Community-acquired pneumonia (CAP) is still a major cause of morbidity and mortality worldwide [1]. It mainly affects adults aged 65 years and older, with increased risk in immunocompromised individuals and those with underlying comorbid conditions such as chronic respiratory disease, chronic heart disease, diabetes, and high alcohol intake [2]. In adults, noninvasive pneumococcal pneumonia is responsible for most CAP burden, while invasive pneumonia accounts for less than 10% of the cases [3].

In Spain, pneumococcal conjugate vaccines (PCVs) have demonstrated substantial effectiveness in reducing pneumococcal disease due to vaccine serotypes [4]. The 13-valent PCV (PCV13) that includes serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, and 23F was introduced by Spain in 2010 for pneumococcal disease due to vaccine serotypes [4]. The 13-valent PCV (PCV13) that includes serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, and 23F was introduced by Spain in 2010 for immunization of healthy children mainly through the private market [5]. Madrid (June 2010) [6] and Galicia (January 2011) [7] regions had publicly funded National Immunization Programs (NIPs), which were expanded nationally in 2015–2016 [8] with a 2 + 1 schedule. In 2018, the coverage of the booster dose reached 94.8% [9]. For adults, the current Spanish vaccination policy recommends PCV13 followed by 23-valent pneumococcal polysaccharide (PPV23) for high-risk adults aged 18 years or older, PPV23 for those older than 2 years who...
are at risk due to underlying conditions [10], and PPV23 as the preferred pneumococcal vaccine for all adults aged 65 years and older [11]. Nationally, PPV23 uptake for persons older than 60–65 years in Spain was 43.8% during 2013–2014 [12]. During 2016–2019, 6 regions (Madrid, Galicia, Castilla and Leon, La Rioja, Asturias, and Andalucia) [13–18] have included in their immunization programs PCV13 for adults older than 18 years who are at risk based on underlying conditions and for adults older than 60–65 years. For the current study, only 1 of the hospitals was in a region (Galicia) that recommends PCV13 for adults aged 65 years. This recommendation has existed as of 2017 [17]. Supplementary Table 1 shows recommendations on pneumococcal vaccination for adults in the regions where the study was conducted.

PCV13 use in childhood NIPs has been associated with rapid and sustained reductions in overall and vaccine-type invasive pneumococcal diseases (IPDs) in young children and unvaccinated older age cohorts [19]. However, recent reports indicate that the indirect effects have plateaued in many geographic regions, even those with high coverage, and primarily for serotypes 3, 7F, 19A, and 19F [20]. In fact, a previous study on the burden of PCV13 serotypes in Spanish adults showed an insufficient indirect protection from childhood vaccination [21]. One potential solution is direct immunization of adults, since in a randomized controlled trial of older Dutch adults, PCV13 demonstrated efficacy against primarily nonbacteremic CAP due to serotypes 3, 7F, and 19A (too few 19F cases occurred to assess efficacy) [22]. To inform this decision, and for decisions regarding adult use of extended future PCVs, it is critical to understand the serotype distribution of pneumococcal CAP in particular locales.

From 2011 to 2018, we conducted an observational, multicenter, prospective, hospital-based study to determine the contribution of specific serotypes to CAP in immunocompetent adults by using serotype-specific urinary antigen detection tests (UAD1/UAD2). The study included serotype-specific contribution to disease severity, evolution, and associated comorbidities after the introduction of PCV13 in children.

**METHODS**

**Participants**

Between November 2011 and November 2018 immunocompetent adults aged 18 years or older prospectively admitted with CAP to the following 4 tertiary-care hospitals from the National Spanish Health System were included in the study (patients included in each hospital): Hospital Clinic i Provincial, Barcelona (Catalonia) (total number of included CAP, n = 610; 19.6% of all CAP cases); Hospital La Fe, Valencia (Valencia) (1012; 32.6%); Hospital Galdakao-Usansolo, Bizkaia (Basque country) (1020; 32.8%); and Hospital Álvaro Cunqueiro, Pontevedra (Galicia) (465; 15.0%). Inclusion criteria are detailed in the Supplementary Material. The ethics committee at each hospital approved the study and patients provided written informed consent.

As per standard clinical practice, data were recorded on age, gender, underlying conditions (chronic obstructive pulmonary disease, chronic kidney failure, asthma, diabetes mellitus, chronic heart failure, chronic liver disease, cerebrovascular disease, cancer), alcohol consumption, tobacco cigarette smoking, history of previous pneumonia, history of hospitalization for at least 48 hours within the 2 weeks prior to current admission, and influenza and pneumococcal vaccination history. The CURB-65 score, Pneumonia Severity Index (PSI), and the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) minor criteria were used to evaluate severity on hospital admission. The evolution and outcome were also recorded.

