Invasive Pneumococcal Disease among Adults: Associations among Serotypes, Disease Characteristics, and Outcome

Angelique G. S. C. Jansen, Gerwin D. Rodenburg, Arie van der Ende, Loek van Alphen, Reinier H. Veenhoven, Lodewijk Spanjaard, Elisabeth A. M. Sanders, and Eelko Hak

1Department of Pediatric Immunology and Infectious Diseases, Wilhelmina Children’s Hospital, and 2Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, 3Academic Medical Center Amsterdam, Center for Infection and Immunity Amsterdam, Department of Medical Microbiology, and the Netherlands Reference Laboratory for Bacterial Meningitis, Amsterdam, *Netherlands Vaccine Institute, Bilthoven, 4Department of Pediatrics, Spaarne Hospital, Hoofddorp, and 5Department of Epidemiology, University Medical Center Groningen, Groningen, the Netherlands

Background. The *Streptococcus pneumoniae* polysaccharide capsule may be related to invasive pneumococcal disease (IPD) course.

Methods. We performed a retrospective cohort study with nationally representative surveillance data from 1075 hospitalized patients with IPD from the Netherlands from 1 June 2004 through 31 May 2006 in the pre-vaccination era. Serotypes were grouped according to invasive disease potential, rate of the most serious clinical syndromes of meningitis and bacteremia without focus, and case-fatality rates. Multivariable logistic regression analysis was performed to obtain odds ratios adjusted for baseline confounders for the association of serotypes and these outcomes, using the serotypes with the lowest rates as reference.

Results. IPD caused by serogroups with low invasive disease potential concerned meningitis or bacteremia without focus in 22% of cases, and 74% of patients had an underlying comorbidity. For highly invasive serogroups these figures were 10% (P < .01) and 56% (P < .01). Individual serotypes varied in the relative rate by which they caused meningitis or bacteremia without focus. Compared with the reference group composed of serotypes 1, 5, 7F, 15B, 20, and 33F, the group of serotypes 3, 19F, 23A, 16F, 6B, 9N, and 18C was associated with increased case-fatality rates (group adjusted odds ratio, 2.6; 95% confidence interval, 1.5–4.7).

Conclusions. The serotype appeared to be independently associated with IPD severity in adults, which indicates that careful monitoring of IPD after implementation of conjugate vaccines is necessary.
neclelible in all age groups in the Netherlands [7], and antibiotic resistance has traditionally been low [8, 9].

METHODS

Identification of patients. The Netherlands Reference Laboratory for Bacterial Meningitis (Academic Medical Center/National Institute of Public Health and the Environment, Amsterdam, the Netherlands) is a laboratory-based surveillance system that collects nationwide pneumococcal isolates from blood and cerebrospinal fluid (CSF) samples. Isolates from other normally sterile bodily fluids constitute <3% of samples. Nine sentinel microbiology regional laboratories across the Netherlands, covering a representative proportion of ~25% of the Dutch population with ~4.1 million inhabitants, reported all pneumococcal isolates from sterile sites from 2004 on. These sentinel laboratories identified 1150 mainly hospitalized patients (age, ≥18 years) with IPD during 1 June 2004 through 31 May 2006, before the implementation of PCV7 in the national infant immunization program. Pneumococcal isolates received by the Netherlands Reference Laboratory for Bacterial Meningitis were typed by coagglutination and serotyped by the capsular swelling method (Quellung reaction) using antisera (Statens Serum Institute).

Diagnosis and other covariates. Information about the disease syndrome, information on the presence of underlying conditions at the time of diagnosis, and follow-up information on admission to the intensive care unit (ICU) and case fatalities (in-hospital death or death within 30 days after the first culture of a normally sterile site positive for S. pneumoniae) were extracted from hospital medical records using a standard data collection form. Meningitis was defined as a CSF culture positive for S. pneumoniae (or a positive CSF polymerase chain reaction result) or a clinical diagnosis of meningitis in combination with a blood culture positive for S. pneumoniae. Invasive pneumonia included physician-diagnosed pneumonia with a blood culture positive for S. pneumoniae. Bacteremia with other focus was defined as a positive blood culture in combination with a clinical focus other than meningitis or pneumonia. If no clinical focus could be identified, it was recorded as bacteremia without focus.

