Pneumococcal Bacteremia Among Infants With Fever Without Known Source Before and After Introduction of Pneumococcal Conjugate Vaccine in the Basque Country of Spain

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Background: The introduction of vaccination with the heptavalent pneumococcal conjugate vaccine (PCV7) has produced an important decrease in the incidence of Streptococcus pneumoniae occult bacteremia (OB). In Spain, PCV7 became available in the last months of 2001, but, to date, it has not been included in the official vaccination schedule of the public health system.

Objective: To describe the impact of pneumococcal vaccination with PCV7 on the incidence of OB caused by S. pneumoniae in infants aged 3–36 months presenting to our pediatric emergency department.

Patients and Methods: This is a retrospective case series of all blood cultures obtained from January 1, 2000 to December 31, 2005 in our pediatric emergency department from infants with fever without known source. We evaluated rates of blood cultures positive with S. pneumoniae before (January 1, 2000–December 31, 2001) and after (January 1, 2004–December 31, 2005) PCV7 introduction, excluding 2 transitional years (January 1, 2002–December 31, 2003).

Results: Implementation of vaccination with PVC7 in our area resulted in a 57.5% reduction of OB caused by S. pneumoniae (1.62–0.69%) (P < 0.05). There were 30 cases of bacteremia caused by S. pneumoniae, 19 before and 11 after PCV7 introduction. Between the 2 periods of time studied the number of cases of infants aged 3–36 months with fever without known source, increased from 8052 to 9799 (21.6%) and the total blood cultures drawn significantly increased from 1171 to 1575 (34.5%) (P < 0.01). Despite more frequent blood culturing in febrile patients, the rate of OB caused by PCV7-serotypes decreased significantly by 79% (1.62–0.69%) (P < 0.05). There were 30 cases of bacteremia caused by nonvaccine serotypes increased minimally from 0.42 to 0.44%. In the post-PVC7 period, 4 infants presented with S. pneumoniae OB caused by PCV7 serotypes; 2 had not received PCV7, and 2 (6 and 7 months old) had received one dose.

Conclusion: After PCV7 introduction in our area, rates of S. pneumoniae OB caused by vaccine serotypes decreased significantly despite only moderate use of the vaccine in our population.

Key Words: pneumococcal bacteremia, febrile infants, pneumococcal conjugate vaccine

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of PCV7 in the various Spanish regions is irregular; attending to the percentage of vaccinated children presenting to our emergency department, the current coverage with PCV7 in children less than 2-year-old is approximately 50% in Basque Country.10 The vaccine targeted 80–85% of serotypes prevalent in the United States, (4, 6B, 9V, 14, 18C, 19F, and 23F) in children aged 2 months to 2 years; that coverage is alent in the United States, (4, 6B, 9V, 14, 18C, 19F, and 23F) in children aged 2 months to 2 years; that coverage is also not available in the United States. 

The objective of this study was to describe the impact of incomplete pneumococcal immunization on the incidence of pneumococcal bacteremia in infants aged 3–36 months presenting to our pediatric emergency department.

**PATIENTS AND METHODS**

**Study Design.** This was a retrospective case series of all blood cultures collected from children aged 3 months to 3 years with FWS at our pediatric emergency department from January 1, 2000 to December 31, 2005. From our computerized database we identified infants diagnosed with FWS and recorded their medical record number, gender, date of birth, date of visit, ancillary tests practiced, and organism identified in blood culture.

**Study Period.** The study period extended from January 1, 2000 through December 31, 2005. Thus we defined a pre-PCV7 period (January 1, 2000–December 31, 2001), a 2-year transition period (January 1, 2002–December 31, 2003) to allow vaccine uptake in the population and a post-PCV7 study period (January 1, 2004–December 31, 2005).

**Case Definition.** Cases were defined as infants with FWS who had blood cultures obtained in our pediatric emergency department. FWS was defined as axillary or rectal temperature taken at home or rectal temperature in the pediatric emergency department of a temperature 38°C or higher without catarrhal or respiratory symptoms/signs, or a diarrheal process in a patient with a normal physical examination. Subjects selected had been previously healthy, and those with immunodeficiency or oncology diagnoses were excluded. Children with asthma receiving either inhaled or oral steroid therapy were not excluded.

**S. pneumoniae OB Definition.** Only well-appearing infants aged 3–36 months diagnosed with FWS and positive blood culture with S. pneumoniae were considered as having an S. pneumoniae OB. We obtained serotype information on all cases of S. pneumoniae causing OB. During the post-PCV7 study period immunization status with PCV7 was also recorded.

**Statistical Analysis.** Data were expressed as mean and standard deviation for quantitative variables or numbers and percentages for categorical variables. Continuous data were compared with the Student’s t test. Categorical data were examined using the χ² test or the Fisher’s exact test probability test. The SPSS 10.0 for Windows (SPSS Inc., Chicago, IL) was used for all statistical calculations. Statistical significance was defined as P < 0.05.