**Microbiological Studies**

Microbiological tests were performed at each participating hospital according to standard clinical practice and based on clinical judgment of the attending physician. Cultures were performed on available samples from blood (n = 2120), pleural fluid (n = 231), and on high-quality sputum samples (<10 epithelial cells and >25 leukocytes per field; magnification ×100) (n = 1186). Sputum cultures with unique or abundant *Streptococcus pneumoniae* growth and compatible Gram staining were considered as positive for pneumococcus. The BinaxNow *S. pneumoniae* Urinary Antigen Test (n = 2921) and BinaxNow *Legionella pneumophila* Urinary Antigen Test (n = 2921) were used. Other diagnostic tests (n = 724) were performed if indicated by the attending physician and included polymerase chain reaction (PCR) for viruses and serological studies for the detection of antibodies to *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Coxiella burnetii*, and *L. pneumophila*. The Pfizer serotype-specific urinary antigen detection tests UAD1, detecting PCV13 serotypes (from 2011), and UAD2, detecting serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F (starting in 2016), were performed for urine samples from all patients (N = 3107). Serotyping was also performed on isolates from blood or pleural fluid cultures. Isolates and urine samples were processed as described in the Supplementary Material.

**Definitions**

Pneumococcal CAP was defined as chest X-ray (CXR)–confirmed CAP with a positive result from any microbiological test for *S. pneumoniae* (BinaxNow test, UAD test, blood culture, pleural culture, and sputum culture). The CXR confirmation was based on clinician judgment. Invasive pneumococcal CAP was defined as isolation of *S. pneumoniae* from blood or pleural fluid. Noninvasive pneumococcal CAP was defined as pneumococcal CAP excluding invasive pneumococcal CAP. Pneumococcal serotypes were categorized as follows—PCV13-VT: 4, 6B, 9V, 14, 18C, 19F and 23F; 1, 3, 5, 6A, 7F, 19A; PCV15: PCV13-VT plus 22F and 33F; and PCV20: PCV15-VT plus 8, 10A, 11A, 12F and 15 B/C. Clinical characteristics defining complicated CAP are described in the Supplementary Material.
are described in Supplementary Figure 2. Other frequently detected micro-organisms were noninvasive. Among complicated pneumococcal pneumonia cases, 149 (16.6%) were invasive and 746 (83.4%) were noninvasive. Pneumococcal serotype was identified in 617 patients by UAD1/UAD2 tests or culture. Six isolates of invasive pneumococcal pneumonia cases in adults with chronic heart failure and with diabetes mellitus. With regard to patients aged 65 years and older, the highest percentage of pneumococcal CAP caused by serotypes was 10.5% in the site located in Pontevedra (Galicia) versus 17.7% (P = .057) in Barcelona (Catalonia), 12.3% (P = .209) in Valencia (Valencia), and 15.5% (P = .131) in Bizkaia (Basque Country) (Supplementary Table 2).

In 2016–2018, serotypes included in PCV13 accounted for 46.3%, 30.9%, and 37.4% of pneumococcal CAP in patients with 1, 2, and at least 3 underlying conditions, respectively (P = .146). PCV20 serotypes accounted for 75%, 66%, and 65.9% of pneumococcal isolates in patients with 1, 2, and at least 3 comorbidities, respectively (P = .352). PCV13 serotypes in pneumococcal CAP decreased significantly from 2011–2012 to 2017–2018 (P < .001) in all studied conditions except for chronic heart failure and asthma (Figure 1).

Overall, the percentage of patients aged 18–64 years (n = 1164) with at least 1 underlying condition was 76.4%, and 93.5% in those aged 65 years and older (n = 1943). Table 4 shows serotype distribution by underlying conditions by age group for the study period 2016–2018. Among the patients aged 18–64 years, PCV13 serotypes accounted for 40% of pneumococcal CAP cases in adults with chronic heart failure and with diabetes mellitus. With regard to patients aged 65 years and older, the highest percentage of pneumococcal CAP caused by PCV13 serotypes was found in patients with asthma (33.3%). In this age group, the percentage due to PCV20 serotypes ranged from 45.5% to 75% in patients with chronic heart failure and cigarette smokers, respectively.

Pneumococcal Serotypes and Disease Severity
Serotypes associated with severity on admission were 3, 8, 19A, and 7F (Supplementary Table 3). Those serotypes were also predominant
in patients with complicated CAP (Figure 2 and Supplementary Table 4). Specifically, serotype 3 was found in 24.8% of pneumococcal CAP cases associated with complications occurring during hospitalization, with the highest representation of serotype 3 found in patients with renal failure (35.4% of patients with pneumococcal CAP and renal failure) or pleural effusion (25%) and those requiring invasive mechanical ventilation (30.4%). A univariate analysis was used to evaluate the association between serotypes causing pneumococcal pneumonia and severity on admission or complications occurring during hospitalization (Table 5).

