Proportion of Invasive Pneumococcal Infections in German Children Preventable by Pneumococcal Conjugate Vaccines

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The incidence and serotype distribution of Streptococcus pneumoniae as a cause of invasive diseases are unknown with regard to most European countries. From January 1997 through December 1998, population-based nationwide prospective surveillance was undertaken for invasive pneumococcal disease (IPD) in children in Germany, based on monthly independent reports from all pediatric hospitals and from clinical microbiology laboratories. On the basis of 896 reported IPD cases (including 404 with meningitis), the incidences per 105 children in different age groups were as follows: children aged <1 year, 18.9 (9.7 for meningitis); children aged <2 years, 16.0 (7.2 for meningitis); for children aged <5 years, 8.9 (3.9 for meningitis); and for children aged <16 years, 3.2 (1.4 for meningitis). The proportions of cases involving strains (304 serotyped) included in conjugate vaccines were as follows: for the 7-valent vaccine, 52%; for the 9-valent, 62%; and for the 11-valent, 71%. None of the isolates were resistant to penicillin or cefotaxime. Although the rate for meningitis is similar, other manifestations of IPD are less commonly diagnosed in Germany than in other countries. The serotype distribution only partially matched that used in the recent development of pneumococcal conjugate vaccines.

Streptococcus pneumoniae is a significant cause of meningitis and septicemia in early infancy. High case-fatality rates and proportions of serious sequelae have been reported [1–6]. In a recent trial in California, a heptavalent pneumococcal polysaccharide conjugate vaccine (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) was safe and immunogenic infants aged 2 months [7]. A first clinical trial has demonstrated 100% efficacy in preventing vaccine-type invasive pneumococcal disease (IPD) among 37,000 children [8].

The magnitude of the impact of conjugate pneumococcal vaccine, however, may vary with the pneumococcal serotype distribution in the respective population. There are 90 known capsular serotypes of S. pneumoniae, 20 of which account for ~90% of infections in humans, whereas conjugate vaccines currently under clinical investigation include at most 11 pneumococcal capsular polysaccharides. The present study was performed to evaluate the burden of IPD and the potential impact of a 7-, 9-, or 11-valent conjugate pneumococcal vaccine in Germany.

Patients and Methods

Study design. The study was based on prospective, active surveillance of IPD in the German population aged <16 years. As of 31 December 1997, the size of the population at risk was 14,025,867, according to the Federal Statistics Office, in Wiesbaden, Germany. The study period was from 1 January 1997 through 31 December 1998.

Case definition. Patients were enrolled in the study if they had been admitted to a pediatric hospital and if S. pneumoniae had been isolated from at least 1 culture of blood, CSF, or a sample from any other normally sterile body site. Isolates from middle ear fluid were not included.

Cases were identified through 2 independent surveillance systems, a hospital-based surveillance system (HSS) and a laboratory-based surveillance system (LSS). The cases were independently reported both by pediatric hospitals (420 reporting physicians), which care for almost all children with IPD treated as inpatients in Germany, and by microbiology laboratories (n = 294) on a monthly basis by means of postcards and questionnaires. A zero option was included in order to estimate participation in the surveillance system. Physicians reporting cases of IPD received a questionnaire and were asked to give additional information about the site of the infection, the outcome, and any underlying conditions such as...
asplenia, immunodeficiency, or ongoing immunosuppressive therapy. On their monthly postcards, laboratories gave information on the body site from which S. pneumoniae had been isolated and on the age of the child concerned.

All microbiology laboratories were invited to send pneumococcal strains isolated from a normally sterile body site to the German National Reference Center for Streptococci, where the species identification was confirmed and antimicrobial susceptibility testing and serotyping were performed for free.

Cases in which S. pneumoniae was isolated from CSF were categorized as meningitis, irrespective of whether other cultures (e.g., of blood) were positive. When S. pneumoniae was isolated from other body sites, cases were categorized as nonmeningitis, unless there was a positive blood culture and a physician’s diagnosis of meningitis, based on the clinical picture and the cell count in the CSF. The incidence of IPD among children in Germany was estimated by adding up all identified cases and by the 2-source capture-recapture method [9, 10]. The HSS and LSS were linked on the basis of reports by the HSS and LSS.

