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Reduced incidence of invasive pneumococcal disease after introduction of the 13-valent conjugate vaccine in Navarre, Spain, 2001–2013

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ABSTRACT

Pneumococcal conjugate vaccines (PCVs) were licensed for use in children and became available for private purchase in Spain in 2001 (PCV7), 2009 (PCV10) and 2010 (PCV13). This study evaluates changes in the incidence of invasive pneumococcal disease (IPD) and the pattern of serotypes isolated in Navarre, Spain, between the period of use of PCV7 (2004–2009) and that of PCV13 (2010–2013). The percentage of children <2 years who received at least one dose of PCV in these periods ranged from 25 to 61% and 61 to 78%, respectively.

Between the periods 2004–2009 and 2010–2013 IPD incidence declined by 37%, from 14.9 to 9.4 cases/100,000 inhabitants ($p < 0.001$). In children <5 years it fell by 69% ($p < 0.001$), in persons aged 5–64 years, by 34% ($p < 0.001$), and in those ≥65, by 23% ($p = 0.024$). The incidence of cases due to PCV13 serotypes declined by 81% ($p < 0.001$) in children <5 years and by 52% ($p < 0.001$) in the whole population. No significant changes were seen in the distribution of clinical presentations or in disease severity.

The incidence of IPD has declined and the pattern of serotypes causing IPD has changed notably in children and moderately in adults following the replacement of PCV7 by PCV13.

1. Introduction

Streptococcus pneumoniae remains an important worldwide cause of morbidity and mortality, particularly in young children, the elderly and those who are immunocompromised [1,2]. Invasive pneumococcal disease (IPD) is of particular interest because of its high rate of complications and mortality [3,4]. Several conjugate vaccines have proven to be effective in preventing childhood cases of IPD caused by the serotypes included in these vaccines [5–7]. The effectiveness of each pneumococcal conjugate vaccine (PCV) is largely determined by the match between the serotypes in circulation and the vaccine serotypes, which is one reason for the large differences in effectiveness depending on the region or period studied [8,9]. In many countries, introduction of the heptavalent pneumococcal conjugate vaccine (PCV7) in the childhood vaccination schedule was followed by a decline in the overall incidence of IPD [8,10,11]; in other places however, the impact was considerably smaller [12–16].

PCV7 became available in Navarre, Spain in June 2001; the 10-valent vaccine (PCV10) was introduced in November 2009, and the

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PCV7 was replaced by the 13-valent vaccine (PCV13) in June 2010. The PCVs are financed by the public health system only for high-risk children. The Spanish Association of Paediatrics recommends a schedule with doses at 2, 4 and 6 months plus a booster dose at 12–15 months for all children [17], and coverage has increased progressively through the private market. The effectiveness of PCV7 in children <5 years was low due to the increased risk of IPD caused by non-vaccine serotypes among those vaccinated [18,19]. After coverage with PCV7 was expanded, there was considerable replacement by non-vaccine serotypes which largely neutralised its impact [12,13]. The 23-valent polysaccharide pneumococcal vaccine (PPV23) was initially used in persons aged ≥2 years with high-risk conditions and in late 2007 a widespread vaccination campaign targeting all persons ≥65 years of age was carried out.

To date, few studies have described the impact on the epidemiology of IPD of the change to the new PCVs with additional serotypes [20–24]. The present study aims to evaluate changes in IPD incidence and the pattern of serotypes isolated in the population of Navarre following the replacement of PCV7 by PCV13 in children, taking into account the changes previously produced after the introduction of PCV7.

2. Methods

2.1. IPD surveillance system

This study was based on active population-based IPD surveillance in Navarre (~640,000 inhabitants). Since September 2000, all microbiology laboratories have reported all cases of *S. pneumoniae* detected in invasive samples. Health professionals complete the search for cases by reviewing laboratory reports, and collect clinical and epidemiological information from the medical records.

The Navarre Ethical Committee for Medical Research approved the study protocol.