**DISCUSSION**

Our results showed that *S. pneumoniae* was the most frequent causative agent of hospitalized CAP identified in our

Table 1. Characteristics of Study Population in the Whole Cohort and in Pneumococcal Community-Acquired Pneumonia

|                        | All-Cause CAP (n = 3107) | Pneumococcal CAP (n = 895)* |
|------------------------|--------------------------|-----------------------------|
| **Age**                |                          |                             |
| 18–64 y                | 1164 (37.5)              | 326 (36.4)                  |
| ≥ 65 y                 | 1943 (62.5)              | 569 (63.6)                  |
| Mean ± SD, y           | 66.8 ± 17.2              | 67.3 ± 16.8                 |
| **Male gender**        | 1283 (41.5)              | 540 (60.3)                  |
| One or more underlying condition | 2704 (87.0)              | 773 (86.4)                  |
| COPD                   | 583 (18.8)               | 172 (19.2)                  |
| Chronic heart failure  | 337 (10.8)               | 78 (8.7)                    |
| Diabetes mellitus      | 714 (23.0)               | 178 (19.9)                  |
| Chronic liver disease  | 104 (3.3)                | 33 (3.7)                    |
| Chronic renal failure  | 297 (9.6)                | 74 (8.3)                    |
| Stroke                 | 250 (8.0)                | 72 (8.0)                    |
| Asthma                 | 271 (8.7)                | 86 (9.6)                    |
| Cured neoplasia        | 327 (10.5)               | 104 (11.6)                  |
| Previous hospitalization | 91 (2.9)               | 28 (3.1)                    |
| Previous pneumonia     | 571 (18.4)               | 159 (17.8)                  |
| Tobacco cigarette smokingb | 553 (17.8)               | 169 (18.9)                  |
| Alcoholismc            | 114 (3.7)                | 38 (4.2)                    |
| **Vaccination history**|                          |                             |
| Influenza vaccine      | 1547 (49.8)              | 434 (48.5)                  |
| Pneumococcal vaccined  | 441 (14.2)               | 104 (11.6)                  |
| PPV23e                 | 376 (85.3)               | 89 (85.6)                   |
| 18–64 y                | 40 (10.6)                | 6 (6.7)                     |
| ≥ 65 y                 | 336 (9.94)               | 83 (93.3)                   |
| PCV13f                 | 43 (9.8)                 | 11 (10.6)                   |
| 18–64 y                | 5 (11.6)                 | 2 (18.2)                    |
| ≥65 y                  | 38 (88.4)                | 9 (81.8)                    |
| Both                   | 11 (2.5)                 | 2 (1.9)                     |
| 18–64 y                | 0 (0)                    | 0 (0)                       |
| ≥65 y                  | 11 (100)                 | 2 (100)                     |
| **Severity**           |                          |                             |
| PSI score IV–V         | 1250 (40.6)              | 395 (44.4)                  |
| CURB-65 risk score 3–5 | 401 (13.8)               | 148 (17.5)                  |
| ≥3 IDSA/ATS minor criteria for severe CAP | 299 (9.6) | 114 (12.7) |
| **Outcomes**           |                          |                             |
| ICU admission          | 313 (10.1)               | 119 (13.3)                  |
| Inpatient mortality    | 81 (2.6)                 | 22 (2.5)                    |
| 30-Day mortality (after discharge) | 10 (0.4) | 2 (0.3) |

Data are presented as n (%) unless otherwise indicated.
Abbreviations: CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; CURB 65, Score for Pneumonia Severity: Confusion, BUN > 19 mg/dL (>7 mmol/L), Respiratory Rate ≥ 30, Systolic BP < 90 mmHg or Diastolic BP ≤ 60 mmHg, Age ≥ 65; ICU, intensive care unit; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society; PSI, Pneumonia Severity Index.

*Polymicrobial etiology: 12.3% of the cases. Influenza virus was the most frequently identified agent in the pneumococcal cases.

*Tobacco cigarette smoking: smokers of ≥10 cigarettes per day within the previous year or quitting smoking less than 6 months before.

*Alcoholism: intake ≥80 g/day during at least the previous year.

*Only 2 patients received a pneumococcal vaccine in the 30 days before to be included in the study.

*23-Valent pneumococcal polysaccharide vaccine [1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 20, 22F, 23F, 33F serotypes].