Immunocompromising conditions included primary immunodeficiency, human immunodeficiency virus infection (with or without progression to AIDS), current lymphoma, leukemia, myeloma, solid organ or stem cell transplantation, current immunosuppressive therapy for malignancy or autoimmune disease, asplenia, sickle cell disease, renal insufficiency or need for dialysis, and nephrotic syndrome. Other comorbidities included the presence of a malignant neoplasm not considered immunocompromising, chronic obstructive pulmonary disease or asthma, diabetes mellitus, cardiovascular disease (history of myocardial infarction, coronary artery condition, history of a cerebrovascular accident or transient ischemic attack, cardiomyopathy or heart failure, heart valve disease, or cerebral, abdominal, or thoracic aneurysms), liver disease, and (a history of) long-term alcohol abuse.

Statistical analysis. All data were analyzed with the statistical software package SPSS, version 12.0.1 (SPSS), and Episheet [10]. The potential association between serogroups or serotypes and disease severity was assessed in 3 ways: (1) patient characteristics and disease severity were determined by the invasive disease potential of the infecting serotype or serogroup, (2) the serotype-specific relative rate of the more serious clinical syndromes was determined (meningitis and bacteremia without focus proved to be the most severe clinical syndromes of IPD in our data set), and (3) the serotype-specific case-fatality rate was determined.

The invasive disease potential describes the tendency of bacteria to become invasive and cause IPD while colonizing the nasopharynx. As Sjöström et al. [5] previously did, pneumococcal serogroups were grouped by invasive disease potential according to the meta-analysis of Brueggemann et al. [1] in which nasopharyngeal carriage rates of serogroups were compared with their rates of IPD. Low invasive serogroups cause invasive disease infrequently relative to their high nasopharyngeal colonization rates, whereas high invasive serogroups frequently cause IPD relative to their low colonization rates. According to Brueggemann et al. [1], with serotype 14 as reference and set to 1, serogroups were grouped as having high invasive disease potential when they had an OR >1 (i.e., serogroups 1, 5, and 7), intermediate invasive disease potential when they had an OR >0.5 but <1 (i.e., serogroups 4, 14, 18, and 9), and low invasive disease potential when they had an OR <0.5 (i.e., serogroups 3, 6, 8, 15, 19, 23, and 33). For these groups, the relative rate of the more serious clinical syndromes of meningitis and occult bacteremia (i.e., the share of these clinical syndromes as part of all IPD cases caused by these serotypes or serogroups), the proportion of patients with certain characteristics (e.g., age, >79 years, and presence of underlying conditions), the proportion of patients requiring ICU admission, and case-fatality rates were determined.

The relative rate of the more serious clinical syndromes of IPD was determined separately for each serogroup or serotype with at least 5 reported isolates. Taking the serogroups or serotypes with the lowest relative rate as reference, ORs with 95% confidence intervals (CIs) for the more serious disease syndromes of IPD were determined for all serogroups or serotypes in a multivariable logistic regression model, correcting for other patient and disease characteristics using P<.05 as the cutoff for statistical significance. The Hosmer-Lemeshow test was applied to assess goodness of fit of the model.

The ORs with 95% CIs for case fatalities were also determined for all serogroups or serotypes with at least 5 reported
isolates. For statistical reasons, serotypes were subsequently clustered in groups according to their case-fatality rates. The group of serotypes with the lowest case-fatality rates served as reference in the model. Again, ORs were assessed independent of other covariates, including sex, age, and underlying conditions, and the disease syndrome was assessed using a multivariable logistic regression model. Because not all more serious disease courses are captured by the outcome of death alone, we also assessed associations with an alternative combined outcome (i.e., case-fatality [as previously defined] and/or prolonged hospitalization [defined as a hospital stay beyond the 75th percentile—that is, >19 days]).

### RESULTS

In total 1150 patients with IPD were described, and in 1142 patients (99%), the isolate could be typed. Clinical information from hospital records was available for 1107 patients (96%). This information concerned almost exclusively hospitalized patients (99%).

**Disease severity and patient characteristics by invasive disease potential.** Compared with IPD caused by serogroups with high invasive disease potential (serogroups 1, 5, and 7), IPD caused by serogroups with low invasive disease potential (serogroups 3, 6, 8, 15, 19, 23, and 33) concerned more often the most serious clinical syndromes of meningitis and bacteremia without focus (21.7% vs. 9.9% for the high invasive serotypes 1, 5, and 7), which had higher rates of admission to the ICU and higher case-fatality rates (table 1). More fragile persons (i.e., those who were older and/or had underlying conditions, such as immunocompromising conditions and current malignancy) were particularly affected by the intermediate and low invasive pneumococcal serogroups; high invasive serogroups or serotypes were often associated with milder disease manifestations and affected more often individuals without comorbidities.

