considered once). One hundred eight (14%) were resistant to penicillin. Of these,

Table 3. Invasive pneumococcal disease: serotype distribution for children <10 years of age.

<table>
<thead>
<tr>
<th>Serotype</th>
<th>≤10 years (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>23F</td>
<td>13</td>
</tr>
<tr>
<td>19F</td>
<td>16</td>
</tr>
<tr>
<td>6B</td>
<td>8</td>
</tr>
<tr>
<td>6A</td>
<td>8</td>
</tr>
<tr>
<td>9V</td>
<td>5</td>
</tr>
<tr>
<td>18C</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>19A</td>
<td>7</td>
</tr>
<tr>
<td>16A</td>
<td>2</td>
</tr>
<tr>
<td>23A</td>
<td>0</td>
</tr>
<tr>
<td>18F</td>
<td>2</td>
</tr>
<tr>
<td>23B</td>
<td>2</td>
</tr>
<tr>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td>13A</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE. Data are %.
94 (87%) were of intermediate resistance and 14 (13%) were highly resistant.

Of 83 isolates with intermediate resistance to penicillin (11 were not tested), 56 (67%) and 27 (33%) were susceptible and of intermediate resistance to cefotaxime, respectively. Of 14 isolates highly resistant to penicillin, 1 (7%) and 13 (93%) were susceptible and of intermediate resistance to cefotaxime, respectively. All isolates were susceptible to vancomycin.

Over the 3-year study period, the rate of resistance to penicillin did not change; however, among penicillin-resistant isolates, the percentage of isolates with high-level resistance (MIC ≥2 µg/mL) increased significantly from 4% to 21% (χ² for trend = 4.3, P < .04). The likelihood of resistance varied by age. Nineteen percent of isolates from children ≤2 years of age were of intermediate or high resistance to penicillin compared with 12% from persons >2 years of age (RR = 1.6, CI = 1.1–2.3). There were no regional differences in resistance to penicillin within the KPSCR.

Discussion

We performed this study to provide necessary epidemiologic information to design and conduct a PCV efficacy trial in Southern California. We found an overall annual incidence of IPD of 12.5/100,000 population, more than 95% of which was bacteremic disease. Other studies in the United States have shown a rate of pneumococcal bacteremia of 15–19 episodes/100,000 persons [16–18]. In our study population, the incidence of IPD was greatest at the extremes of life: children ≤2 years old and adults ≥65 years old. Children ≤2 years of age, an age group for which the currently available pneumococcal polysaccharide vaccines are not immunogenic, were nearly five times more likely to develop IPD than were older adults. Moreover, the incidence of disease in young children was equal to or of greater magnitude than noted with Hib disease before the widespread use of Hib conjugate vaccines. Preliminary data suggest that administration of two or three doses of PCV during the first 6 months of life induces an antibody response in infants [6]; use of an effective PCV during the first year of life, therefore, should have significant impact on the overall incidence of IPD.

Microbiologic diagnosis of pneumococcal pneumonia and occult bacteremia is problematic. The only definitive way to diagnose pneumococcal pneumonia is by lung aspirate or biopsy, procedures not commonly done. In our study, pneumococcal pneumonia was identified by a positive blood culture and chart review; however, blood culture is positive in only 5%–30% of cases [19, 20]. Our data, therefore, underestimate the true incidence of pneumococcal disease. Diagnosis of occult pneumococcal bacteremia in young children presents a different problem. The likelihood of identifying pneumococcal bacteremia in febrile children 3–36 months of age is 3%–11% [21], yet blood is often not obtained for culture since many patients are relatively well and are frequently treated empirically with antimicrobials as outpatients. Despite these limitations in identifying IPD, ascertainment of invasive site isolates in our population is high since all cultures are processed through one centralized laboratory. Prior extensive audits of this laboratory (in the context of similar epidemiologic studies of Hib disease) have shown that >95% of cases were identified by laboratory surveillance alone [22].

