Factors Associated With Severe Nonmeningitis Invasive Pneumococcal Disease in Adults in France

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Background. In France, pneumococcal vaccination in adults is recommended for risk groups (chronic conditions/immunosuppression). We conducted a study on invasive pneumococcal disease (IPD) in adults to identify factors associated with disease severity and death.

Methods. We included IPD cases, excluding meningitis, from 25 acute care hospitals in 6 regions. We defined severe cases as those with shock or severe sepsis or intensive care unit admission/mechanical ventilation. We included deaths occurring within 30 days of hospitalization. Infectious disease specialists collected clinical/microbiological data on cases.

Results. During 2014–2017, 908 nonmeningitis IPD cases were diagnosed; 48% were severe, 84% had comorbidities, 21% died. Ninety percent of cases with comorbidities who previously sought health care were not vaccinated against pneumococcus. Compared with previously healthy cases, the risk of severe IPD increased from 20% (adjusted risk ratio [aRR], 1.2; 95% CI, 1.0–1.4) in cases with 1–2 chronic diseases to 30% (aRR, 1.3; 95% CI, 1.0–7.0) in those with >2 chronic diseases. Among risk groups, 13-valent pneumococcal conjugate vaccine (PCV13) serotypes and 23-valent pneumococcal polysaccharide vaccine (PPSV23) nonPCV13 serotypes were more likely to induce severe IPD compared with nonvaccine serotypes (aRR, 1.5; 95% CI, 1.3–1.9; aRR, 1.3; 95% CI, 1.0–1.5, respectively).

Conclusions. We observed a cumulative effect of concurrent comorbidities on severe IPD. Vaccine serotypes were more likely to induce severe IPD among risk groups. The missed opportunities for vaccination underscore the need to enhance vaccination in risk groups.

Keywords. invasive pneumococcal disease; pneumococcal conjugate vaccine; surveillance; Streptococcus pneumoniae; mortality; outcome.

Streptococcus pneumoniae or pneumococcus remains an important cause of mortality among adults worldwide [1–3]. Pneumococci differ markedly in their pathogenicity according to their serotype, with the existence of serotype-specific differences in mortality following invasive pneumococcal disease (IPD) [4–7]. Some serotypes are associated with increased risk of invasiveness or disease severity [8]. Besides serotypes, host factors are also crucial in developing IPD, with certain underlying medical conditions or risk behaviors such as smoking or alcohol abuse having been associated with IPD [9, 10]. IPD-related mortality has been previously associated with increasing age and clinical complications (such as sepsis and septic shock) [11, 12]. Several studies have reported an increase in IPD incidence with increasing number of underlying conditions [9, 13]. However, the role of comorbidities and specifically the cumulative effect of concurrent comorbidities on poor outcomes among IPD patients, accounting for the potentially confounding effect of aging, is less well known [14].

In France, 7-valent pneumococcal conjugate vaccine (PCV7) was recommended for children at risk aged ≤2 years in 2003 and for all children ≤2 years in 2006. In 2010, PCV7 was replaced by PCV13 for all children ≤2 years. Since 2011, PCV13 coverage for the primo-vaccination series at 9 months of age has been exceeding 91% (https://www.santepubliquefrance.fr/determinants-de-sante/vaccination/articles/donnees-de-couverture-vaccinale-pneumocoque-par-groupe-d-age). PPSV23 vaccination has been recommended for children aged ≥2 years and adults with comorbidities for decades. During 2012–2016, pneumococcal vaccination with PCV13 followed by PPSV23 was recommended for immunocompromised or
immunosuppressed children aged ≥5 years, adults, and those with a cochlear implant, regardless of age (high-risk patients) or for children aged 2–5 years with medical chronic or immunosuppressive conditions, if they had not previously received PCV13 [15]. For immunocompetent adults with medical chronic conditions or history of alcoholism or current smoking (at-risk patients), the previous strategy (1 dose of PPSV23) was maintained. In 2017, recommendations were harmonized for both high-risk and at-risk patients based on the combined schedule (PCV13 and PPSV23 in series) [16]. To estimate the impact of these updated recommendations for vaccination, the identification of the population groups most likely to develop severe disease or poor outcomes following IPD at baseline was required.

Between June 2014 and December 2017, we conducted a prospective study among ≥18-year-old patients with nonmeningitis IPD in France to describe their underlying diseases and identify factors associated with disease severity and fatality.

METHODS

Study Population
The study was based on the French network of 23 regional laboratories (Regional Observatories of Pneumococcus [ORP]), which coordinate microbiological surveillance of IPD in children and adults at the regional level [18]. Twenty-five acute care hospitals from 6 of the 13 French regions of metropolitan France (population 4,716,969, accounting for 7% of the French adult population) participated in the study; all serve as referent facilities for the residents of the study area and include intensive care units (ICUs) to ensure ability to care for severe infectious diseases. During the study period, PCV13 coverage for 3 doses at 24 months of age was >90% in the study area (https://geodes.santepubliquefrance.fr/#c = indicator&i= cv_cs24_pneumo.cv_pneu3&s = 2017&t = a01 &view = map2).

