The burden of PCV13 serotypes in hospitalized pneumococcal pneumonia in Spain using a novel urinary antigen detection test. CAPA study

Rosario Menéndez a,f,⇑, Pedro Pablo España b, Emilio Pérez-Trallero c,f, Ane Uranga b, Raul Méndez a, Catia Cilloniz d, José María Marimón c,f, Isabel Cifuentes e, Cristina Méndez e, Antoni Torres d,f,⇑

a H. Universitario y Politécnico la Fe, Valencia, Spain
b H. Galdakao-Usansolo, Galdácano, Spain
c H. Universitario Donostia, San Sebastián, Spain
d H. Clinic, Barcelona, Spain
e Pfizer S.L.U., Madrid, Spain
f Biomedical Research Center Network for Respiratory Diseases (CIBERES), Madrid, Spain

Abstract

Background: Streptococcus pneumoniae serotypes distribution in community-acquired pneumonia (CAP) requiring hospitalization in adults after introduction of PCV13 in children is not well known. Our aim was to evaluate the distribution of serotypes in pneumococcal pneumonia according to risk factors and comorbidity conditions after the introduction of PCV13 in children in 2010.

Methods: A prospective study from 2011 to 2014 was performed in immunocompetent adults hospitalized with CAP in 3 Spanish hospitals. Microbiological confirmation was obtained using a serotype specific urinary antigen detection test (UAD test), Binax Now and conventional cultures.

Results: 1258 adults were enrolled and pneumococcal pneumonia (invasive disease in 17.7%) was confirmed in 368 (29.3%) and 17.6% of the any-cause CAP were caused by PVC13 serotypes (3.5% PCV7 serotypes). Around 60% of pneumococcal CAP were caused by PCV13 serotypes (74.6% in invasive episodes vs 57.4% in non-invasive ones). The most prevalent serotypes in invasive disease were 1, 3, 7F, 19A and 14. No significant differences were observed in the distribution of PCV13 serotypes across the study periods. Regarding comorbidity, the rate of PCV13 serotypes was similar among them, and it was slightly higher in those with no underlying conditions.

Conclusions: Serotypes included in PCV13 caused a significant proportion of CAP in adults with underlying conditions and in healthy adults, with no significant changes in cases due to PCV7 or PCV13 from 2011 to 2014, suggesting an insufficient indirect protection from childhood vaccination. Strategies for implementing pneumococcal vaccination of adults are encouraged to reduce the incidence of pneumococcal episodes.

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1. Introduction

Pneumococcal disease in adults, including community-acquired pneumonia (CAP) and invasive pneumococcal disease (IPD), is a global health problem, mainly affecting individuals with chronic diseases such as COPD, diabetes mellitus and heart disease. The increased risk for pneumococcal pneumonia is present all year around [1] and the total disease burden comes mainly from non-invasive episodes, because IPD represents only a fraction [2].

There are more than 90 different pneumococcal serotypes showing diverse clinical expression, invasiveness and outcome. The distribution of circulating pneumococcal serotypes depends on several factors including the presence of underlying diseases, contact with children, and vaccination status, and changes over time making continuous monitoring necessary. Vaccinating children with the 7-valent pneumococcal conjugate vaccine (PCV7) achieved a reduction in adult invasive pneumococcal disease caused by serotypes included in the vaccine and a drift in others...
The impact that the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) in 2010 for healthy children has had on the burden of pneumococcal pneumonia in adults due to PCV13 serotypes, particularly CAP without bacteraemia and CAP in high risk groups, is not well known [4]. Moreover, its indirect effect on pneumococcal pneumonia in adults is uncertain, although some impact has been found in the UK, where infant PCV coverage is around 95% [5]. In adults aged 65 and older, PCV13 has demonstrated efficacy in the prevention of pneumococcal pneumonia and invasive pneumococcal disease [6].

We hypothesized that the distribution of pneumococcal serotypes in adults, in both invasive and non-invasive pneumonia, might have changed after the introduction of PCV13 for children [7] and that this distribution may vary depending on the patients’ comorbidity and/or risk factors [8]. Given the fact that hospitalization for pneumonia is not decreasing [9] and that S. pneumoniae is the main causative microorganism, updated information will be a key factor for implementing effective strategies to decrease the incidence of CAP.