**RESULTS**

During the 3 study periods, 8052, 8358, and 9799 episodes, respectively, of FWS in infants aged 3–36 months were registered in the pediatric emergency department. The total blood cultures drawn in post-PCV7 years were 34.5% greater than in the pre-PCV7 period from 1171 to 1575. The general characteristics of the study population are described in Table 1.

Of 37 cases of S. pneumoniae OB identified between January 1, 2000 and December 31, 2005, 7 (19%) occurred during the transition years. The study population comprised the remaining 30 cases from 2 pre-PCV7 years (n = 19) and 2 post-PCV7 years (n = 11). Pneumococcal serotypes isolated are showed in Table 2. During the period of study, 5 blood cultures were positive with other bacteria in infants aged 3–36 months with FWS, 3 in pre-PCV7 years (S. pyogenes, Haemophilus influenzae, and Salmonella enteritidis), 1 in the transition years (Neisseria meningitidis) and 1 (Salmonella enteritidis) in post-PCV7 years. From 30 cases of S. pneumoniae OB in study population, 18 (60%) were caused by PCV7 serotypes: 6 (6B), 5 (14), 3 (19F), 2 (18C), 1 (23F), and 4 (1), and 12 caused by nonvaccine serotypes: 7 (19A), 1 (6A), 1 (12), 1(23A), 1 (3), and 1 (15A). Fourteen cases (77.7%) caused by vaccine serotypes occurred in pre-PCV7 years.

Implementation of vaccination with PCV7 in our area coincided with in a 57.5% reduction in the rate of positive blood cultures for S. pneumoniae in infants

### TABLE 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre-PCV7 (n = 8052)</th>
<th>Transitional Years (n = 8358)</th>
<th>Post-PCV7 (n = 9799)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4347</td>
<td>4798</td>
<td>5336</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>3705</td>
<td>3740</td>
<td>4463</td>
<td>NS</td>
</tr>
<tr>
<td>Age, mo, mean (SD)</td>
<td>16.75 (8.3)</td>
<td>16.32 (7.9)</td>
<td>16.13 (8.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Workup studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (%)</td>
<td>1299 (16.1)</td>
<td>1443 (16.9)</td>
<td>1653 (16.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Blood culture (%)</td>
<td>1171 (14.5)</td>
<td>1117 (13.1)</td>
<td>1575 (16.1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Lumbar puncture (%)</td>
<td>185 (2.3)</td>
<td>184 (2.1)</td>
<td>165 (1.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stay in the observation unit (%)</td>
<td>250 (3.1)</td>
<td>255 (2.9)</td>
<td>305 (3.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital admission (%)</td>
<td>87 (1.1)</td>
<td>94 (1.1)</td>
<td>85 (0.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Comparison between pre and post-PCV7 years.
checked for OB (1.62–0.69%) (P < 0.05). The rate of OB caused by PCV7-serotypes also significantly decreased by 79% (1.19–0.25%) (P < 0.01). The incidence of OB caused by nonvaccine serotypes increased from 0.42% to 0.44% (Fig. 1). In the post-PCV7 period, 4 infants presented with \( S. pneumoniae \) OB caused by vaccine serotypes; 2 had not received PCV7 and 2 (6 and 7 months old) had only received one dose.

Twenty-seven patients (90%) with \( S. pneumoniae \) OB had a favorable clinical course and most of them were treated as outpatients with oral amoxicillin. Six patients (31.5%) in the pre-PCV7 period were admitted and treated with parenteral ceftriaxone. Eleven patients (7 in the pre-PCV7 and 4 in post-PCV7 years) did not initially receive antibiotics, 6 of them were without fever 48 hours after pediatric emergency department consultation, 5 were again evaluated and 3 treated with oral amoxicillin after being diagnosed with otitis. Three patients, all of them in the pre-PCV7 years were again evaluated in pediatric emergency department in the following 48 hours and diagnosed with meningitis. Two patients had not received antibiotics when blood culture was taken at their first consultation. One of these patients developed severe hydrocephalus and neurologic impairment from meningitis. There were no differences in characteristics of \( S. pneumoniae \) OB patients in pre and post-PCV7 years (Table 3).

During the study years 9 patients diagnosed with diseases other than OB had positive blood cultures with \( S. pneumoniae \). Three patients in the pre-PCV7 years [2 cases of periorbital cellulitis (serotypes 14 and 19A) and one case of bacteremic pneumonia (serotype 11)] and 6 in the post-PCV7 years (4 cases of bacteremic pneumonia, serotypes 19A, 24, 1 year 6A and 2 cases of meningitis, serotypes 7 and 19A). Including these patients, we would have a more pronounced increase (0.59–0.82) (0.49) of nonvaccine serotypes isolated in blood cultures after implementation of PCV7.