Definitions
We defined as cases IPD patients with isolation of S. pneumoniae from a normally sterile site (blood, pleural fluid, joint fluid, peritoneal fluid), according to the 2012 European Commission (EC) case definition [18]. We excluded pneumococcal meningitis cases, as those were monitored in another dedicated study. We used 2 main outcomes: severe IPD and death/surviving cases, as those were monitored in another dedicated (EC) case definition [18]. We defined multiple comorbidities as >2 chronic conditions, excluding smoking and alcoholism.

Laboratory Methods
S. pneumoniae isolates were identified in the microbiology laboratory of each participating hospital. All S. pneumoniae isolates were transferred for identity confirmation to the National Reference Centre for Pneumococci (NRCP), where serotyping was performed with the use of latex particles sensitized with pool, group, type, and factor antisera provided by the Statens Serum Institut (Copenhagen, Denmark). This panel of antisera enabled recognition of 92 known serotypes. Susceptibility to penicillin G, amoxicillin, ceftotaxime, and ceftriaxone was determined at the NRCP using the broth dilution method, and susceptibility to erythromycin was determined using the disk diffusion method according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [20]. The results were interpreted according to EUCAST breakpoints (version 7.1, 2017) [20]. Intermediate or resistant isolates were considered nonsusceptible.

Data Collection
Once nonmeningitis IPD cases were diagnosed at a participating hospital, infectious disease specialists prospectively collected data on demographics, hospitalization dates, clinical manifestations, underlying conditions, and disease outcomes of all diagnosed cases, using a bespoke data collection form. Vaccination status data were collected by infectious diseases specialists using patients’ vaccination cards, medical records, and patient general practitioner (GP) or family interviews.

Statistical Analysis
We calculated proportions using the total number of nonmissing values as the denominator, age-specific incidence, case fatalities (CFs), and risk ratios (RRs). We classified serotypes according to their potential for causing invasive disease and death, as previously described [21–26]. Serotypes with previous strong associations with fatality included serotypes 3, 19A, 12F, 9N, 24F, 11A, 20, 23A, 10A, 19F, 6C, 35B, 15B/C, 35F, 16F, 14, 6A, 6B, 18C, and 23F; medium effects included serotypes 22F, 15A, 33F, and 9V; low or no association included serotypes 8, 7F, 1, 4, and 5. We estimated survival probabilities using Kaplan-Meier survival curves. To identify factors independently associated with survival, we calculated adjusted hazard ratios (aHRs) using parametric survival analysis assuming a Weibull distribution.
To compare individual serotypes, we used serotype 8 as a reference, which was the second most frequent serotype that had not been previously associated with severe disease. To identify factors independently associated with severity, we calculated adjusted RRs (aRRs) using multivariable binomial regression. We included in the initial regression models all variables with a P value <.30. To simplify the models, we removed variables 1 at a time depending on the significance testing (P < .05) by the likelihood ratio (LR) test. We performed the analysis using STATA software (version 12; Stata Corporation, TX, USA).

Ethical Issues
The French National Data Protection Commission approved the data collection procedures (approval reference No. 909028). The study did not require further ethical committee approval, as it was part of ongoing surveillance.

RESULTS

Descriptive Characteristics
Between June 2014 and December 2017, 908 (67%) nonmeningitis IPD cases were recorded. Their age ranged from 18 to 101 years (median, 71); 53% (480/908) were male. The age and serotype distribution of the cases in the study did not differ significantly from those reported from metropolitan France during the same period through the ORP surveillance system (data not shown). In addition, the annual IPD incidence rates in the study area were similar to those in metropolitan France.

Severe Outcomes
Of all cases, 48% (431/899) had severe nonmeningitis IPD, 31% were admitted to an intensive care unit (ICU; median stay [range], 5 [1–70] days); 74% (669/908) presented with pneumonia; 12% (108/908) bacteremia without known focus, 7% (67/908) with pneumonia and/or pleuritis, and the remaining 7% (64/908) with infections in other sites (Table 1). The median duration of hospitalization of cases (range) was 9 (0–432) days. Of all cases, 22% (201/908) died during hospitalization and 21% (188/908) died within 30 days after admission, 33% (61/188) of whom died within the first 48 hours after admission. The median time to death from date of admission (range) was 4 (0–115) days.