*13-Valent pneumococcal conjugate vaccine [1, 3, 4, 5, 6A, 6B, 7F, 9V, 10A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 23F serotypes].
**Table 2. Distribution of Vaccines Serotypes in All-Cause Community-Acquired Pneumonia and Pneumococcal Community-Acquired Pneumonia by Study Period**

| Study Period | 2011–2012 | 2012–2013 | 2013–2014 | 2014–2015 | 2015–2016 | 2016–2017 | 2017–2018 | Total |
|--------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-------|
| n            | %         | n         | %         | n         | %         | n         | %         | n     |
| All-cause CAP| 431       | 14.3      | 434       | 14.4      | 393       | 13.0      | 339       | 11.2  | 489    | 16.2   | 507     | 16.8   | 514     | 17.0   | 3,107  | 100   |
| PCV13 serotypes | 77      | 17.9      | 83        | 19.1      | 59        | 15.0      | 44        | 13.0  | 44     | 9.0    | 64      | 12.6   | 68      | 13.2   | 439    | 14.1  |
| PCV15 serotypes | ND      | ND        | ND        | ND        | ND        | ND        | ND        | ND    | 113    | 22.3   | 130     | 25.3   | 243     | 23.8   |       |
| PCV20 serotypes | ND      | ND        | ND        | ND        | ND        | ND        | ND        | ND    | 73     | 14.4   | 75      | 14.6   | 148     | 14.5   |       |
| Most prevalent serotypes (≥1% in total cases) | 13     | 3.0       | 12        | 2.8       | 6         | 1.5       | 2         | 0.6   | 2      | 0.4    | 0       | 0.0    | 1       | 0.2    | 36     | 1.2   |
| 3            | 25        | 5.8       | 32        | 7.4       | 23        | 5.9       | 22        | 6.5   | 28     | 5.7    | 40      | 7.9    | 45      | 8.8    | 215    | 6.9   |
| 7F           | 11        | 2.6       | 8         | 1.8       | 9         | 2.3       | 4         | 1.2   | 2      | 0.4    | 3       | 0.6    | 2       | 0.4    | 39     | 1.3   |
| 8            | 1         | 0.2       | 4         | 0.9       | 1         | 0.3       | 1         | 0.3   | 5      | 1.0    | 32      | 6.3    | 39      | 7.6    | 83     | 2.7   |
| 14           | 6         | 1.4       | 10        | 2.3       | 5         | 1.3       | 2         | 0.6   | 0      | 0.0    | 6       | 1.2    | 5       | 1.0    | 34     | 1.1   |
| 19A          | 8         | 1.9       | 12        | 2.8       | 6         | 1.5       | 2         | 0.6   | 4      | 0.8    | 6       | 1.2    | 5       | 1.0    | 43     | 1.4   |
| CAP due to *Streptococcus pneumoniae* | 114     | …         | 143       | …         | 111       | …         | 80        | …    | 100    | …       | 167     | …       | 180     | …       | 895    | 28.8  |
| PCV13 serotypes | 77      | 67.5      | 83        | 58.0      | 59        | 53.2      | 44        | 55.0  | 44     | 44.0   | 64      | 38.3   | 68      | 37.8   | 439    | 49.1  |
| PCV15 serotypes | ND      | ND        | ND        | ND        | ND        | ND        | ND        | ND    | 73     | 43.7   | 75      | 41.7   | 148     | 42.7   |       |
| PCV20 serotypes | ND      | ND        | ND        | ND        | ND        | ND        | ND        | ND    | 90     | 66.2   | 112     | 72.3   | 202     | 69.4   |       |
| Non invasive CAP<sup>ab</sup> | 95     | 83.3      | 112       | 78.3      | 96        | 86.5      | 71        | 88.8  | 81     | 81.4   | 136     | 81.4   | 155     | 86.1   | 746    | 83.4  |
| PCV13 serotypes | 64      | 67.4      | 60        | 53.6      | 50        | 52.1      | 43        | 60.6  | 38     | 46.9   | 54      | 39.7   | 64      | 41.3   | 373    | 50.0  |
| PCV15 serotypes | ND      | ND        | ND        | ND        | ND        | ND        | ND        | ND    | 61     | 44.9   | 70      | 45.2   | 131     | 45.0   |       |
| PCV20 serotypes | ND      | ND        | ND        | ND        | ND        | ND        | ND        | ND    | 90     | 66.2   | 112     | 72.3   | 202     | 69.4   |       |
| Invasive CAP<sup>ac</sup> | 19     | 16.7      | 31        | 21.7      | 15        | 13.5      | 9         | 11.3  | 19     | 19.0   | 31      | 18.6   | 25      | 13.9   | 149    | 16.6  |
| PCV13 serotypes | 13      | 68.4      | 23        | 74.2      | 9         | 60.0      | 1         | 11.1  | 6      | 31.6   | 10      | 32.3   | 4       | 16.0   | 66     | 44.3  |
| PCV15 serotypes | ND      | ND        | ND        | ND        | ND        | ND        | ND        | ND    | 12     | 38.7   | 5       | 20.0   | 7       | 30.4   |       |
| PCV20 serotypes | ND      | ND        | ND        | ND        | ND        | ND        | ND        | ND    | 23     | 74.2   | 18      | 72.0   | 41      | 73.2   |       |