Microbiological investigations. Each isolate was confirmed as S. pneumoniae by optochin sensitivity and bile solubility. Capsular typing was carried out by the Quellung reaction, with use of group and factor serum samples provided by the Statens Seruminstitut (Copenhagen). The MICs of penicillin, cefotaxime, and erythromycin were determined for each isolate in Mueller-Hinton broth (Copenhagen). The MICs of penicillin, cefotaxime, and erythromycin were determined for each isolate in Mueller-Hinton broth (Copenhagen). The MICs of penicillin, cefotaxime, and erythromycin were determined for each isolate in Mueller-Hinton broth (Copenhagen). The MICs of penicillin, cefotaxime, and erythromycin were determined for each isolate in Mueller-Hinton broth (Copenhagen). The MICs of penicillin, cefotaxime, and erythromycin were determined for each isolate in Mueller-Hinton broth (Copenhagen). The MICs of penicillin, cefotaxime, and erythromycin were determined for each isolate in Mueller-Hinton broth (Copenhagen). The MICs of penicillin, cefotaxime, and erythromycin were determined for each isolate in Mueller-Hinton broth (Copenhagen).

Results

Case ascertainment and incidence rates. For the HSS, rates of return of the monthly reporting cards were 94% in 1997 and 95% in 1998, and for the questionnaires 93.4% in 1997 and 90.4% in 1998. For the LSS, the rates of return of the monthly reports were 91.4% in 1997 and 95.8% in 1998.

The total number of reported cases from either surveillance system was similar in 1997 (n = 447) and 1998 (n = 449). In each year, the LSS reported more cases than the HSS (LSS, 385 cases in 1997 and 381 cases in 1998; HSS, 205 cases in 1997 and 217 in 1998). This difference was due mainly to the numbers of nonmeningitis cases (1997 plus 1998: HSS, n = 166; LSS, n = 429); the numbers of meningitis cases were closer (1997 plus 1998: HSS, n = 256; LSS, n = 337).

The age distribution of all 896 case patients in the 2-year study period (table 1 and table 2) shows a peak in the first year of life and a rapid decline in all types of IPD thereafter. Age-specific incidence rates were calculated as the sum of all cases reported by either of the 2 sources and as an estimate by the 2-source capture-recapture method, based on the independent sources, the HSS and LSS. The highest incidence of all IPD and also of meningitis cases was observed in the second half of the first year of life. All estimates based on capture-recapture methods were higher than the incidence estimates based on all identified cases. Meningitis accounted for 35.3%-51.2% of all IPD cases.

Clinical aspects and seasonality. Most cases were observed during the cold months, from October to March (figure 1). The male-to-female ratio was 1.5:1 for both the meningitis and nonmeningitis cases. Further information on the site of infection, outcome, and underlying conditions was available for cases reported to the HSS. In the HSS system the total number of nonmeningitis cases was 166. Of those, 150 cases had been included on the basis of isolation of S. pneumoniae in a blood culture, and 79 of them involved occult pneumococcal bacteremia with no evident focus on the origin of the infection. Among the remaining 71 blood culture–positive cases in which there was evidence of a focal infection, 53 involved pneumonia and 18 involved clinical signs of other focal infection (in 7 of
Table 2. Age-specific incidences of pneumococcal meningitis in Germany, 1997–1998.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Reports to HSS and LSS</th>
<th>Capture-recapture method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Incidence per 10^5 persons</td>
</tr>
<tr>
<td>&lt;6 mo</td>
<td>63</td>
<td>7.77</td>
</tr>
<tr>
<td>&lt;1 y (cumulative)</td>
<td>157</td>
<td>9.68</td>
</tr>
<tr>
<td>≥1 and &lt;2 y</td>
<td>73</td>
<td>4.57</td>
</tr>
<tr>
<td>&lt;2 y (cumulative)</td>
<td>230</td>
<td>7.15</td>
</tr>
<tr>
<td>≥2 and &lt;5 y</td>
<td>77</td>
<td>1.63</td>
</tr>
<tr>
<td>&lt;5 y (cumulative)</td>
<td>307</td>
<td>3.86</td>
</tr>
<tr>
<td>≥5 and &lt;16 y</td>
<td>93</td>
<td>0.46</td>
</tr>
<tr>
<td>&lt;16 y (cumulative)</td>
<td>404</td>
<td>1.44</td>
</tr>
</tbody>
</table>

NOTE. HSS, hospital-based surveillance system; LSS, laboratory-based surveillance system; CI, confidence interval.