Underlying Conditions
Of cases, 84% belonged to a risk group; 37% (335/908) were high risk, and 47% (429/908) were at risk. The prevalence of multiple comorbidities was overall 31%, ranging from 16% among cases <65 years of age to 36% among cases ≥65 years of age (P ≤ .001) (Table 1). Compared with older cases, <65-year-olds were more likely to be admitted to an ICU and to be current smokers or alcoholics, but less likely to suffer from heart disease, diabetes, and malnutrition (Table 1). Compared with at-risk cases, high-risk cases were less likely to live in a long-term care facility (LTCF) or present with shock, but more likely to have >2 at-risk conditions (Table 1).

Serotype Distribution and Antimicrobial Resistance
Of the 833 (92%) cases with a known serotype, 249 (30%) had a PCV13 serotype, 353 (42%) had a PPSV23nonPCV13 serotype, and 231 (28%) had a nonvaccine serotype; 32% of high-risk cases were due to a PCV13 serotype, compared with 26% of at-risk cases (P < .001). The most frequent serotypes were 3 (15%), 8 (9%), 22F (8%), and 19A (7%). Among cases with antimicrobial susceptibility tested, 20% (167/836) were nonsusceptible to penicillin (Table 1).

Vaccination Status
Among high-risk or at-risk cases, 10% were vaccinated against pneumococcus within the previous 5 years, 4% with PCV13 and 7% with PPV23 (Table 1). Of those cases with comorbidities who were hospitalized or consulted a specialist or general practitioner in the previous year, 10% received a pneumococcal vaccine.

Factors Associated With Fatality
Thirty-day intrahospital case fatality did not differ significantly (P = .232) among at-risk cases (20%) and high-risk cases (24%). Case fatality was 3.7 (RR, 3.7; 95% confidence interval [CI], 2.7–5.0) times higher among cases with severe disease. Lower survival probabilities were observed among cases with severe disease and cases with >2 at-risk conditions (Figure 1). Case fatality of current smokers or alcoholics did not differ significantly from that of nonsmokers or nonalcoholics (RR, 0.47; 95% CI, 0.30–2.1; RR, 0.74; 95% CI, 0.47–1.1, respectively).

In the final survival analysis model, case fatality increased with increasing age (aHR per year of age, 1.04; 95% CI, 1.03–1.06; P < .001). Compared with others, fatality was higher among cases with >2 chronic at-risk conditions, among those with malignant solid tumors diagnosed within the last 5 years, those with severe sepsis or shock, and those residing in an LTCF (Table 2). In contrast, cases admitted to an ICU and those with a penicillin-nonsusceptible isolate were less likely to die (Table 2). Similarly, case fatality among cases who received at least 1 dose of antipneumococcal vaccine (PCV13 or PPV23) or PCV13 alone was 78% (aHR, 0.22; 95% CI, 0.09–0.56) and 75% (aHR, 0.24; 95% CI, 0.03–0.91) lower, respectively, compared with nonvaccinated cases.