The aim of our study was to evaluate the burden of pneumococcal pneumonia in adults with regard to the distribution of PCV13 serotypes using the new UAD test in urine according to comorbidities and/or risk habits in immunocompetent patients after the introduction of PCV13 in children.

2. Patients and methods

A prospective multicentre epidemiological study was performed in three tertiary-care teaching hospitals from the National Spanish Health System, covering a population around 500,000 inhabitants (Hospital La Fe 285,000, Hospital Clinic 300,000, Hospital Galdakao 310,000) in immunocompetent adults aged ≥18 years, hospitalized during November 2011 to November 2014. Patients were considered to have CAP when they presented a new radiologic infiltrate accompanied by acute signs and symptoms suggestive of lower respiratory tract infection. Exclusion criteria were previous hospitalization that lasted at least 48 h within the 2 weeks prior to the current admission, active pulmonary tuberculosis, sickle cell anemia, immunosuppression (HIV infection/AIDS or immune suppression by any other cause), current cancer treatment or cancer treatment during the year prior to the admission into the intensive care unit (ICU), length of stay, and episodes requiring mechanical ventilation, treatment failure, other than respiratory failure. Treatment failure was considered achieved when vital signs of a patient were stable for a 24 h period (i.e. heart rate <100 beats per minute; respiratory rate <24 breaths per minute; axillary temperature <37.2 °C; systolic blood pressure >90 mmHg; oxygen saturation >90%; good level of consciousness; tolerance to oral via.

2.2. Definitions

Pneumococcal CAP etiology was considered present if any microbiological test was positive (Binax Now test, UAD test, blood culture, pleural culture and sputum culture). Invasive disease was confirmed if S. pneumoniae was isolated in blood and/or pleural fluid. Non-invasive disease was defined as confirmed pneumococcal CAP (by UAD test or Binax Now test) for which blood and/or pleural fluid culture results were negative. Pneumococcal serotypes were categorized as follows: 4, 6B, 9V, 14, 18C, 19F and 23F as “PCV7” serotypes; 1, 3, 5, 6A, 7F, 19A plus PCV7 included serotypes as “PCV13” serotypes.

Complicated CAP at presentation was considered if one of the following was present: multilobar infiltrates, bacteriaemia, pleural effusion or empyema, respiratory failure, severe sepsis or septic shock. Severe sepsis was considered present in cases of any organ failure other than respiratory failure. Treatment failure was considered according to Spanish guidelines [12]. Clinical stability with modified Halm criteria [13] was considered achieved when vital signs of a patient were stable for a 24 h period (i.e. heart rate <100 beats per minute; respiratory rate <24 breaths per minute; axillary temperature <37.2 °C; systolic blood pressure >90 mmHg; oxygen saturation >90%; good level of consciousness; tolerance to oral via.

2.3. Statistical analyses

Data analysis was performed using SPSS 19.0 software and EPI-DAT 3.0. For comparisons of independent samples, the Pearson chi-squared test (or the exact Fisher test for 2 × 2 tables or likelihood ratio for m×n tables, if necessary) for qualitative variables and Student’s t test, single factor ANOVA or its non-parametric equivalent U-Mann-Mann, H-Kruskal_Wallis for quantitative variables were used. The assumptions of normality and homoscedasticity of the variables were studied for use of parametric tests. The pneumococcal CAP group was stratified as invasive and non-invasive CAP.
3. Results

A total of 1258 patients were recruited from November 2011 to November 2014 (Table 1). Microbiological aetiology was found in 573 patients (45.5%); 368 (29.3%) S. pneumoniae, 24 (1.9%) L. pneumophila, 19 (1.5%) Staphylococcus aureus, 21 (1.7%) Influenza virus, 12 (1.0%) other virus, and 129 (10.3%) others microorganisms (Fig. 1). Pneumococcal CAP was diagnosed in 368 patients. No significant changes were observed in the percentage of all-cause CAP due to S. pneumoniae during the three years of the study (Table 2). Of the 368 cases of pneumococcal CAP, 65 (17.7%) were invasive and 303 (82.3%) were non-invasive. Pneumococcal CAP cases showed a higher proportion of asthmatic patients (11.4% vs 7.8%; p < 0.05) and alcohol abuse (4.9% vs 2.4%; p < 0.05), higher PSI (45.8% vs 39% for PSI risk class IV-V; p < 0.05) and CURB65 (1.49 vs 1.26; p < 0.001) punctuations and more ICU admission (13.4% vs 9.4%; p < 0.05).