Abbreviations: CAP, community-acquired pneumonia; ND, not done; PCV, pneumococcal conjugate vaccine; UAD, Pfizer serotype-specific urinary antigen detection test.

<sup>a</sup>PCV15 and PCV20 data were obtained only from 2016 to 2018 when the UAD2 test was available.

<sup>b</sup>Confirmed pneumococcal CAP (by UAD or BinaxNow) for which blood and/or pleural fluid culture result were negative.

<sup>c</sup>Isolate of *S. pneumoniae* in blood and/or pleural fluid. Among 149 cases identified, 6 isolates were not serotyped.
population (28.8%), confirming the results of previous studies conducted in Spain [25, 26] and other countries [27, 28]. While the introduction of PCV13 into pediatric populations—in 2 regions with high coverage and in 1 region for a prolonged period—was associated with a decline in CAP associated with PCV13 serotypes, almost half of the pneumococcal CAP cases were caused by these serotypes, and this proportion increased over the last 3 study years, likely demonstrating a limit to

Table 3. Distribution of Vaccine Serotypes by Age, 2016–2018

|                      | 18–64 Years | ≥65 Years |
|----------------------|-------------|-----------|
|                      | 2016–2017   | 2017–2018 | 2016–2017 | 2017–2018 |
| All-cause CAP        |             |           |           |           |
| n (%)                | 174         | 227       | 333       | 287       |
| PCV13 serotypes      | 21 (12.1)   | 29 (12.8) | 43 (12.9) | 39 (13.6) |
| PCV15 serotypes      | 23 (13.2)   | 30 (13.2) | 50 (15.0) | 45 (15.7) |
| PCV20 serotypes      | 45 (25.9)   | 66 (29.1) | 68 (20.4) | 64 (22.3) |
| Most prevalent serotypes (≥1% in total cases) |             |           |           |           |
| 1                    | 1 (0.0)     | 1 (0.4)   | 0 (0.0)   | 0 (0.0)   |
| 3                    | 15 (8.6)    | 14 (6.2)  | 25 (7.5)  | 31 (10.8) |
| 7F                   | 1 (0.6)     | 2 (0.9)   | 2 (0.6)   | 0 (0.0)   |
| 14                   | 2 (1.1)     | 4 (1.8)   | 4 (1.2)   | 1 (0.3)   |
| 19A                  | 1 (0.6)     | 4 (1.8)   | 5 (1.5)   | 1 (0.3)   |
| 8                    | 19 (10.9)   | 27 (11.9) | 13 (3.9)  | 12 (4.2)  |
| CAP due to *Streptococcus pneumoniae* |             |           |           |           |
| 18-64 years          | 68 (33.3)   | 83 (36.6) | 109 (32.7)| 97 (33.8) |
| ≥65 years            |             |           |           |           |
| PCV13 serotypes      | 21 (36.2)   | 29 (34.9) | 43 (39.4) | 39 (40.2) |
| PCV15 serotypes      | 23 (39.7)   | 30 (36.1) | 50 (45.9) | 45 (46.4) |
| PCV20 serotypes      | 45 (77.6)   | 66 (79.5) | 68 (62.4) | 64 (66.0) |

Among the invasive pneumococcal cases, 6 isolates were not serotyped.

Abbreviations: CAP, community-acquired pneumonia; PCV, pneumococcal conjugate vaccine.