**Association between certain serotypes and disease syndrome.** Serotypes varied widely in the relative rate by which they caused the clinical syndromes of meningitis or bacteremia without focus, which allowed serotypes to be entered separately into the model without the need to cluster these serotypes into groups (table 2). Within serotypes 1 and 4 IPD, relatively small proportions of meningitis or bacteremia without focus were found, whereas serotypes 6B, 9N, 10A, 16F, 18C, 19F, 20, and 22A IPD had relatively high proportions of these clinical syndromes. These differences were found to be independent of age and the presence of asthma or chronic obstructive pulmonary disease, which were statistically the only significant confounders.

**Association between certain serotypes and disease course.** In univariate analysis, both serotype 7F, which was also among the most prevalent serotypes in the current study among adults, and serotype 1 showed case-fatality rates in the lower range, along with serotypes 5, 20, 15B, and 33F (figure 1). The case-fatality rates of these last 4 serotypes were, however, imprecise because of the low number of reported isolates of each. Serotypes 3, 6B, 9N, 16F, 18C, 19F, and 23A had case-fatality rates in the higher range. According to their case-fatality rates, serotypes were grouped into those with the lowest case-fatality rates (reference group composed of serotypes 1, 5, 7F, 15B, 20, and 33F), intermediate case-fatality rates (serotypes 4, 6A, 8,

### Table 1. Patient characteristics and disease course by invasive disease potential of serotypes.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Invasive disease potential of serogroups, %a</th>
<th>Pb</th>
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<tbody>
<tr>
<td></td>
<td>High (serogroups 1, 5, and 7) (n = 212)</td>
<td>Intermediate (serogroups 4, 9, 14, and 18) (n = 380)</td>
</tr>
<tr>
<td>Meningitis or bacteremia without focus</td>
<td>9.9</td>
<td>11.5</td>
</tr>
<tr>
<td>Age, &gt;79 years</td>
<td>12.4</td>
<td>24.1</td>
</tr>
<tr>
<td>Any</td>
<td>56.1</td>
<td>73.3</td>
</tr>
<tr>
<td>Immunocompromise</td>
<td>9.9</td>
<td>18.1</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4.2</td>
<td>6.0</td>
</tr>
<tr>
<td>Asthma or chronic obstructive pulmonary disease</td>
<td>22.2</td>
<td>31.6</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>18.8</td>
<td>22.1</td>
</tr>
<tr>
<td>Fatality</td>
<td>9.9</td>
<td>16.8</td>
</tr>
</tbody>
</table>

a Invasive disease potential was chosen according to Brueggemann et al. [1].
b Univariate P value for differences among the groups.
c Malignancy not defined below immunocompromised.
Table 2. Serotypes and disease syndrome.