Case fatality was significantly higher for 7 individual serotypes (10A, 23A, 19F, 24F, 20, 19A, 11A), compared with that of the second most common serotype 8 (Table 2). Case fatality of serotype 3 was not significantly higher when compared with serotype 8. Serotypes with previously reported high disease potential (serotypes 1, 2, 5, 7F, 12F, 24F, and 38) did not present a higher case fatality (aHR,
| Characteristic | Category | Total (n = 908) | 18–64 y (n = 321) | 65+ y (n = 587) | High Risk (n = 335) | At Risk (n = 429) | Healthy (n = 144) | P  |
|---------------|----------|----------------|------------------|-----------------|-------------------|-----------------|-----------------|----|
| **Age groups, y** |          |                |                  |                 |                   |                 |                 |    |
| 18–49         |          | 140            | 16               | -               | -                 | -               | -               |    |
| 50–64         |          | 181            | 20               | -               | -                 | -               | -               |    |
| 65–84         |          | 391            | 43               | -               | -                 | -               | -               |    |
| 85+           |          | 196            | 22               | -               | -                 | -               | -               |    |
| **Residence**  |          |                |                  |                 |                   |                 |                 |    |
| Institution   |          | 121            | 13               | 5               | 106               | 18              | <.001           |    |
| **Hospitalization in year 1** |          |                |                  |                 |                   |                 |                 |    |
| Yes           |          | 368            | 41               | 115             | 253               | 44              | .036            |    |
| **Severe disease** |          |                |                  |                 |                   |                 |                 |    |
| Yes           |          | 431            | 48               | 155             | 49                | 276             | .401            |    |
| **Severe sepsis** |          |                |                  |                 |                   |                 |                 |    |
| Yes           |          | 341            | 38               | 125             | 39                | 216             | .536            |    |
| **Shock**     |          |                |                  |                 |                   |                 |                 |    |
| Yes           |          | 169            | 19               | 79              | 25                | 90              | .15             |    |
| **Mechanical ventilation** |          |                |                  |                 |                   |                 |                 |    |
| Yes           |          | 368            | 41               | 115             | 36                | 253             | .401            |    |
| **Site of infection** |          |                |                  |                 |                   |                 |                 |    |
| Pneumonia     |          | 669            | 74               | 228             | 71                | 441             | .432            |    |
| Pleuritis & pn. |        | 67             | 7                | 23              | 7                 | 44              | .8              |    |
| Unk/other     |          | 172            | 19               | 70              | 22                | 102             | .17             |    |
| **Chronic lung disease** |          |                |                  |                 |                   |                 |                 |    |
| Yes           |          | 166            | 18               | 121             | 28                | 45              | .004            |    |
| **Smoking (current)** |          |                |                  |                 |                   |                 |                 |    |
| Yes           |          | 166            | 18               | 121             | 38                | 45              | .004            |    |
| **Heart failure** |          |                |                  |                 |                   |                 |                 |    |
| Yes           |          | 166            | 18               | 121             | 38                | 45              | .004            |    |
| **Diabetes mellitus** |          |                |                  |                 |                   |                 |                 |    |
| Yes           |          | 166            | 18               | 121             | 38                | 45              | .004            |    |
| **Main nutrition** |          |                |                  |                 |                   |                 |                 |    |
| Yes           |          | 155            | 18               | 121             | 38                | 45              | .004            |    |
| **Alcoholism** |          |                |                  |                 |                   |                 |                 |    |
| Yes           |          | 155            | 18               | 121             | 38                | 45              | .004            |    |
| **Malignant solid tumors (<5 y)** |          |                |                  |                 |                   |                 |                 |    |
| Yes           |          | 156            | 17               | 107             | 18                | 258             | .258            |    |
| **Hematologic cancer (<5 y)** |          |                |                  |                 |                   |                 |                 |    |
| Yes           |          | 156            | 17               | 107             | 18                | 258             | .258            |    |
| **Immunosuppressive treatment** |          |                |                  |                 |                   |                 |                 |    |
| Yes           |          | 92             | 10               | 43              | 13                | 49              | .016            |    |
| **Vaccinated against:** |          |                |                  |                 |                   |                 |                 |    |
| Influenza     |          | 215            | 26               | 93              | 17                | 56              | .433            |    |
| Pneumococcus  |          | 68             | 8                | 17              | 6                 | 51              | .050            |    |
| **Vaccinated with:** |          |                |                  |                 |                   |                 |                 |    |
| PCV7          |          | 2              | 0.2             | 1               | 0.3              | 0.2             | .677            |    |
| PCV13         |          | 29             | 4               | 8               | 4                | 21              | .343            |    |
| PPSV23        |          | 49             | 6               | 11              | 4                | 38              | .043            |    |
| **Serotypes included in:** |          |                |                  |                 |                   |                 |                 |    |
| PCV7          |          | 42             | 5               | 16              | 5                | 26              | .007            |    |
| PCV13 only    |          | 207            | 26               | 64              | 21                | 143             | .27             |    |
| PPSV23 only   |          | 353            | 42               | 150             | 50                | 203             | .38             |    |
| Nonvaccine    |          | 231            | 28               | 70              | 23                | 161             | .30             |    |
| Other 33 serotypes |          |                |                  |                 |                   |                 |                 |    |
| 3 PCV13       |          | 123            | 15               | 38              | 13                | 85              | .004            |    |
| 8 PPSV23 only |          | 77             | 9               | 38              | 13                | 39              | .043            |    |
| 22F PPSV23    |          | 63             | 8               | 22              | 7                | 41              | .217            |    |
| 19A PCV13     |          | 55             | 7               | 42              | 8                | 13              | .433            |    |
| 12F PPSV23    |          | 50             | 6               | 24              | 5                | 26              | .043            |    |
| 9N PPSV23     |          | 49             | 6               | 28              | 5                | 21              | .043            |    |
| 5A Nonvaccine |          | 38             | 5               | 25              | 5                | 13              | .043            |    |
| 24F Nonvaccine|          | 29             | 4               | 19              | 4                | 10              | .043            |    |
| 11A PPSV23    |          | 28             | 3               | 17              | 3                | 11              | .043            |    |
| 20 PPSV23     |          | 25             | 3               | 13              | 2                | 12              | .043            |    |
| 23A Nonvaccine|          | 24             | 3               | 15              | 3                | 9               | .043            |    |
| 10A PPSV23    |          | 21             | 3               | 10              | 2                | 11              | .043            |    |
| 19F PCV13     |          | 21             | 3               | 11              | 2                | 10              | .043            |    |
| 6C Nonvaccine |          | 21             | 3               | 19              | 4                | 2               | .043            |    |
| 35B Nonvaccine|          | 20             | 2               | 16              | 3                | 4               | .043            |    |
| Penicillin nonsusceptible |      | 166            | 20               | 51              | 17                | 115             | .112            |    |
| Erythromycin nonsusceptible |   | 159            | 19               | 46              | 15                | 113             | .039            |    |
| Cefotaxime nonsusceptible |  | 159            | 19               | 46              | 15                | 113             | .039            |    |

| Abbreviations: ICU, intensive care unit; IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine. |

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However, case fatality among the group of serotypes with previously reported strong associations with fatality was significantly higher compared with the other serotypes (Table 2).