Figure 1. Serotype distribution (%) according to underlying conditions at admission and study period in all-cause (A) and pneumococcal (B) CAP. Note: Differences related to study period 2017–2018. *P < .05; **P < .001. Abbreviations: CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; PCV, pneumococcal conjugate vaccine.
### Table 4. Serotype Distribution in All-Cause Community-Acquired Pneumonia and in Pneumococcal Community-Acquired Pneumonia According to Presence of Underlying Conditions by Age Group, 2016-2018

| Age Group | Diabetes Mellitus | COPD | Previous Pneumonia | Tobacco Cigarette Smokers | Chronic Heart Failure | Chronic Renal Failure | Asthma | No Underlying Diseases |
|-----------|-------------------|------|--------------------|---------------------------|----------------------|----------------------|--------|------------------------|
|           | n | %  | n | %  | n | %  | n | %  | n | %  | n | %  | n | %  | n | %  | n | %  |
| 18–64 y  |               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| All-cause CAP (n = 401) | 46 | 11.5 | 39 | 9.7 | 66 | 16.4 | 141 | 35.2 | 13 | 3.2 | 6 | 1.5 | 48 | 12.0 | 95 | 23.7 |
| PCV13 serotypes | 6 | 13.0 | 5 | 12.8 | 7 | 10.6 | 14 | 9.9 | 2 | 15.4 | 0 | 0.0 | 6 | 12.5 | 11 | 11.6 |
| PCV15 serotypes | 7 | 15.2 | 6 | 15.4 | 7 | 10.6 | 15 | 10.6 | 2 | 15.4 | 0 | 0.0 | 7 | 14.6 | 12 | 12.6 |
| PCV20 serotypes | 12 | 26.1 | 11 | 28.2 | 13 | 19.7 | 37 | 26.2 | 3 | 23.1 | 2 | 33.3 | 15 | 31.3 | 25 | 26.3 |
| Most prevalent serotypes (≥1% in total cases) | 1 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| 14 | 0 | 0.0 | 1 | 2.6 | 0 | 0.0 | 3 | 2.1 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| 19A | 1 | 2.2 | 1 | 2.6 | 1 | 1.5 | 1 | 0.7 | 1 | 7.7 | 0 | 0.0 | 2 | 4.2 | 0 | 0.0 |
| 3 | 3 | 6.5 | 3 | 7.7 | 6 | 9.1 | 7 | 5.0 | 1 | 7.7 | 0 | 0.0 | 4 | 8.3 | 7 | 7.4 |
| 7F | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 3 | 3.2 | 0 | 0.0 |
| 8 | 4 | 8.7 | 3 | 7.7 | 5 | 7.6 | 20 | 14.2 | 1 | 7.7 | 2 | 33.3 | 7 | 14.6 | 11 | 11.6 |
| 12F | 1 | 2.2 | 2 | 5.1 | 0 | 0.0 | 1 | 0.7 | 0 | 0.0 | 1 | 2.1 | 1 | 1.1 | 0 | 0.0 |
| CAP due to *Streptococcus pneumoniae* (n = 141; 35.2%) | 15 | 10.6 | 18 | 12.8 | 19 | 13.5 | 47 | 33.3 | 5 | 3.5 | 2 | 1.4 | 18 | 12.8 | 31 | 22 |
| PCV13 serotypes | 6 | 40.0 | 5 | 31.3 | 7 | 46.7 | 14 | 29.8 | 2 | 40.0 | 0 | 0.0 | 6 | 33.3 | 11 | 35.5 |
| PCV15 serotypes | 7 | 46.7 | 6 | 33.3 | 7 | 36.8 | 15 | 31.9 | 2 | 40.0 | 0 | 0.0 | 7 | 38.9 | 12 | 38.7 |
| PCV20 serotypes | 12 | 80.0 | 11 | 61.1 | 13 | 68.4 | 37 | 78.7 | 3 | 60.0 | 2 | 100.0 | 15 | 83.3 | 25 | 80.6 |
| ≥65 y  |               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| All-cause CAP (n = 620) | 180 | 29.0 | 160 | 25.8 | 132 | 21.3 | 58 | 9.3 | 79 | 12.7 | 79 | 12.7 | 42 | 6.8 | 60 | 9.7 |
| PCV13 serotypes | 17 | 9.4 | 16 | 10.0 | 17 | 12.9 | 9 | 15.5 | 8 | 10.1 | 4 | 5.1 | 8 | 19.0 | 7 | 11.7 |
| PCV15 serotypes | 19 | 10.6 | 20 | 12.5 | 22 | 16.7 | 13 | 22.4 | 9 | 11.4 | 4 | 5.1 | 8 | 19.0 | 7 | 11.7 |
| PCV20 serotypes | 30 | 16.7 | 33 | 20.6 | 32 | 24.2 | 18 | 31.0 | 10 | 17.7 | 9 | 11.7 | 11 | 26.2 | 13 | 21.7 |
| Most prevalent serotypes (≥1% in total cases) | 1 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| 14 | 1 | 0.6 | 1 | 0.6 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 1.3 | 2 | 2.5 |
| 19A | 1 | 0.6 | 1 | 0.6 | 0 | 0.0 | 2 | 3.4 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| 3 | 14 | 7.8 | 10 | 6.3 | 14 | 10.6 | 5 | 8.6 | 5 | 6.3 | 1 | 1.3 | 6 | 14.3 |
| 7F | 1 | 0.6 | 1 | 0.6 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| 8 | 8 | 4.4 | 8 | 5.0 | 8 | 6.1 | 3 | 5.2 | 0 | 0.0 | 2 | 2.5 | 3 | 7.1 |
| CAP due to *S. pneumoniae* (n = 206; 33.2%) | 52 | 25.2 | 50 | 24.3 | 42 | 20.4 | 24 | 11.6 | 22 | 10.7 | 19 | 9.2 | 15 | 7.3 | 20 | 9.7 |
| PCV13 serotypes | 17 | 32.7 | 16 | 32.0 | 17 | 40.5 | 9 | 37.5 | 8 | 36.4 | 4 | 21.1 | 8 | 53.3 | 7 | 35.0 |
| PCV15 serotypes | 19 | 36.5 | 20 | 40.0 | 22 | 52.4 | 13 | 54.2 | 9 | 40.9 | 4 | 21.1 | 8 | 53.3 | 7 | 35.0 |
| PCV20 serotypes | 30 | 57.7 | 33 | 66.0 | 32 | 76.2 | 18 | 75.0 | 10 | 45.5 | 9 | 47.4 | 11 | 73.3 | 13 | 65.0 |