* Calculated as the sum of all cases reported to either source.

b Calculated by 2-source capture-recapture method, on the basis of cases reported to the HSS and LSS.

c No information on age in 4 cases.

these 18, additional pneumococcal isolates were recovered from the focus). In 8 of the 16 additional cases, pneumococci had been isolated from a pleural effusion, and in the other 8 cases, from the joints or mastoid process.

The case-fatality rate for the meningitis cases was 9.8% (95% CI, 6.1%–13.4%), as compared to 1.2% (95% CI, 0%–2.9%) for the nonmeningitis cases. The majority of survivors for whom outcomes were adverse had hearing loss (35 of 422) or CNS-related conditions such as hydrocephalus, hygroma, subdural empyema, epilepsy, brain atrophy, focal brain defects, hemiparesis, developmental delay (24 of 422), and fibrothorax (4 of 422).

A total of 83 (32%) of all 256 meningitis cases (95% CI, 26.7%–38.2%) resulted in death or in recovery with serious sequelae, whereas such outcomes were seen in only 8 (4.8%) of the 166 (95% CI, 1.6%–8.1%) nonmeningitis cases. Risk factors for IPD were documented in 7.6% of the cases: defects in immunoglobulin synthesis (n = 13), asplenia (n = 6), immunosuppressive therapy or anticancer chemotherapy (n = 6), complement defects (n = 6), and diabetes mellitus (n = 1).

Serotypes and resistance to antibiotics. Antibiotic susceptibility testing and serotyping were performed on a total of 304 pneumococcal isolates (127 from meningitis cases) at the National Reference Center for Streptococci. Thus, additional microbiological information was available for 34% of all reported cases and 31% of the meningitis cases. The proportions of serotyped cases were higher in the east and center of Germany (44% in each) than in other parts of the country (27%, north; 31%, west; and 30%, south). The spectrum of serotypes observed, however, was similar in all regions. There were no relevant differences between serotyped and nonserotyped cases with respect to demographics or outcomes.

Table 3 shows the absolute numbers and proportions of serotypes in meningitis and nonmeningitis cases. It was possible to identify 39 different capsular serotypes. The 10 most common of these accounted for 74% of all IPD cases (71% of the meningitis cases). The proportions of cases potentially preventable by the pneumococcal conjugate vaccines would be as follows: by the 7-valent, 52% (53% for meningitis); by the 9-valent, 62% (57% for meningitis); and by the 11-valent, 71% (64% for meningitis).

Ten strains (3.3%) were found to have intermediate penicillin susceptibility but none were found to be resistant to penicillin (MIC ≥2 mg/L). The rates of resistance to cefotaxime and erythromycin were 0% and 13.8%, respectively (table 4).

Discussion

In this study, we estimated the number of all pediatric cases of IPD in Germany on the basis of 2 independent reporting systems, an LSS and an HSS, and using the capture-recapture technique. Participation rates in both active-surveillance systems were well above 90%. Since both systems were designed to operate independently of each other, completeness of each system could be estimated by 2-source capture-recapture meth-
Table 3. Frequency of pneumococcal serotypes (the 10 most common and those in the 11-valent vaccine) among cases of invasive pneumococcal meningitis in children, 1997–1998.

<table>
<thead>
<tr>
<th>Serotype</th>
<th>No. (%)</th>
<th>No. (%)</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 304)</td>
<td>(n = 177)</td>
<td>(n = 127)</td>
</tr>
<tr>
<td>1</td>
<td>49 (16.1)</td>
<td>24 (13.6)</td>
<td>25 (19.7)</td>
</tr>
<tr>
<td>18C</td>
<td>27 (8.9)</td>
<td>17 (9.6)</td>
<td>10 (7.9)</td>
</tr>
<tr>
<td>19</td>
<td>25 (8.2)</td>
<td>20 (11.3)</td>
<td>10 (7.3)</td>
</tr>
<tr>
<td>23F</td>
<td>21 (6.9)</td>
<td>13 (7.3)</td>
<td>8 (6.3)</td>
</tr>
<tr>
<td>3</td>
<td>20 (6.6)</td>
<td>14 (7.9)</td>
<td>6 (4.7)</td>
</tr>
<tr>
<td>6B</td>
<td>20 (6.6)</td>
<td>10 (5.6)</td>
<td>7 (5.7)</td>
</tr>
<tr>
<td>19F</td>
<td>14 (4.6)</td>
<td>8 (4.5)</td>
<td>6 (4.7)</td>
</tr>
<tr>
<td>6A</td>
<td>12 (3.9)</td>
<td>4 (2.4)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>9V</td>
<td>7 (2.3)</td>
<td>3 (1.7)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>3</td>
<td>9 (3.0)</td>
<td>5 (2.9)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Other</td>
<td>19 (1.1)</td>
<td>3 (0.1)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