3.1. Serotype distribution

Serotype distribution showed that 17.6% of all-cause CAP was caused by serotypes included in PCV13 without significant differences throughout the study period. Pneumococcal pneumonia was caused in 60% of the cases by PCV13 serotypes and it was greater in invasive diseases (74.6%) with no significant differences during the three years of the study (Table 2). The percentage of cases due to PCV7 serotypes was 12% for pneumococcal pneumonia and 9.5% in invasive episodes. The distribution of PCV13 serotypes identified in invasive pneumococcal pneumonia and in non-invasive pneumonia is shown in Fig. 2. Although invasive cases were caused more frequently by PCV13 serotypes than were in non-invasive cases (74.6% vs 57.4%; p < 0.05), no significant differences were observed for individual serotypes except for serotype 1 (27% vs 46%; p < 0.001). The most prevalent serotypes (representing at least 5%) identified in the invasive cases were 1 (27%), 3 (16%), 7F (14.3%), 14 (7.9%), 19A (7.9%) and 8 (6.3%). For the non-invasive pneumococcal pneumonia cases, the most frequent serotypes were 3 (23.1%), 7F (6.9%) 19A (6.9%) and 14 (5.3%). No significant differences were found within each hospital for all-cause CAP or pneumococcal pneumonia cases due to PCV7 or PCV13 serotypes during the study period.

The distribution of PCV13 serotypes according to initial presentation of pneumococcal pneumonia cases is depicted in Supplementary file 1. Serotype 3 was the most frequent serotype in all the variables related to initial severity except for cases complicated with bacteraemia which was serotype 1, with empyema which were serotypes 3 and 1 and, for cases complicated with severe sepsis which was serotype 7F.

Regarding serotype distribution according to underlying conditions, serotypes included in PCV13 accounted for 72.7% of cases in patients with no underlying conditions, for 69.3% (70/101) in patients with 1 underlying condition, and for 52.1% (110/211) in patients with at least two underlying conditions. Table 3 shows serotypes distribution according to the most prevalent underlying conditions in CAP and pneumococcal CAP episodes. In those with no underlying conditions there was a significantly higher total burden of PCV13 serotypes compared to patients with at least one underlying condition (72.2% vs 57.7%; p = 0.032).

3.2. Complications, LOS and outcome

During hospitalization, 358 patients presented new complications. Death occurred in 35 patients (2.8%), most of them (32 cases) during hospitalization. PCV13 serotypes distribution according to complications, length of stay and mortality are shown in Supplementary file 2. Serotype 3 was the most frequent in patients presenting complications during hospitalization, with the exception of the cases complicated with sepsis where 3 and 14 were equally frequent serotypes. Serotype 3 was also the most frequent serotype in patients requiring invasive mechanical ventilation, in cases with a length of stay at hospital or in the ICU longer than 7 days and, in cases taking more than 4 days to become clinically stable.

4. Discussion

The most outstanding findings of our study are 1. More than 60% of pneumococcal CAP cases in immunocompetent adults were caused by PCV13 serotypes (74.6% in invasive episodes and 57.4% in non-invasive episodes) showing no significant changes from 2011 to 2014. 2. The most frequent serotypes in pneumococcal CAP were 3, 1, 7F and 19A. 3. The percentage of CAP caused by PCV13 serotypes varied slightly according to the presence of underlying conditions (from 49.2% in previous CAP to 64.9% in diabetics) and was higher in patients without comorbidities and/or risk factors.

In our cohort, 29.3% of patients had pneumococcal CAP of whom 17.7% had invasive episodes. Regarding underlying conditions, 85.3% of our patients with pneumococcal CAP had at least one comorbidity and/or risk habit. Some chronic conditions, such as respiratory disease, current smoking, heart disease or diabetes, increase the risk for pneumococcal pneumonia between 3 and 9-fold [1]. That increase in risk is accumulative in patients with multiple risk factors mainly in those with 3 or more chronic conditions [14,15].