| Serotype | No. of isolates | No. (%) of cases of meningitis or bacteremia without focus | No. of cases of invasive pneumonia or bacteremia with other focus | Multivariable OR (95% CI)
|-----------|----------------|----------------------------------------------------------|---------------------------------------------------------------|------------------------
| 5         | 5              | 0 (0)                                                    | 5                                                             | Referent
| 1         | 66             | 2 (3.0)                                                  | 64                                                            | Referent
| 4         | 100            | 7 (7)                                                    | 93                                                            | Referent
| 11A       | 12             | 1 (8.3)                                                  | 11                                                            | 1.8 (0.2–16.2)
| 14        | 140            | 12 (8.6)                                                 | 128                                                           | 2.0 (0.8–5.0)
| 19A       | 33             | 3 (9.1)                                                  | 30                                                            | 2.1 (0.5–8.4)
| 9V        | 97             | 9 (9.3)                                                  | 88                                                            | 1.8 (0.7–4.9)
| 7F        | 140            | 18 (12.9)                                                | 122                                                           | 2.6 (1.1–6.0)
| 3         | 67             | 9 (13.4)                                                 | 58                                                            | 3.1 (1.2–8.4)
| 8         | 86             | 12 (14.0)                                                | 74                                                            | 3.1 (1.2–7.8)
| 33F       | 13             | 2 (15.4)                                                 | 11                                                            | 3.0 (0.6–15.9)
| 24F       | 5              | 1 (20.0)                                                 | 4                                                             | 5.1 (0.5–54.9)
| 22F       | 21             | 5 (23.8)                                                 | 16                                                            | 5.6 (1.6–19.3)
| 6A        | 31             | 8 (25.8)                                                 | 23                                                            | 6.5 (2.1–19.5)
| 23F       | 68             | 18 (26.5)                                                | 50                                                            | 6.5 (2.7–15.7)
| 9N        | 26             | 7 (26.9)                                                 | 19                                                            | 8.8 (2.8–27.3)
| 23A       | 7              | 2 (28.6)                                                 | 5                                                             | 6.0 (1.0–35.8)
| 12F       | 17             | 5 (29.4)                                                 | 12                                                            | 6.0 (1.7–21.2)
| 6B        | 27             | 9 (33.3)                                                 | 11                                                            | 9.5 (3.3–27.6)
| 16F       | 10             | 4 (40.0)                                                 | 6                                                             | 11.8 (2.8–50.7)
| 15B       | 5              | 2 (40.0)                                                 | 3                                                             | 7.8 (1.1–54.0)
| 20        | 7              | 3 (42.9)                                                 | 4                                                             | 15.3 (2.7–87.5)
| 19F       | 37             | 16 (43.2)                                                | 21                                                            | 19.1 (7.2–50.6)
| 10A       | 15             | 7 (46.7)                                                 | 8                                                             | 25.8 (7.0–95.2)
| 18C       | 18             | 9 (50.0)                                                 | 9                                                             | 21.3 (6.5–70.0)
| 22A       | 5              | 3 (60.0)                                                 | 2                                                             | 25.9 (3.7–178.4)

NOTE. Serotypes with statistically significant multivariable odds ratios (ORs) are presented in boldface font. CI, confidence interval.

{**Serotypes ranked according to their relative rate of meningitis or bacteremia without focus.**

b Independent of age and chronic obstructive pulmonary disease or asthma (the only 2 covariates remaining significant in the multivariable model); \( P = .80 \), by Hosmer-Lemeshow test.

9V, 10A, 11A, 12F, 14, 19A, 22A, 22F, 23F, and 24F), and the highest case-fatality rates (serotypes 3, 6B, 9N, 16F, 18C, 19F, and 23A) (figure 1). In a multivariable model, the latter group of serotypes remained significantly associated with a higher case-fatality rate, as well as immunocompromising conditions (OR, 1.5; 95% CI, 1.0–2.4), cardiovascular disease (OR, 1.6; 95% CI, 1.1–2.3), the severe clinical syndromes of meningitis or bacteremia without focus (OR, 2.9; 95% CI, 1.9–4.4), and age (ORs ranging from 3.6 [95% CI, 1.7–7.9] in 40–59-year-olds to 13.5 [95% CI, 6.2–29.3] in persons aged \( \geq 80 \) years). On the contrary, underlying diabetes (OR, 0.5; 95% CI, 0.3–0.8) was found to be associated with a lower case-fatality rate.

Ranking the serotypes according to case-fatality and/or prolonged hospitalization (>19 days) showed similarity with the case-fatality rate alone, again with serotypes 1 and 7F showing a relatively low rate of this unfavorable outcome and serotypes 3, 6B, 9N, 18C, and 23F in the highest range of case-fatality and/or prolonged hospitalization (table 3). The group of serotypes with the highest rates of this outcome (serotypes 3, 6B, 9N, 18C, 22A, 22F, 23F, and 33F) remained significantly associated with a higher case-fatality or prolonged hospitalization rate (OR, 1.9; 95% CI, 1.4–2.7) in a multivariable model. In addition, older age (ORs ranging from 3.6 [95% CI, 1.7–7.9] in 40–59-year-olds to 13.5 [95% CI, 6.2–29.3] in persons aged \( \geq 80 \) years), the severe clinical syndromes of meningitis or bacteremia without focus (OR, 3.4, 95% CI, 2.4–4.9), and (a history of) alcohol abuse (OR, 2.0; 95% CI, 1.1–3.5) were associated with higher rates of case-fatality or prolonged hospitalization, whereas underlying diabetes again was associated with a lower rate (OR, 0.7; 95% CI, 0.5–0.9).