The burden of IPD in children ≤2 years of age in our population was considerable: They accounted for >30% of IPD cases but represent only 2.9% of the population in the KPSCR. We also found that the incidence of disease increased over time for both young children and adults ≥65 years old; this does not appear to reflect a change in clinical practice resulting in increased performance of blood cultures (data not shown). During a vaccine efficacy trial, bacterial culture remains the reference standard for identification of cases. Improvement of rapid diagnostic techniques could significantly improve case ascertainment, but currently available rapid antigen detection systems [23] and molecular probe techniques using the polymerase chain reaction [24] are not of sufficient sensitivity or widespread availability to be of substantial value. Conduct of a vaccine efficacy trial in young children will require extensive efforts to enlighten primary care providers regarding these issues and to encourage aggressive diagnostic testing in persons with suspected IPD.

Few studies have reported prospectively the incidence of IPD in young children. Risk of IPD in our population was highest among children 13–18 months of age, similar to that reported among non-natives in Alaska [25] but slightly older than seen in Israel [26], Finland [27], native Alaskans [25], and a US population evaluated in 1986 [28]. Also, all populations studied to date show low rates of disease in the neonatal period: 30- to 50-fold less than the rate of neonatal early-onset group B streptococcal disease [29] (the most common bacterial pathogen of neonates), likely due to a protective effect of maternal antibody. The age distribution of IPD in our population is slightly older than that seen with meningococcal disease nationally [28] or Hib disease [4, 30] before use of Hib vaccine. An age shift in bacteremic IPD seen later in infancy (than Hib and meningococcal disease) may reflect an extended protective effect of maternal antibody and/or earlier and greater acquisition of nasopharyngeal pneumococcal carriage during early infancy [31] with resultant development of protective antibody.

Population-based estimates of the incidence of other manifestations of IPD are limited. The rate of pneumococcal meningitis (0.8/100,000 population) is similar to rates reported previously for the United States [28, 32, 33]. Our rate of meningitis among children ≤2 years of age as well as rates from Israel [26] and Finland [27] are substantially lower than that reported in native Alaskans (79/100,000 population) [25], which reflects the very high incidence of IPD overall in that community. The age distribution of meningitic IPD, with infants <6 months of age at greatest risk, is similar to other populations, without the comparative age shift we found with bacteremic disease. Our
data provide a minimum estimate of the incidence of pneumococcal pneumonia in all age groups; older adults and young children had an increased risk of bacteremic pneumonia compared with other age groups. It is clear, however, that the majority of adults with bacteremia have concomitant pneumonia, which is clearly different from children ≤2 years of age, of whom <12% had pneumonia. Other manifestations of IPD, such as arthritis and osteomyelitis, though well-described, are less common.

Although children ≤2 years of age had the highest incidence of disease, older adults were significantly more likely to die of their disease. The presence of meningitis did not appear to affect the likelihood of death, although older adults were more likely to have pulmonary disease. The case-fatality ratio in adults in our population is about one-half of that reported in other US studies [17, 18, 28, 34, 35]. Variation in the incidence of disease and case fatality between published reports may reflect several factors, including study population differences such as socioeconomic status, varied levels of medical practice and access to medical care, or the presence of particular serious underlying conditions. Although of lesser importance, some reports of case-fatality rates in adults may be inflated due to underreporting of the proportion of cases of uncomplicated bacteremia seen in the outpatient setting (16% of cases >15 years of age in our study). This emphasizes the usefulness of population-based surveillance and the need for increased awareness among health care providers to aggressively pursue microbiologic diagnoses, a particular concern in the context of PCV efficacy trials.