### Factors Associated With Severe Nonmeningitis IPD

PCV13 serotypes and PPSV23nonPCV13 serotypes were more likely to induce severe nonmeningitis IPD compared with nonvaccine serotypes (aRR, 1.6; 95% CI, 1.3–1.9; and aRR, 1.2; 95% CI, 1.1–1.4, respectively) (Table 3). Those risks were similar (aRR, 1.5; 95% CI, 1.3–1.9; aRR, 1.3; 95% CI, 1.0–1.5, respectively) when the analysis was restricted to risk groups, but not for previously healthy individuals (aRR, 1.6; 95% CI, 0.94–2.8; aRR, 0.7; 95% CI, 0.36–1.3, respectively). The risk of severe disease increased with increasing number of at-risk conditions, with those with 1–2 chronic conditions (excluding smoking and alcoholism) and those with >2 conditions having 20% and 30% higher risk of developing severe nonmeningitis IPD, respectively, compared with those without at-risk conditions. Those having received vaccination for seasonal influenza were less likely to develop severe nonmeningitis IPD. Antipneumococcal vaccination did not remain significant (aRR, 0.87; 95% CI, 0.62–1.2).

Figure 1. Kaplan-Meier survival estimates for time since diagnosis of all cases of invasive pneumococcal disease by (A) disease severity and (B) number of at-risk conditions.
Table 2. Number of Deaths During Hospitalization Among Cases With Invasive Pneumococcal Disease by Different Factors/Serotypes and Adjusted Hazard Ratios From the Final Parametric Survival Analysis Assuming a Weibull Distribution, France, 2014–2017a