**DISCUSSION**

In this large retrospective study of hospitalized adults with IPD, we found that serogroups known to have high invasive disease potential in children [1] (serogroups 1, 5, and 7) affected relatively healthy adults, whereas those previously shown to have low or intermediate invasive disease potential (serogroups 3, 6, 9, 10A, 11A, 12F, 14, 19A, 22A, 22F, 23F, and 24F), and the highest case-fatality rates (serotypes 3, 6B, 9N, 16F, 18C, 19F, and 23A) (figure 1). In a multivariable model, the latter group of serotypes remained significantly associated with a higher case-fatality rate, as well as immunocompromising conditions (OR, 1.5; 95% CI, 1.0–2.4), cardiovascular disease (OR, 1.6; 95% CI, 1.1–2.3), the severe clinical syndromes of meningitis or bacteremia without focus (OR, 2.9; 95% CI, 1.9–4.4), and age (ORs ranging from 3.6 [95% CI, 1.7–7.9] in 40–59-year-olds to 13.5 [95% CI, 6.2–29.3] in persons aged \( \geq 80 \) years). On the contrary, underlying diabetes (OR, 0.5; 95% CI, 0.3–0.8) was found to be associated with a lower case-fatality rate.

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Pneumococcal Disease Outcome by Serotype

Figure 1. Serogroup- or type-specific case-fatality rates. Asterisk indicates independent of age (P < .01), clinical syndrome of meningitis or occult bacteremia (P < .01), diabetes mellitus (P < .01), cardiovascular disease (P = .02), and underlying immunocompromising conditions (P = .04). P = .38, by Hosmer-Lemeshow test. Error bars indicate 95% confidence intervals (CIs).

8, 15, 19, 23, 33, and 38) were more likely to affect more fragile individuals at an older age and/or those with underlying conditions. Independent of patient (and disease) characteristics, a wide variation was seen among pneumococcal capsular serotypes regarding their relative rate of causing the clinically most serious syndromes of meningitis or bacteremia without focus but also regarding case-fatality rate and/or rate of prolonged hospitalization. The group of serotypes that included serotypes 3, 6B, 9N, 18C, and 19F was more often associated with an unfavorable outcome than the group that included serotypes 1 and 7F, even after correction for underlying patient and disease characteristics.

The currently licensed PCV7 is targeted against 7 serotypes common in pediatric IPD and has proven to be highly effective against vaccine-serotype invasive disease in children [11]. After implementation of PCV7 in the United States in 2000, not only was a sharp decrease in vaccine-serotype IPD in the target group of young children observed but also a considerable decrease in IPD in other unvaccinated age groups was seen, which has been attributed to a herd effect [4]. However, a gradual but progressive increase in several nonvaccine serotype IPDs has also been observed [12]. This emergence of nonvaccine serotype IPD may be a natural temporal trend but may also be caused by widespread conjugate vaccination. Infants and toddlers represent the largest reservoir for spreading pneumococci in the community, and although after conjugate vaccination the overall pneumococcal carriage rates in children have remained more or less similar, vaccine serotypes have decreased but have been concomitantly replaced by nonvaccine serotypes in carriage studies [13, 14]. In view of the results of the current study, the question is whether shifts in serotype distribution of IPD may be accompanied by a change in disease severity.

Our study was based on detailed information about the clinical syndrome and its underlying conditions, which was available for each patient, allowing assessment of the association between capsular serotype and disease severity in a multivariable model that corrected for other patient and disease characteristics. However, to appreciate the results of the current study, some potential weaknesses should be addressed. The invasive disease potential of pneumococci with certain serogroups was chosen according to Brueggemann et al. [1]. These investigators determined the invasive disease potential of serogroups by comparing serotype distribution in asymptomatic nasopharyngeal carriage with that in IPD among children. Although we worked with the assumption that the invasive potential of serogroups in adults is similar to that in children, this is unknown and requires further study. Furthermore, despite the inclusion of 1142 patients with available pneumococcal capsular serotyping, the number of isolates per serotype was still relatively small and prohibited evaluation of case-fat-
Table 3. Longer hospital stay and/or case-fatality, by serotype.