Regarding circulating serotypes, there is much more information in IPD [16–18] than on non-invasive disease despite the fact that pneumococcal CAP is responsible for the major burden of pneumococcal disease. Prior to PCV13 introduction, data on secular
### Table 2
Distribution of PCV7 and PCV13 vaccine serotypes in any-cause CAP and in invasive\(^a\) and non-invasive\(^b\) pneumococcal CAP by study period.

<table>
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<td>N = 431</td>
<td>N = 434</td>
<td>N = 393</td>
<td>N = 1258</td>
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<td>85 (19.6)</td>
<td>59 (15.0)</td>
<td>221 (17.6)</td>
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<td>13 (3.3)</td>
<td>44 (3.5)</td>
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<td>3 (25; 5.8%)</td>
<td>3 (32; 7.4%)</td>
<td>3 (23; 5.9%)</td>
<td>3 (80; 6.4%)</td>
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<td>7F (11; 2.6%)</td>
<td>7F (10; 2.3%)</td>
<td>7F (9; 2.3%)</td>
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<td>19A (8; 1.9%)</td>
<td>19A (12; 2.8%)</td>
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<td>19A (26; 2.1%)</td>
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<td>CAP due to \textit{S. pneumoniae}</td>
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<td>368 (29.3)</td>
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<td>31 (21.7)</td>
<td>15 (13.5)</td>
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<td>9 (60.0)</td>
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<td>5 (16.1)</td>
<td>6 (40)</td>
<td>16 (24.6)</td>
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<td>Most prevalent serotypes</td>
<td>1 (6; 31.5%)</td>
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<td>1 (3; 20%)</td>
<td>1 (17; 26.1)</td>
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<td>3 (2; 10.5%)</td>
<td>3 (5; 16.1%)</td>
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<td>7F (4; 21.1%)</td>
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<td>19A (1; 5.3%)</td>
<td>19A (3; 9.7%)</td>
<td>19A (1; 6.7%)</td>
<td>19A (5; 7.7%)</td>
<td>0.839</td>
</tr>
<tr>
<td></td>
<td>8 (1; 5.2%)</td>
<td>8 (2; 6.4%)</td>
<td>8 (1; 6.7%)</td>
<td>8 (4; 6.1%)</td>
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<td>22F (1; 5.3%)</td>
<td>22F (1; 3.2%)</td>
<td>22F (1; 6.7%)</td>
<td>22F (3; 4.6%)</td>
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<td>6C (2; 10.3%)</td>
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<td>6C (0)</td>
<td>6C (2; 3.0%)</td>
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<td>12F (0)</td>
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<td>12F (2; 3.0%)</td>
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<tr>
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<td>29 (0)</td>
<td>29 (0)</td>
<td>29 (1; 6.7%)</td>
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<td>0.232</td>
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<td></td>
<td>9V (0)</td>
<td>9V (1; 3.2%)</td>
<td>9V (0)</td>
<td>9V (1; 1.5)</td>
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</tr>
<tr>
<td>Non-invasive CAP(^b)</td>
<td>95 (83.3)</td>
<td>112 (78.3)</td>
<td>96 (86.5)</td>
<td>303 (82.3)</td>
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<td>PCV13 serotypes</td>
<td>64 (57.4)</td>
<td>60 (53.6)</td>
<td>50 (52.1)</td>
<td>174 (57.4)</td>
<td>0.057</td>
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<tr>
<td>PCV7 serotypes</td>
<td>13 (13.7)</td>
<td>12 (10.7)</td>
<td>13 (13.5)</td>
<td>38 (12.5)</td>
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<td>Most prevalent serotypes</td>
<td>3 (23; 24.2%)</td>
<td>3 (27; 24.1%)</td>
<td>3 (20; 20.8%)</td>
<td>3 (70; 23.1%)</td>
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<td>7F (7; 7.4%)</td>
<td>7F (7; 6.2%)</td>
<td>7F (7; 7.3%)</td>
<td>7F (21; 6.9%)</td>
<td>0.937</td>
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<td>19A (7; 7.4%)</td>
<td>19A (9; 8.0%)</td>
<td>19A (5; 5.2%)</td>
<td>19A (21; 6.9%)</td>
<td>0.701</td>
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<td>14 (6; 6.3%)</td>
<td>14 (5; 4.5%)</td>
<td>14 (5; 5.2%)</td>
<td>14 (16; 5.3%)</td>
<td>0.839</td>
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<td>1 (7; 7.4%)</td>
<td>1 (4; 3.6%)</td>
<td>1 (3; 3.1%)</td>
<td>1 (14; 4.6%)</td>
<td>0.327</td>
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<td>6A (6; 6.3%)</td>
<td>6A (1; 0.9%)</td>
<td>6A (2; 2.0%)</td>
<td>6A (9; 2.9%)</td>
<td>0.067</td>
</tr>
</tbody>
</table>