| Characteristic Category | Deaths, No. | Case Fatality, % | Ratio of CFs | 95% CI | Adjusted HR | 95% CI |
|-------------------------|-------------|------------------|--------------|--------|-------------|--------|
| **Age groups, y**       |             |                  |              |        |             |        |
| 18–49                   | 11          | 8                | Ref          | Ref    | Ref         | Ref    |
| 50–64                   | 37          | 21               | 2.6          | 1.4–4.9| 3.7         | 1.5–9.1|
| 65–84                   | 72          | 18               | 2.3          | 1.3–4.3| 3.5         | 1.5–9.0|
| 85+                     | 68          | 35               | 4.4          | 2.4–8.0| 9.3         | 3.7–23 |
| **Residence**           |             |                  |              |        |             |        |
| House                   | 141         | 18               | Ref          | Ref    | Ref         | Ref    |
| Institution             | 46          | 38               | 2.1          | 1.6–2.8| 2.3         | 1.5–3.5|
| **Severe IPD**b         |             |                  |              |        |             |        |
| Yes                     | 145         | 34               | 3.7          | 2.7–5.0| -           | -      |
| No                      | 43          | 9                | Ref          | Ref    | -           | -      |
| **Severe sepsis**       |             |                  |              |        |             |        |
| Yes                     | 128         | 38               | 3.5          | 2.7–4.7| 2.8         | 1.8–4.3|
| No                      | 60          | 11               | Ref          | Ref    | Ref         | Ref    |
| **Shock**               |             |                  |              |        |             |        |
| Yes                     | 83          | 49               | 3.4          | 2.7–4.3| 8.9         | 5.4–15 |
| No                      | 105         | 14               | Ref          | Ref    | Ref         | Ref    |
| **Mechanical ventilation** |         |                  |              |        |             |        |
| Yes                     | 66          | 35               | 2.0          | 1.6–2.6| -           | -      |
| No                      | 122         | 17               | Ref          | Ref    | -           | -      |
| **ICU admission**       |             |                  |              |        |             |        |
| Yes                     | 75          | 27               | 1.5          | 1.2–1.9| 0.19        | 0.11–0.33|
| No                      | 112         | 18               | Ref          | Ref    | Ref         | Ref    |
| **Level of risk**       |             |                  |              |        |             |        |
| High riskc              | 80          | 24               | 1.7          | 1.1–2.5| -           | -      |
| At riskc                | 87          | 21               | 1.4          | 0.90–2.2| -           | -      |
| Healthy                 | 21          | 15               | Ref          | Ref    | -           | -      |
| No. of comorbidities    |             |                  |              |        |             |        |
| 0–2                     | 156         | 19               | Ref          | Ref    | Ref         | Ref    |
| >2                      | 32          | 36               | 1.9          | 1.4–2.6| 1.9         | 1.1–2.5|
| **Heart failure**       |             |                  |              |        |             |        |
| Yes                     | 52          | 32               | 1.7          | 1.3–2.3| -           | -      |
| No                      | 136         | 18               | Ref          | Ref    | -           | -      |
| **Oxygen therapy at home** |          |                  |              |        |             |        |
| Yes                     | 12          | 41               | 2.1          | 1.3–3.3| -           | -      |
| No                      | 176         | 20               | Ref          | Ref    | -           | -      |
| **Chronic renal failure** |         |                  |              |        |             |        |
| Yes                     | 35          | 35               | 1.9          | 1.4–2.5| -           | -      |
| No                      | 153         | 19               | Ref          | Ref    | -           | -      |
| **Solid tumors (<5 y)** |             |                  |              |        |             |        |
| Yes                     | 52          | 33               | 1.8          | 1.4–2.4| 2.7         | 1.8–4.0|
| No                      | 136         | 18               | Ref          | Ref    | Ref         | Ref    |
| **PCV13 vaccination**   |             |                  |              |        |             |        |
| At least 1 dose         | 3           | 10               | 0.51         | 0.17–1.0| 0.25       | 0.03–0.91|
| None                    | 160         | 20               | Ref          | Ref    | Ref         | Ref    |
| **Penicillin nonsusceptible** |      |                  |              |        |             |        |
| Yes                     | 45          | 26               | 1.4          | 1.0–1.9| 0.57        | 0.34–0.95|
| No                      | 121         | 18               | Ref          | Ref    | Ref         | Ref    |
| **Group of serotypes with previously reportedd**: | | | | | | |
| High case fatality      | 140         | 26               | 5.4          | 2.3–13| 2.9         | 1.1–8.1|
| Medium case fatality    | 18          | 16               | 3.3          | 1.3–8.6| 2.0         | 1.0–6.2|
| Low case fatality       | 5           | 5                | Ref          | Ref    | Ref         | Ref    |
| **Serotype 3**          |             |                  |              |        |             |        |
| PCV13                   | 25          | 20               | 3.9          | 1.4–11| 2.0         | 0.63–7.1|
| 10A                     | 7           | 33               | 6.4          | 2.0–19| 27         | 6.1–119 |
| 23A                     | 7           | 29               | 5.6          | 1.8–18| 18         | 4.7–72  |
| 19F                     | 5           | 24               | 4.6          | 1.4–18| 12         | 2.6–56  |
| 24F                     | 6           | 21               | 4.0          | 1.3–13| 8.9        | 2.2–37  |
| 20                      | 8           | 32               | 6.2          | 2.0–19| 6.6        | 1.7–26  |
| 19A                     | 23          | 42               | 8.1          | 3.0–21| 5.8        | 1.6–21  |
| 11A                     | 9           | 32               | 6.2          | 2.1–18| 5.7        | 1.4–22  |
| **Others**              |             |                  |              |        |             |        |
| i33 serotypes; n < 20i  | 39          | 21               | 3.9          | 1.5–11| 5.0         | 1.5–17  |
| 12F                     | 7           | 14               | 2.7          | 0.83–8.7| 4.3        | 0.98–18 |
| 15A                     | 6           | 16               | 3.0          | 0.91–10| 4.2        | 0.94–18 |
| 22F                     | 10          | 16               | 3.1          | 1.0–9.3| 3.9        | 0.99–14 |
| 35B                     | 7           | 35               | 6.7          | 2.2–21| 2.5        | 0.58–11 |
| 6C                      | 4           | 19               | 3.7          | 1.0–14| 2.6        | 0.50–13 |
| 9N                      | 8           | 16               | 3.1          | 1.0–10| 2.3        | 0.57–9.4|

Abbreviations: CF, case fatality; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

Notes:

- Only includes factors with a P value < .30 in the univariable analysis.
- Severe IPD = either admitted to an ICU or were under mechanical ventilation or had severe sepsis or shock.
- High-risk group = immunocompetent with a chronic medical condition; high-risk group = immunosuppression due to malignancy, hemopathy, autoimmune disease, immunosuppressive therapy, asplenia, sickle cell disease, nephrotic syndrome, transplantation and other cause of immunosuppression, or cochlear implant.
- Serotypes were grouped according to their potential for causing death in previous studies [22–27]; high case fatality = 3, 19A, 12F, 9N, 24F, 11A, 20, 23A, 10A, 19F, 12F, 6C, 35B, 15B/C, 35F, 31, 16F, 17F, 14, 6A, 6B, 18C, 23F; medium = 22F, 15A, 33F, 9N; low = 8, 7F, 1, 4, 5.
**Table 3. Number of Severe Cases Among Patients With Invasive Pneumococcal Disease by Selected Factors and Most Prevalent Serotypes, France, 2014–2017**