As shown previously, we found that the presence of a concurrent underlying condition increased the risk for development of IPD. The likelihood of IPD in children with sickle cell disease has declined over the last 20 years [36, 37], but mortality rates in this population have not changed substantially. Despite this, rates of disease among these children remain substantially greater than among unaffected children. In the KPSCR, rates of disease among children with sickle cell disease are similar to those in previous reports [37] and reflect, in part, aggressive penicillin prophylaxis and pneumococcal vaccination campaigns. The nearly 7-fold increased risk of IPD among the HIV-positive population is slightly lower than previously reported [38, 39]. It has been suggested that declining CD4 cell counts with depressed IgM and subclass responses may predispose to increased rates of IPD in this population [40, 41]. We did not have information regarding degree of immunosuppression, antimicrobial prophylaxis, or exposure risk, yet the clinical presentation in this group was similar to the rest of the cohort, consistent with other evaluations of IPD among HIV-positive persons [38, 42]. Preliminary studies suggest that certain high-risk groups, including those with HIV infection or sickle cell anemia, respond to PCVs. Therefore, complete evaluation of the effectiveness of PCV should specifically include groups at increased risk for IPD.

To date, there are 90 known pneumococcal capsular serotypes [43], and the distribution differs by age and geographic location. Since immunogenicity of PCV is serotype-specific, the serotype composition of a given PCV must be determined with consideration given to the targeted populations and age groups. The serotype distribution in Southern California is very similar to that seen nationally [44] among children ≤2 years of age: Serotypes 14, 6B, 19F, 18C, 23F, 4, and 9V account for 80% of isolates. This differs from the serotype distribution among children from other countries [45], where serotypes 1 and 5 are more prevalent than in the United States. If there is cross-protection against serotypes with related serotypes (e.g., 6A and 6B) [46], then a conjugate vaccine containing the 7 serotypes above could potentially prevent 85% of IPD in children in the KPSCR. However, this represents <50% of serotypes in adults nationally [47, 48], suggesting a continued need for polysaccharide vaccine in adults. The PCV candidate vaccines are targeted for young children and thus should be evaluated in this population.

In our population-based study, we found that 14% of isolates were resistant to penicillin. Of these, 13% were highly resistant to penicillin, and 32% were also resistant to cefotaxime. We also found that among resistant isolates, high-level resistance to penicillin significantly increased over a 3-year period. In the United States, only one other large, population-based, multiyear assessment of drug-resistant pneumococci has been reported. A report from Alaska noted an intermediate resistance rate of 3.8% of isolates collected during 1986–1990; no isolate had high-level penicillin resistance [49]. A more recent study from metropolitan Atlanta reported an overall rate of penicillin resistance of 25% among invasive isolates collected over a 10-month period in 1994 (nearly 30% of which were highly resistant) [11]. In addition, we found higher levels of resistance among young children, though we were not able to independently assess potential confounders such as day care attendance, racial/ethnic distribution, or prior antimicrobial use in this group. Our finding of an ongoing rise in prevalence of high-level resistance to penicillin by pneumococci in the KPSCR reinforces the need to evaluate PCVs, which have the potential to significantly decrease the morbidity associated with this serious problem.

This report focuses on the epidemiology of IPD. The greatest burden of clinical illness, however, includes pneumonia and mucosal illness (sinusitis, otitis media). Surveillance for invasive disease alone, in the context of a PCV efficacy trial, may therefore significantly underestimate the overall direct clinical impact of a vaccination program. Other end points, such as otitis media or pneumonia, would ideally be considered in such a trial, but specific etiologic diagnosis is difficult; thus, estimates of protective efficacy are problematic. Other effects of vaccine use, therefore, such as decreased utilization of medical resources associated with pneumococcal disease, should be evaluated concurrently during a trial to evaluate efficacy against IPD.
Clearly, groups at high risk for IPD, including children, would benefit greatly from immunization with an effective pneumococcal vaccine. We believe that a PCV efficacy trial should target children ≤2 years of age and evaluate protection against invasive disease. It is clear from our findings that enhanced surveillance for IPD in the outpatient setting would greatly facilitate the conduct of such a trial. As such, proactive education of health care providers regarding the need for diagnostic blood cultures in febrile children and development of more sensitive rapid detection methods should be aggressively pursued. This differs sharply from studies of vaccine efficacy for other common bacterial pathogens such as Hib and Neisseria meningitidis, for which nearly all cases will ultimately result in hospitalization.

Acknowledgments

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References