\(^a\) Isolate of \textit{S. pneumoniae} in blood and/or pleural fluid. Among 65 cases identified, 2 isolates not serotyped.

\(^b\) Confirmed pneumococcal CAP (by UAD or Binax Now) for which blood and/or pleural fluid culture result were negative. Data of non-PCV13 serotypes causing invasive CAP are included in italic font.
trend of pneumococci serotypes in Spain indicated that the percentage of PCV13 isolates among IPD cases showed an increasing trend until 2001, reaching nearly 90%, followed by a decrease, which was most prominent since 2010 when they accounted for around 70% of the isolates. A decrease of 32.3% was found in the percentage of PCV13 isolates from 2010 to 2013 [19].

We studied the burden of pneumococcal disease from PCV13 serotypes using a serotype specific urinary antigen detection test (Pfizer UAD test) [10] in addition to conventional serotyping of strains from blood or pleural fluid cultures. These tests achieve a more accurate determination of pneumococci serotypes in non-invasive pneumonia [20–22] than can be achieved by serotyping samples from lower respiratory tract. In fact, some serotypes might be underestimated if only invasive disease is taken into account and samples from the lower respiratory tract might confound colonization with infection.

Our findings showed that 13 years after introduction of PCV7/PCV13 for children in our country, mainly with private funding and with an estimated uptake of around 61% [23], 17.6% of CAP was caused by PCV13 serotypes, and that 3.5% of CAP was caused by PCV7 serotypes, indicating that a significant proportion of adults continue to develop vaccine serotype CAP. In addition, these

Table 3
Serotype distribution according to presence of underlying conditions. a

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Diabetes mellitus n (%)</th>
<th>COPD n (%)</th>
<th>Previous CAP n (%)</th>
<th>Smoking n (%)</th>
<th>Heart failure n (%)</th>
<th>Chronic renal failure n (%)</th>
<th>Asthma n (%)</th>
<th>No underlying conditions n (%)</th>
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<tr>
<td>Any- cause CAP</td>
<td>301 (23.9)</td>
<td>232 (18.4)</td>
<td>206 (16.4)</td>
<td>201 (16.0)</td>
<td>159 (12.6)</td>
<td>117 (9.3)</td>
<td>111 (8.8)</td>
<td>155 (12.3)</td>
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<td>PCV13 serotypes</td>
<td>50 (16.6)</td>
<td>37 (15.9)</td>
<td>31 (15.0)</td>
<td>37 (18.4)</td>
<td>20 (12.6)</td>
<td>20 (17.1)</td>
<td>22 (19.8)</td>
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<td>7 (3.4)</td>
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<td>Pneumococcal CAP</td>
<td>77 (25.6)</td>
<td>73 (31.5)</td>
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<td>PCV13 serotypes</td>
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<td>37 (50.7)</td>
<td>31 (49.2)</td>
<td>37 (62.7)</td>
<td>20 (54.1)</td>
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<td>Invasive CAP b</td>
<td>11 (14.3)</td>
<td>4 (5.5)</td>
<td>4 (6.3)</td>
<td>16 (27.1)</td>
<td>6 (6.2)</td>
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<td>3 (75.0)</td>
<td>10 (62.5)</td>
<td>3 (50.0)</td>
<td>5 (83.3)</td>
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<td>0 (0.0)</td>
<td>1 (12.5)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Non-invasive CAP b</td>
<td>66 (85.7)</td>
<td>69 (94.5)</td>
<td>59 (93.7)</td>
<td>43 (72.9)</td>
<td>31 (83.8)</td>
<td>27 (81.8)</td>
<td>34 (81.0)</td>
<td>42 (77.8)</td>
</tr>
<tr>
<td>303 (82.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCV13 serotypes</td>
<td>41 (62.1)</td>
<td>34 (49.3)</td>
<td>28 (45.7)</td>
<td>27 (62.8)</td>
<td>17 (54.8)</td>
<td>15 (55.6)</td>
<td>15 (44.1)</td>
<td>27 (64.3)</td>
</tr>
<tr>
<td>PCV7 serotypes</td>
<td>6 (9.1)</td>
<td>8 (11.6)</td>
<td>7 (11.9)</td>
<td>5 (11.6)</td>
<td>8 (25.8)</td>
<td>3 (11.1)</td>
<td>2 (5.9)</td>
<td>3 (7.1)</td>
</tr>
</tbody>
</table>