2.2. Inclusion criteria and definitions

We included the cases of IPD in Navarre residents diagnosed between 2001 and 2013. An IPD case was defined as isolation of *S. pneumoniae* from a normally sterile body site. Culture-negative cases were not included in this analysis. Meningitis was defined as *S. pneumoniae* identified in cerebrospinal fluid, or clinical diagnosis of meningitis by attending physicians with *S. pneumoniae* isolated from blood culture. Pneumonia was defined as *S. pneumoniae* in pleural fluid or in blood with clinical and/or radiologic diagnosis of pneumonia by attending physicians, and was considered complicated pneumonia when the diagnosis included pleural empyema, lung abscess, necrotising pneumonia, or parapneumonic effusion requiring drainage, lung decortication or lobectomy. Bacteraemia was defined as *S. pneumoniae* cultured in blood with no distinctive clinical syndrome. Only one IPD episode per patient was included unless clinical sample dates were >30 days apart or the serotypes of isolates were different. Patients were considered to be hospitalised if admitted for >24 h or in the event of intrahospital death.

Three periods were considered: 2001–2003, when PCV7 use was limited; 2004–2009, when use of PCV7 was expanded; and 2010–2013, when it was replaced by PCV13.

2.3. Pneumococcal vaccination

Pneumococcal vaccine coverage in the population and the information on doses received by cases were obtained from the regional vaccination register [25], including those acquired in the private market. In cases, only doses administered up to 15 days before the date of symptom onset were considered. In accordance with the 3 + 1 schedule initially recommended by the manufacturer, we defined complete vaccination as: three doses of PCV, if vaccination began between 2 and 6 months of age; two doses, if it began between 7 and 23 months; and one dose if vaccination began at 24 months or older. A booster dose was also required during the second year of life in children ≥12 months who began vaccination before that age.

2.4. Microbiological methods

Pneumococcal isolates were serotyped at the national reference laboratory (Instituto de Salud Carlos III, Spain) by the Quellung reaction or by dot-blot assay [26]. Serotypes 6A and 6C were prospectively distinguished from each other from 2010 onwards by PCR and retrospectively retested for previous years. Serotypes were assigned to the following mutually exclusive categories: PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F and 23F), additional PCV13 serotypes (1, 3, 5, 6A, 7F and 19A), PPV23 serotypes that are not included in PCV13 (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F), and non-vaccine serotypes (all other types).

2.5. Data analysis

The denominators for calculating the rates were the population residing in Navarre on 1 January of each year, obtained from the National Statistics Institute. We estimated the mean annual incidence rates of IPD in each of the three periods, and the percentage change in the rates was computed using the relative difference between one period and the preceding one. For rate calculations, cases with missing serotype data were distributed according to those with known serotype for the same period and age group. Exact methods were used in the rate comparisons. Proportions were compared by using the χ^2 test or Fisher exact test, as appropriate. Continuous variables were described as median and interquartile ranges and compared by using the Mann–Whitney *U* test. Values with $p < 0.05$ in a two-tailed test were considered statistically significant. The analyses were conducted using Stata version 10.1 (StataCorp LP).

3. Results

3.1. Pneumococcal vaccine coverage

Since the introduction of PCV in Navarre, its coverage has increased progressively. The percentage of children <2 years who had received any dose of PCV at the end of 2003, 2009 and 2013 was 25%, 61% and 78%, respectively. Beginning in 2010 PCV13 was used predominantly, while the maximum coverage achieved with PCV10 was only 13% at the end of 2010. Most of the vaccinated children had received a complete schedule by age 2 years (Fig. 1). Since late 2007, coverage with PPV23 in persons aged ≥65 years has remained at around 57%.

3.2. Incidence of invasive pneumococcal disease

Between 2001 and 2013, 1050 cases of IPD were reported in Navarre, of which 206 (20%) were in children <5 years and 423 (40%) were in adults ≥65 years; 565 (54%) had an underlying medical condition, most frequently, chronic heart disease, immunosuppression or diabetes; 923 (88%) were hospitalised, and 123 (12%) died.

In the period 2001–2003 the incidence of IPD was 15.6 cases per 100,000 inhabitants, and was higher in children <5 years (87.1 per 100,000) and in persons aged ≥65 years (33.6 per 100,000) than in those 5–64 years (7.3 per 100,000). Between this and the following period (2004–2009), the incidence of IPD due to PCV7 serotypes declined by 57% ($p < 0.001$), and was especially pronounced in children <5 years (86%, $p < 0.001$), although a reduction of 46% was also