* Not included in the 7-valent vaccine.
* Not included in the 9-valent vaccine.
* Not included in the 11-valent vaccine.
* Seven cases with type 15C; 4 cases with types 18B and 33F; 3 cases with types 17, 23A, 24F, 8, 9A, and untypeable; 2 cases with types 11A, 13F, 15A, 22F, 23B, 28F, and 38; and 1 case with types 10A, 11B, 12A, 15B, 16F, 18F, 28A, 34, 35F, and 9N.
* Three cases with types 8, 9A, 15C, and 18B; 2 cases with type 22F; and 1 case with types 11A, untypeable, 12A, 12F, 23A, 23B, 24F, 28F, 33F, and 38.
* Four cases with type 15C; 3 cases with types 33F and 17F; 2 cases with types 13F, 15A, 23A, 24F, and untypeable; and 1 case with types 9N, 10A, 11A, 11B, 15B, 16F, 18B, 18F, 23B, 28A, 28F, 34, 35F, and 38.

The observed ascertainment rates were 69.1% for the LSS and 38.1% for the HSS.

The LSS identified more cases, mainly because of a higher ascertainment rate of nonmeningitis cases (usually bacteremia). Such infections are clinically less dramatic and usually have a better prognosis, which explains why they often go undetected by the HSS. Neither of the surveillance systems, however, was complete, underscoring the need for at least 2 data sources for a valid population-based calculation of the incidence of IPD. With both systems combined, 88.5% of the meningitis cases and 80.9% of all IPD cases could be ascertained.

Seasonal variations and male-to-female ratios were similar to those reported from other countries [4, 5, 12, 13] and in a previously published non-population–based study in Germany [14]. In this survey we asked only for definite risk factors for IPD, according to the statement of the Advisory Committee on Immunization Practices (ACIP) on prevention of pneumococcal disease [15]. With the exception of chronic renal failure and nephrotic syndrome, all other medical risk factors listed in the ACIP document were observed. The proportion of IPD cases with documented risk factors (7.6%) is lower than the recently published figure (27%) from a multicenter study that included a wider range of preexisting chronic conditions as underlying diseases.

A total of 57.4% of all pediatric IPD cases and 56.9% of the pneumococcal meningitis cases involved children aged <24 months. This proportion is considerably lower than that seen in a recently published multicenter study done in the United States, where 66.5% of all IPD cases and 73% of the meningitis cases involved patients aged <2 years [16]. Children aged ≥2 years, who accounted for 42.6% of all IPD cases in Germany, might also benefit from the 23-valent polysaccharide vaccine, which covers 83% of the observed serotypes.

The rates of pneumococcal meningitis among children aged <5 years in our study (3.9 per 10^5; 4.3 per 10^5 as estimated by the capture-recapture technique) were equal to or higher than rates reported from the United States [17, 18] and Finland [5]. The annual incidence of IPD among children aged <5 years (8.9 per 10^5; 10.6 per 10^5 as estimated by the capture-recapture technique) was considerably lower, however, than the incidence revealed in most other studies, in which rates in the range of 18–82 per 10^5 were observed [13, 19–22].

The most important cause for underreporting of pneumococcal bacteremia in the present study may be the underuse of blood culture for pediatric patients in Germany. In contrast to the Finnish study [5], in the present survey pediatricians were not trained to obtain blood culture specimens from all children with fever of unknown origin. Furthermore, the majority of children with fever in Germany are not seen in hospitals or in emergency departments but in private pediatirc offices, where it is not a standard procedure to perform blood cultures for all febrile patients. Therefore, many cases of occult pneumococcal bacteremia remain undiagnosed in Germany but are managed and resolve well with either oral antibiotics or no specific therapy.

In contrast, as many as 76% of all IPD cases reported in a recent study in the United States involved outpatients [23]. It thus appears reasonable to assume that underuse of blood cultures for young patients in Germany and confinement of their performance to patients admitted to a hospital account for the lower rates for nonmeningitis cases in our study. Similarly, low incidence estimates for all cases of IPD were recently reported from Switzerland, which has a comparable health care system and similar diagnostic practices [20].