a Patients might have more than one underlying condition.

b Isolate of S. pneumoniae in blood and/or pleural fluid. Among 65 cases identified, 2 isolates not serotyped.

c Confirmed pneumococcal CAP (by UAD or Binax Now) for which blood and/or pleural fluid culture result were negative.

Please cite this article in press as: Menéndez R et al. The burden of PCV13 serotypes in hospitalized pneumococcal pneumonia in Spain using a novel urinary antigen detection test. CAPA study. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.08.007
results also suggest that childhood immunization has not elimi-
nated the circulation of PCV7 serotypes. This finding is similar to
that of Sherwin et al. [21] in USA and Bewick et al. in UK [20], with
a higher infant uptake, pointing out the insufficient indirect protec-
tion from pneumococcal CAP in adults as a result of childhood
vaccination.

Serotype 3 was the most prevalent serotype in CAP accounting
for 21.7% of the cases, followed by serotypes 1, 7F and 19A. Never-
thless, serotype 1 was the most prevalent (17 cases; 27%) in
invasive pneumococcal CAP, whereas serotype 3 was more fre-
quent (70 cases; 23%) in non-invasive pneumococcal CAP. Ser-
types 1 and 3 have been associated with complicated pneumonia,
specifically with empyema and necrotizing pneumonia [24,25]. The
different distribution of serotypes 1 and 3 in in-
vasive and non-invasive cases found in our study does not seem to be
explained by differences in nasopharyngeal carriage and patho-
genic potential. Serotype 1 is rarely identified in carriage but has
high pathogenic potential, whereas serotype 3 has low carriage
prevalence and high pathogenic potential [26]. On the other hand,
the high prevalence of PCV13 serotypes on pneumococcal CAP
found in our study, mainly for serotypes 3, 1, 7F and 19A, suggests
that indirect protection of adults against pneumococcal CAP is not
as evident as that observed against IPD [3,18] or against pneumo-
coccal CAP [5,26] in countries with well-established pneumococcal
vaccination programs for children using PCV7/PCV13. Neverthe-
less, we observed a non-significant decreasing trend in the per-
centage of non-invasive CAP cases due to PCV7/13 serotypes
throughout the study period. This decrease could be explained by
a possible early indirect effect of PCV13 infant vaccination, as pre-
viously reported [3,5]. However it should be taken into account
that a longer period of time and higher vaccine uptake is needed
for the herd effect to substantially decrease pneumococcal disease
at a population level [27].

We confirmed more invasive episodes in patients who smoked
(27%) followed by patients with asthma, and chronic renal and heart
disease. Interestingly, there were a considerable number of episodes
in patients without underlying conditions (22%). With regard to the
serotypes identified in invasive cases, we found that the percentage
of PCV13 serotypes ranged from 100% in those with no underlying
conditions to 75–85% in those with diabetes, COPD, chronic renal
disease and asthma. Ardany et al. [17] studied IPD episodes in
patients >65 years and found that PCV13 serotypes (19A, 3, 7F, 14
and 1) were the most prevalent, causing 59.3% of episodes.