Patients might have >1 underlying condition. Six isolates of invasive pneumococcal pneumonias were not serotyped due to lack of sample or lysis.

Abbreviations: CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; PCV, pneumococcal conjugate vaccine.
herd immunity. This finding has been seen in other locations [20, 29] and may reflect for some serotypes—specifically, 3, 7F, 19A, and 19F—insufficient impact of PCV13 against carriage, short duration of protection against carriage, or transmission pathways other than from young children to adults.

We also found evidence that the plateau in pediatric PCV13 indirect effects may be influenced by pediatric PCV13 coverage. Specifically, Galicia had the highest coverage and the lowest proportion of PCV13-VT in pneumococcal CAP while Catalonia showed the reverse. Nevertheless, in both regions,

Figure 2. Serotype distribution (number of cases) in pneumococcal CAP by complications during hospitalization (≥5% in total cases). Abbreviations: CAP, community-acquired pneumonia; DPP, parapneumonic pleural effusion; ICU, intensive care unit; LoS, length of stay.

Table 5. Serotypes Associated WithSeverity on Admission or Complications During Hospitalization

| Serotype | P   | OR         | 95% CI          |
|----------|-----|------------|-----------------|
| CURB-65 risk classes 3–5 |
| 3        | .000 | 2.410      | 1.722–3.373     |
| Complicated pneumonia |
| 1        | .049 | 2.595      | 1.005–6.701     |
| 18C      | .014 | .070       | .008–.581       |
| 3        | .018 | 1.496      | 1.071–2.091     |
| 7F       | .014 | 3.663      | 1.297–10.343    |
| Sepsis/septic shock |
| 14       | .000 | 7.632      | 3.060–19.038    |
| 19A      | .016 | 3.653      | 1.270–10.511    |
| 8        | .000 | 4.879      | 2.415–9.859     |
| 22F      | .049 | 4.452      | 1.004–19.747    |
| ICU admission |
| 1        | .031 | 2.515      | 1.089–5.807     |
| 19A      | .008 | 2.758      | 1.306–5.825     |
| 3        | .000 | 2.165      | 1.480–3.168     |
| 12F      | .017 | 3.472      | 1.250–9.645     |

Only serotypes with significant values are shown in the table. For comparisons, no serotype identified is the reference parameter.

Abbreviations: CI, confidence interval; CURB 65, Score for Pneumonia Severity: Confusion, BUN > 19 mg/dL (7 mmol/L), Respiratory Rate ≥ 30, Systolic BP < 90 mmHg or Diastolic BP ≤ 60 mmHg, Age ≥ 65; ICU, intensive care unit; OR, odds ratio.
a plateau followed by an increase over the last study years was seen, consistent with data from the United Kingdom where similar findings were seen despite high pediatric PCV13 coverage [29].

Regardless of pediatric coverage and the specific mechanism involved, direct immunization of adults with high-valency PCVs may provide a solution. This approach is supported by robust vaccine efficacy against CAP due to serotypes 3, 7F, and 19A in a randomized controlled trial [22] and specifically for serotype 3 vaccine effectiveness in a “pooled analysis” [30]. While PCV13 could provide substantial benefit in preventing adult CAP, PCVs under development (PCV15 and PCV20), if licensed and efficacious, could provide marginally more value. For example, PCV20 serotypes were identified in 24% of CAP cases, compared to 14% for PCV13. The actual benefit of any particular PCV will depend on the specific serotypes, the contribution of these serotypes to CAP, the association of these serotypes with complicated or severe disease, and the serotype-specific vaccine effectiveness against CAP.