Immunity to S. pneumoniae is specific for each capsular serotype.


<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Susceptible</th>
<th>Intermediately susceptible</th>
<th>Resistant</th>
<th>MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>96.7</td>
<td>3.3</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>100.0</td>
<td>0</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>86.2</td>
<td>13.8</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

NOTE. MIC interpretive breakpoints, according to the National Center for Clinical Laboratory Standards (NCCLS), were as follows: Susceptible penicillin, ≤0.06 mg/L; cefotaxime, ≤0.5 mg/L; and erythromycin, ≤0.25 mg/L. Intermediately resistant: penicillin, 0.12–1 mg/L; cefotaxime, 1 mg/L; and erythromycin, 0.5 mg/L. Resistant: penicillin, >2 mg/L; cefotaxime, >2 mg/L; and erythromycin, >1 mg/L [11].
type, but currently only 7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), 9 serotypes (containing additionally serotypes 1 and 5), or 11 serotypes (containing additionally serotypes 3 and 7F) are covered by pneumococcal conjugate vaccines. Thus, a prerequisite for the introduction of such vaccines into a country is adequate knowledge of the most commonly encountered capsular types. Although serotyping was achieved in only about one-third of IPD cases in this study, the serotype distribution may still be assumed to be representative of all strains causing IPD in Germany, for the following reasons: (1) there were no relevant differences in demographics between serotyped and nontyped cases; (2) there was no evident regional clustering of serotypes; and (3) there were no relevant differences in the outcome of IPD between serotyped and not serotyped cases (data not shown).

Analysis of the serotype distribution data showed that serotypes 14, 18C, and 1 are those primarily responsible for IPD in Germany. Pneumococcal serotype 1, accounting for 8.2% of the cases, however, is not covered by the 7-valent conjugate vaccine. An even higher prevalence of type 1 infections (20% of 213 cases) was observed in a 2-year (October 1988 through September 1990) prospective, nationwide surveillance of all invasive pediatric pneumococcal infections in Israel [21]. Another recent hospital surveillance study of S. pneumoniae disease, in India, demonstrated serotype 1 to be responsible for 13.9% of pneumococcal infections of children aged <5 years [6].

Three of the 10 most commonly observed pneumococcal serotypes in Germany (4, 6A, and 19A) were not included in a recently suggested “optimal nanovalent vaccine” for global use [24], and 2 of the 10 most common serotypes (6A and 19A) were not even included in the 11-valent vaccine. The potential of the 7-, 9-, and 11-valent vaccines to prevent IPD falls within a range of 52%–71% for all cases and within a range of 53%–64% for pneumococcal meningitis cases only. An optimized vaccine for the German population might be an 11-valent vaccine in which type 19A replaces type 3. This vaccine would cover 74% of all IPD (73% of meningitis cases). The proportion of vaccine-preventable cases, however, is further reduced by infections occurring within the first months of life: 6.1% of all IPD cases and 6.2% of the meningitis cases were observed in children aged <2 months. Some of these might benefit from maternal vaccination with the 23-valent polysaccharide vaccine during pregnancy.

The rate of penicillin and cefotaxime resistance in Germany is one of the lowest in the world, confirming the results from previous studies on IPD in both children [14] and adults [25]. However, because of the high mobility of Germans, who frequently spend their vacation in Mediterranean countries where β-lactam and macrolide resistance is common [26], resistant strains are imported to Germany [27]. As antibiotic resistance in pneumococci is related to certain serotypes (e.g., serotypes 6B, 9, and 23F) [25], additional benefit of conjugate vaccines may arise by coverage of these serotypes.

An important finding of the present investigation is that macrolide resistance in S. pneumoniae is an increasing problem in Germany. This has also been observed with regard to adults with either invasive or noninvasive disease (Reinert, unpublished data); nevertheless, macrolide resistance rates are still lower than in Spain and France [26, 28].

The high burden of disease in early childhood and the availability of an effective vaccine to prevent virtually all cases of invasive Haemophilus influenzae b infections were the forces motivating the rapid and effective implementation of vaccination against H. influenzae type b in Germany. The potential for the 7-, 9-, and 11-valent pneumococcal conjugate vaccines to prevent mortality and serious IPD-induced long-term sequelae in German children is considerably lower. The serotype mix of conjugate pneumococcal vaccines can be optimized to include serotypes more prevalent in the German population.

Acknowledgments

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References