The distribution of PCV13 serotypes in pneumococcal disease
related to comorbidity conditions and/or risk factors is quite
unknown although it has been suggested that different conditions
may predispose to different serotypes. The highest percentage
of PCV13 serotypes was found in diabetics (64.9%), smokers (62.7%),
and in patients with chronic renal disease, while it was lowest in
those with previous pneumonia (49.2%). Interestingly in those with
no underlying conditions the total burden of PCV13 serotypes was
the highest, and significantly higher than in patients with at least
one underlying condition. PCV7 serotypes showed higher percentages
in patients with heart disease or COPD. Except in asthmatic
patients, serotype 3 was the most prevalent, followed by 19A
and 7F. In COPD patients with exacerbations and pneumonia, ser-
types 10A, 11A, and 33F were found more frequently found in
sputum while 1, 3, 5 and 8 were more frequent in blood causing
bacteraemia [28].

The serotypes most frequently found in invasive episodes were
3, 1, 7F and 19A. Serotype 3 has been frequently associated with
complications such as empyema [29], septic shock [30] and respi-
ratory failure [31]. The different capacities of serotypes to adhere
to the respiratory epithelium due to the expression of different
adhesins has been found to be related to virulence [32]. In an
animal model, it has been shown that the different capsular types pro-
voke diverse inflammatory responses, with 14 and 23F among
those responsible for the most severe responses [33]. Nevertheless,
we found no significant differences in mortality [34] as it has been
reported that host factors have greater influence on outcomes [35].

This study has some limitations: 1) the CAP cases included were
only those admitted to hospital and thus, the characteristics and
distribution of serotypes in non-hospitalized patients is not
known; 2) incidence rates could not be calculated and thus, the
potential impact of childhood pneumococcal vaccination on pneu-
 mococcal CAP is not well characterized; 3) only 65 invasive sam-
plies were sent to the central microbiology laboratory and thus,
invasive episodes may have been underestimated. Nevertheless,
the results of this study offer some insights and suggestions as to
the distribution of serotypes in pneumococcal CAP, and especially
in non-invasive pneumococcal CAP.

In summary, we found that pneumococcal serotypes included in
PCV13 cause a significant proportion of CAP in adults, but found no
significant changes in cases due to PCV7 or PCV13 serotypes from
2011 to 2014, suggesting an insufficient indirect protection from
pneumococcal vaccination of infants with PCV7/PCV13 during the
study period. That proportion varied slightly according to the
presence of underlying conditions and was higher in healthy
adults, suggesting that a high percentage of adults would benefit
from direct pneumococcal CAP protection. There is a need for
strategies to implement pneumococcal conjugate vaccination to
prevent pneumococcal pneumonia in adults in order to drastically
reduce the current burden of the disease and to continue monitor-
ing serotype distribution of non-invasive cases in the future.

Acknowledgements

Members of the CAPA study team are: A. Torres, C. Cilloniz, A.
San José, F. Marco, E. Polverino, R. Amaro, (H. Clinic, Barcelona,
Spain); R. Menéndez, R. Méndez, I. Amara, J.L. López Hontangas,
B. Montull, A. Gimeno, A. Gil (H. Universitario y Politécnico La Fe,
Valencia, Spain); PP. España, A. Uranga, A.P. Martínez de la Fuente,
(H. Galdakao-Usanoso, Galdácano, Spain); E. Pérez-Trailero, J.M.
Marimón, M. Ercibengoa (H. Universitario Donostia, San Sebastián,
Spain); A. Fernández-Villar, M.I. Botana, F. Vasallo (H. Alvaro Cun-
quero, Vigo, Spain); C. Méndez, I. Cifuentes, C. Balseiro, A. García,
M. Del Amo, J. Sáez and M.L. Samaniego (Pfizer S.L.U., Madrid,
Spain).

Funding
This study was sponsored by Pfizer.

Disclaimer
The views expressed in this publication are those of the author(s)
and not necessarily those of the sponsor.

Competing interests
R.M., A. T., P.P. E. and E. P-T report grants to their Institutions from
Pfizer S.L.U., Madrid, Spain, for this study, and support from Pfizer
S.L.U. for travelling to meetings for the study or other purposes
during the conduction of the study.
C.M., I.C., C.B., A.G., J.S. and M.L. S. are employees of Pfizer S.L.U.,
Madrid, Spain.

Ethics approval
The ethics committee of each hospital approved the study. Patients
provided written informed consent to participate in the study.