<table>
<thead>
<tr>
<th>Serotype</th>
<th>No. of isolates</th>
<th>No. of cases involving longer hospital stay or case-fatality&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Unadjusted OR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Adjusted OR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Reference serotypes</td>
<td>5</td>
<td>0 (0)</td>
<td>Referent</td>
<td>Referent&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>20</td>
<td>7</td>
<td>1 (14.3)</td>
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<td></td>
<td>15B</td>
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<td>1</td>
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<td>4</td>
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<tr>
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<td>22A</td>
<td>5</td>
<td>4 (80.0)</td>
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</table>

**NOTE.** CI, confidence interval; OR, odds ratio.
<sup>a</sup> Hospital stay >19 days and/or in-hospital death or death <30 days after the first blood or cerebrospinal fluid culture positive for *Streptococcus pneumoniae*.
<sup>b</sup> Adjusted for age (P<.01), clinical syndrome of meningitis or occult bacteremia (P<.01), diabetes mellitus (P=.02), and alcohol abuse (P=.68, by Hosmer-Lemeshow test).
<sup>c</sup> The ORs are estimated for the whole group of serotypes with the reference serotypes as a reference.

tality rates by individual serotype. Clustering of serotypes was necessary, and consequently no firm conclusions may be drawn about individual serotypes. In the Netherlands, as in most of Europe, referral patterns for invasive disease are considerably different from the United States for infants, but less so for adults. If proven invasive disease is present among adults, most adults will end up in the hospital for further diagnosis and treatment. We therefore do not believe that such bias has affected our results. In addition, we have estimated relative risks for different groups of serotypes that are unlikely to be affected by such referral bias.

Several studies have been performed on the relation between pneumococcal serotypes and disease. A smaller Swedish study of 494 adults with IPD showed that pneumococci with serotypes with low invasive disease potential behave as opportunistic pathogens, which means that they especially cause disease in fragile persons, whereas pneumococci with serotypes 1 and 7F, known to have high invasive disease potential, acted as primary pathogens, causing infections in previously healthy individuals [5]. Our results are also in agreement with the observation in that study that IPD caused by pneumococci with these high invasive serotypes often had a favorable outcome. In a large study of 5579 adults with IPD aged ≥50 years, serotypes 3, 11A, 19F, and 23F were found to be associated with significantly higher case-fatality rates than was serotype 14 (chosen to be the reference type because it was the most frequently occurring serotype) [4]. This study was however performed during the first 4 years after introduction of PCV7 in the United States, where PPV23 is also widely used. A Danish study of 464 hospitalized adults with IPD demonstrated that infection with serotype 3 was associated with an increased risk of death, whereas serotype 1 was associated with a decreased risk of death [3]. Our findings are in agreement with the higher observed case-fatality rates of serotypes 3 and 19F IPD and the lower case-
fatality rate of serotype 1 IPD. We also observed lower case-fatality rates of serotype 7F disease. Another international study (in 10 western and nonwestern countries together) restricted to 796 hospitalized patients with bacteremia aged ≥15 years concluded that neither serotypes defined as invasive or pediatric (serotypes commonly causing IPD in children) nor PCV7 serotypes as a group were significantly associated with a higher mortality rate [6]. However, this observation does not exclude the possibility of an association between individual serotypes and a higher or lower case-fatality rate.

In our study, diabetes appeared to be associated with a lower case-fatality rate independent of other patient and disease characteristics. This finding seems counterintuitive because diabetes is a risk factor for acquiring IPD [15]. However, there is evidence that tight glucose control during critical illness might favor the outcome [16]. It may be that diabetic patients are particularly more closely monitored for blood glucose fluctuations once hospitalized and critically ill and, consequently, may benefit from tight glucose regulation, but evidence is required to support this theory.

This and previous studies have focused on the association between capsular polysaccharide serotype and disease severity. Apart from the polysaccharide capsule, however, many other components of the pneumococcus, including its genotype, are implicated in virulence and in interaction with the immune system and may affect disease severity. This warrants further study, although the capsule is strongly linked to the bacterial genotypic clones for many serotypes circulating in a defined geographic region and for the majority of strains of a serotype causing invasive disease [17].

The current study indicated that, in the presence of negligible coverage rates of PCV7 and the PPV23 and very low antibiotic resistance of pneumococci, disease severity of IPD, including case fatalities, varies by serogroup or serotype. Although no firm conclusions can be drawn for individual serotypes, it appears that several serotypes, including several not covered by PCV7, are associated with relatively high proportions of the more serious clinical syndromes and/or higher case-fatality rates. This information is valuable in the development and introduction of future pneumococcal conjugate vaccines. Because the introduction of PCV7 among young children has been associated with obvious shifts in serotype carriage rates and (discrete) shifts in serotype distribution in IPD, shifts in disease severity may occur. This warrants careful monitoring of nasopharyngeal carriage and IPD in the future both for serotypes and in case of disease for clinical syndromes and outcome.

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