| Characteristic | Category | Severe Cases, No. | % | Risk Ratio | 95% CI | Adjusted RR | 95% CI |
|---------------|----------|------------------|---|-----------|-------|------------|-------|
| No. of comorbidities | 0 | 139 | 42 | Ref | Ref | Ref | Ref |
| | 1–2 | 243 | 51 | 1.2 | 1.0–1.4 | 1.2 | 1.0–1.4 |
| | ≥2 | 49 | 54 | 1.3 | 1.0–1.6 | 1.3 | 1.0–1.7 |
| Serotype category | PCV13 | 148 | 60 | 1.5 | 1.3–1.9 | 1.6 | 1.3–1.9 |
| | PPSV23nonPCV13 | 157 | 45 | 1.2 | 1.0–1.4 | 1.2 | 1.1–1.4 |
| Influenza vaccination | Yes | 90 | 39 | Ref | Ref | Ref | Ref |
| | No | 301 | 50 | Ref | Ref | Ref | Ref |

Abbreviations: CI, confidence interval; IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; RR, risk ratio.

DISCUSSION

Our study indicated a moderate dose response effect of comorbidities on severe outcomes and an effect on mortality for >2 chronic conditions. Although the association between comorbidities and risk of IPD is established, with some studies suggesting that multiple comorbidities may increase the risk of IPD [9, 13], the effect of comorbidities on severe IPD outcomes is less clear. Some studies have reported a significant association between the presence of underlying conditions and mortality following IPD [11, 12], with few reporting a cumulative effect of comorbidities on fatality [14]. However, other studies have suggested no or only a limited impact of comorbidities on case fatality [27], or no convincing association using the Charlson index [28]. Our results reinforce previous findings of an impact of stacking comorbidities on nonmeningitis IPD risk, adding evidence of an effect of stacking comorbidities on poor IPD outcomes, although a moderate one. Taking into account that multiple chronic diseases are more common in older adults (36% of our cases ≥65 years of age had >2 chronic diseases), the additional evidence in this study may inform discussions on recommendations for adult pneumococcal immunization and disease prevention.

The low proportion of vaccinated cases may reflect the low vaccination coverage among risk groups in France, as reported in other countries [29, 30]. In addition, the low uptake among cases with comorbidities that sought health care within the previous year in our study indicates missed opportunities for vaccination. Previous French studies have suggested that the main reason for the low uptake among risk groups was that physicians did not offer pneumococcal vaccination [31]. Implementation of PCV13 in children aged ≤2 years in France led to a marked reduction in the incidence of IPD in adults, with the IPD incidence having decreased by 37% in adults aged 16–64 years and by 28% in adults aged ≥65 years in 2017 compared with 2008–2009 (https://www.santepubliquefrance.fr/...maladies-et-traumatismes/maladies-a-prevention-vaccinale/infections-a-pneumocoque/donnees/#tabs). PCV implementation also influenced the serotype distribution among IPD cases, with the overall incidence of IPD due to PCV7 serotypes significantly decreasing after PCV7 implementation and accounting for 6.7% of all IPD cases in 2017, as compared with 49% in 2001–2002 (before PCV7 implementation). The effectiveness of PCV has been reported to be high even in patients with immunocompromising conditions [32]. Given that 84% of patients were eligible for vaccination, 71% of those were due to PCV13 or PPSV23 serotypes, and assuming a vaccine effectiveness of 45% for PPSV23 [33, 34] to 75% for PCV13 [32], 27%–45% of cases were potentially preventable with the use of those vaccines. Moreover, despite the low number of vaccinated cases involved, vaccination with PCV13 (or any pneumococcal vaccine, but not with PPSV23 alone) was independently associated with reduced fatality in our study after adjusting for other significant factors. Those findings suggest that targeted vaccination for adults remains an integral part of preventive strategies against IPD and underscore the need for promoting vaccination and improving uptake.

Four to 7 years after the implementation of PCV13 in children aged <2 years, 72% of adult nonmenigitis IPD cases were due to vaccine serotypes, 30% due to PCV13 serotypes, and 42% due to PPSV23nonPCV13 serotypes. Our study indicated that PCV13 serotypes, but also PPSV23nonPCV13 serotypes to a lesser extent, significantly increased the risk of severe nonmeningitis IPD outcomes among risk groups. PCV13 serotypes have been previously associated with severe IPD outcomes, but PPSV23nonPCV13 serotypes have been less often reported to cause severe IPD [25, 35–38]. These findings underscore the need to ensure adherence to the current pneumococcal vaccine recommendations, including PCV13 and PPSV23 in series, to reduce the risk of severe IPD in vulnerable groups.
Consistent with the literature, the groups of serotypes previously associated with high or medium fatality also had significantly increased fatality in our study [19]. In contrast, the group of highly invasive serotypes did not account for higher fatality, as previously reported [36]. In addition, our study indicated that 7 individual serotypes were independently associated with fatality (10A, 23A, 19F, 24F, 20, 19A, 11A). PCV13 serotypes 19A and 19F have been consistently associated with higher mortality, increased risk of meningitis, reduced quality-adjusted life-years (QALY), and complicated and necrotizing pneumonia [25, 35–38]. The PPSV23 serotypes 10A and 11A have been previously associated with increased risk of meningitis and reduced QALY, and 11A has also been associated with increased case fatality [6–9, 37]. The nonvaccine serotype 23A and PPVS23 serotype 20 have rarely been associated with increased mortality, although they were occasionally associated with increased risk of meningitis [37]. The nonvaccine serotype 24F, most common in children, was responsible for a significant increase in the incidence of meningitis in <2-year-old children in 2015–2016 in France [39], but an association with higher mortality of this serotype in adults has not been previously reported.