**DISCUSSION**

This study showed a decline in \( S. pneumoniae \) OB after implementation of vaccination with PCV7 in our area (1.6–0.6%). This change was attributed to a decrease in the rate of disease caused by PCV7-serotypes. This finding has been broadly reported in the United States, but to date, this is the first study of OB rates in infants in Europe before and after PCV7 arrival. The total number of children in the 3–36 months age group increased only slightly during study period. Any change in the number of blood cultures was likely due to more frequent obtaining of blood cultures rather than a larger population of patients.

Invasive pneumococcal disease incidence reported by some Western European countries before the availability of PCV7 was 4- to 8-fold less than those reported in the United States. The serotype coverage by PCV7 in European children is 5–15% less than that of the overall invasive pneumococcal disease burden in US children. These facts have delayed adoption of universal vaccination with PCV7 in Europe. Recent US data have reported vaccine efficacy for prevention.
of invasive pneumococcal disease extending to nonvaccinated children and adults (herd effect) and a lack of a significant increase of invasive pneumococcal disease caused by non-PCV7 serotypes. Moreover, new data about invasive pneumococcal disease incidence in more recent European studies have led to some European countries, such as France, Germany, England, Norway, Holland, and Belgium to adopt universal vaccination with PCV7 in their official schedules.

In Spain, invasive pneumococcal disease is not obligatorily reported which precluded the collection of official data about its incidence, morbidity, and mortality before and after PCV7 availability in Spain. This lack of data has led to criticism that published epidemiologic studies on invasive pneumococcal disease in Spain have limited value. This is one of the reasons that although PCV-7 was licensed for usage in Spain in 2001, it has not been included in the official vaccination schedule of the Public Health System. However, the Spanish Pediatric Association does recommend its use, and advises pediatricians to use the vaccine, at least in children less than 2 years of age. This situation has led to variable usage of PCV7 in Spanish children depending on factors as influence of local health leaders and family finances and the pediatrician’s knowledge about the vaccine. PCV7 coverage is variable in different regions of Spain. In one recent study carried out in our pediatric emergency department, we found that nearly 50% of infants 3–36 months old with FWS had been vaccinated with PCV7.

Our results shows a similar S. pneumoniae OB rate in infants aged 3–36 months in pre-PCV7 years as recorded in US studies, and a serotype coverage of 75%. The serotype coverage is consistent with that reported in published studies on pneumococcal serotype prevalence causing invasive pneumococcal disease in Europe and Spain. However, the main reason for this difference could be the current vaccination rate in our area, around 50%. On the other hand, the decrease in S. pneumoniae OB observed in the disease caused by PCV7 serotypes is consistent with that reported in other studies and higher than expected knowing PCV7 vaccination rates in our area. It is possible that indirect protection of unvaccinated children played a roll in this unexpected result. Other potential explanations for the decrease in S. pneumoniae OB other than from vaccination with PCV7 should be considered. Changes in the diagnoses or treatment of infectious diseases in infants are unlikely to account for the change in S. pneumoniae OB rate. Although guidelines for the evaluation of infants have changed in our pediatric emergency department leading to a decrease in the frequency of obtaining blood cultures in children vaccinated with PCV7, the overall number of blood culture drawn has increased, mainly involving the nonvaccinated population. This fact could have caused a higher S. pneumoniae OB detection in post-PCV7 years and a lesser difference in S. pneumoniae OB rate between the 2 study periods.

The vaccine effectiveness in this study is also supported by the absence of higher S. pneumoniae OB caused by PCV7 serotypes in fully vaccinated infants. Although we did not observe an increased rate of non-PVC7 serotypes, we had limited power to detect such an increase. Among non-PCV7 serotypes isolated before and after PCV7, the most notable serotype is 19A (58% in OB cases). This serotype has been described to be increasing after vaccination with PCV7 showing that the levels and functional activity of the cross-reactive antibodies to serotype 19F induced by PCV7 are not sufficient to provide cross-protection against diseases caused by serotype 19A.

The present results should be interpreted taking into account some limitations of the study, including its retrospective basis that limited the collection of data and the small sample size that could have altered the S. pneumoniae OB rate in both study populations. We think that these facts would have probably affected both groups in the same proportion. On the other hand, differences encountered in patient management between the 2 study periods, especially in the number of blood cultures drawn, could underestimate S. pneumoniae OB rate in the pre-PCV7 years. Our results cannot be applied to other Spanish regions owing to their different PCV7 coverage rates.

Since PCV7 introduction in our area (Basque Country—Spain), rates of S. pneumoniae OB caused by vaccine serotypes have decreased significantly. Our results provide further indirect evidence that PCV7 could have resulted in herd immunity because the decrease in S. pneumoniae OB rate observed is higher than expected resulting from PCV7 coverage in our area. New guidelines are needed to approach the previously healthy febrile infant in the outpatient setting.

REFERENCES


670