In our cohort, cases of complicated and severe CAP were common, and these were associated with specific serotypes. Serotype 3 was associated with both severe disease on admission and complications during hospitalization, consistent with results in children [31], in accordance with our results in adults. Serotype 8 is uncommonly carried in children but colonization in young adults has been observed before, and this population may represent the reservoir from which adult pneumococcal infections occur [32]. Both serotypes 3 and 8 remain commonly associated with adult CAP and their association with severe and complicated outcomes emphasizes the potential utility of existing and future vaccines.

Serotype 8 identification increased markedly over the last years of the study. Studies of hospitalized adults with CAP in the United Kingdom or in adults with IPD in Spain have reported similar results [29, 33]. In other countries, such as the United States, no increase in serotype 8 has been described [34]. Reasons for these disparities remain unknown but are consistent with an overall lower level of replacement disease in the United States versus Europe. Differences in serotype distribution at the time of pediatric PCV introduction may contribute. Additionally, the 2 regions have used pneumococcal vaccines in different ways. For example, Spain and the United Kingdom use a 2 + 1 pediatric PCV13 schedule, did not employ a pediatric catch-up strategy, and focus on PPSV23 for direct adult immunization [29, 33]; the United States uses PCV13 in a 3 + 1 infant schedule, employed a catch-up strategy to age 5 years, and uses both PCV13 and PPSV23 for direct adult immunization [34].

While our study design did not allow calculation of disease incidence, chronic conditions are recognized risk factors for CAP and pneumococcal disease [35]. Consistent with this, almost 90% of patients with CAP in our study had at least 1 comorbidity. Moreover, PCV13 serotypes were as common among persons with comorbidities as among persons without comorbidities. However, only 14.2% of the participants had received pneumococcal vaccination. These results reinforce the need for increasing awareness about the risk of CAP for patients with underlying conditions and about the pneumococcal serotype distribution in CAP according to the presence of comorbidities.

This study has some limitations. First, incidence rates could not be calculated and thus the possible impact of pediatric pneumococcal immunization on pneumococcal CAP in adults could not be properly assessed. Also, we report vaccination coverage of persons hospitalized with CAP, and this was substantially lower than national estimates from 2013–2014; however, we do not know the vaccination coverage specifically in most of the study regions, or among the persons most at risk of pneumonia. On the other hand, microbiological etiology could not be identified in 56% of the study participants. This is still a big challenge and, consequently, the majority of studies report a high percentage of undiagnosed pneumonia [36]. In addition, in our study, the UAD2 test was only available from 2016, limiting the analysis of the evolution in PCV20 serotypes to the last 2 study periods. Additionally, UAD1/2 assays are highly sensitive and specific for bacteremic pneumonia compared with the gold standard of blood culture. However, UAD1/2 sensitivity for nonbacteremic pneumonia is unknown because no reference standard exists [37]. Consequently, we may have underestimated the contribution of UAD1/2 serotypes to nonbacteremic pneumonia in our study. Moreover, while methodology and thus cutoffs for UAD1/2 positivity are similar across populations, some populations may have differences in cases that affect results—for example, antigenuria may, in theory, be lower in settings where patients present early or after pretreatment with antibiotics. On the other hand, our study did not enroll patients systematically, but this should not have affected results since characteristics of our study cohort are comparable to another Spanish study in which data on adults hospitalized with pneumococcal pneumonia were obtained from a national surveillance system for hospital data [38]. However, only hospitalized CAP cases were included in the study and results may not be representative of nonhospitalized patients with CAP. Finally, we included only immunocompetent patients and results may not apply to immunocompromised patients. A study of CAP cases in the United States found that approximately 46% of adults aged 65 years and older had an immunocompromising condition, emphasizing the importance of collecting information on this population [39].

Despite limitations, this large prospective cohort study describes trends in pneumococcal serotypes implicated in adult CAP over 8 years. Although the burden of PCV13 serotypes as a cause of pneumococcal CAP in immunocompetent adults in
Spain is decreasing, it remains high. Given the current distribution of serotypes in Spain, direct vaccination with PCV13 currently and with extended spectrum vaccines in the future may help address CAP burden among adult populations, if combined with programs to improve coverage. Additionally, ongoing surveillance to monitor serotype evolution will be critical to optimizing immunization policy.

Supplementary Data

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

Notes

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Supplementary Data

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