The case fatality observed in our study (21%) was consistent with other recent studies, ranging from 16% [4, 11] to 31% [27]. However, the proportion of cases admitted to the ICU in our study (31%) was higher than that reported elsewhere [32]. This proportion was significantly lower for older age groups. The protective effect of ICU on fatality may reflect the younger age distribution of ICU admitted cases or a better level of care, resulting in a better outcome.

Nonsusceptibility to penicillin was associated with lower fatality in our study. Previous studies have reported conflicting results on this effect [40–44]. Serotypes with low invasive disease potential but high carriage are more often challenged by antibiotics and are more likely to develop resistance to penicillin [40]. Therefore, regardless of clinical management and antibiotic therapy, the protective effect of nonsusceptibility to penicillin might reflect the lower disease potential of penicillin-nonsusceptible serotypes.

We did not identify significant differences in risk of severe disease or death between high-risk and at-risk patients. This is in contrast with IPD incidence studies indicating a dramatic increase of IPD incidence among patients with immunosuppressive conditions compared with at-risk patients [12]. This suggests different patterns in risks of IPD and mortality among vulnerable groups. In addition to host factors, the greater contribution of PCV13 invasive serotypes in at-risk patients in our study compared with high-risk patients may partly explain this discrepancy. Our findings support the change in vaccination policy in 2017 in France, harmonizing the vaccination scheme for both high-risk and at-risk groups [16].

Having a solid tumor in the previous 5 years was the only individual risk condition that remained significantly associated with increased fatality, as previously reported [9, 11]. In 1 study, the effect of solid-organ malignancies on case fatality was only observed when linked with concurrent chemotherapy [45]. It is not clear from our study whether this effect was due to immunosuppressive treatment or a direct effect due to the decrease in immune functions caused by cancer. The association between living in an LTCF and a fatal outcome might reflect poorer health, worse living conditions, or other factors not accounted for in the analysis.

Our study was prospective, using well-defined risk criteria and bespoke data sets with good hospital-quality data and high data completeness exceeding 92% for almost all the variables. However, it had a number of limitations. First, we did not include meningitis IPD cases that were part of another dedicated study. Meningitis IPD cases may have a higher fatality and a specific tropism for some pneumococcal serotypes, and this may have affected the comparison with other studies. However, during the study period, pneumococcal meningitis accounted for <10% of all IPD cases in France. Second, we only included intrahospital deaths within 30 days of admission, as we did not follow up cases after discharge from the hospital, and we did not link cases with death certificate registers. This may have led to underestimation of case fatality and may limit comparison with other studies. Third, we started follow-up at the time of admission and not at the time of disease onset. The severity of disease at the time of presentation at the hospital may differ among different age or risk groups, affecting their survival probabilities. However, given the severity of IPD, the time elapsed between disease onset and time to admission is likely to be short. Fourth, we did not collect data on antibiotic therapy either before or at admission, or the delay to prescription of antibiotherapy. The current French guidelines recommend prescription of antibiotics as soon as possible within 4–8 hours after admission. Those factors may affect the IPD prognosis or act as potential confounders of different effects on poor outcomes. Finally, we did not use the Charlson index score to assess patients’ comorbid conditions and did not take into account the severity of comorbid conditions. However, this score increases with increasing number of at-risk conditions [7].

CONCLUSIONS

In conclusion, our study indicated a moderate cumulative effect of at-risk conditions on severe outcomes following nonmeningitis IPD, adding to the existing body of evidence that can inform discussions on future recommendations for vaccination strategies among aging populations. Vaccine serotypes were more likely to induce severe nonmeningitis IPD outcomes in vulnerable groups. Finally, the considerable missed opportunities for vaccination and the large proportion of potentially preventable IPD cases and deaths highlight the need
for a focused strategy to vaccinate the most at-risk patients for poor IPD-related outcomes and increase vaccine uptake in targeted risk groups.

**Supplementary Data**

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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