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Effectiveness of different vaccine schedules for heptavalent and 13-valent conjugate vaccines against pneumococcal disease in the Community of Madrid

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ABSTRACT

Introduction: The heptavalent pneumococcal conjugate vaccine (PCV-7) was added to the childhood routine vaccination program in the Community of Madrid in November of 2006 with 3 + 1 recommended doses and a catch-up for those under 2 years old. In June 2010, PCV-7 was replaced by 13-valent vaccine (PCV-13) with 2 + 1 recommended doses. In July of 2012, the PCV-13 was removed from the funded program and reintroduced again (2 + 1 recommended doses) in December 2014. In between, children were vaccinated privately with 3 + 1 recommended doses of PCV-13. The aim of this study was to evaluate the effectiveness of each vaccination schedule used in the Community of Madrid.

Methods: We included all cases of invasive pneumococcal disease (IPD) reported between 2007 and 2015 to the Notifiable Diseases Surveillance System. Vaccination information was obtained from the Immunization Registry. Vaccine effectiveness (VE) was estimated using the indirect cohort design for cases with serotype information.

Results: A total 779 cases were included in the study. Among them 47.6% of the cases were primo-vaccinated with booster, 20% primo-vaccinated, 15.9% incompletely primo-vaccinated and 16.5% not vaccinated. The VE for ≥1 doses of any PCV was 82% (CI 95%: 67.8–89.9%): 91.9% (CI 95%: 76.5–97.2%) for PCV-7 and 77.2% (48.6–89.9%) for PCV-13. VE in those receiving the full 2 + 1 or 3 + 1 schedules was 100% for both vaccines.

Conclusions: A high number of vaccine failures were reported in children before they had the opportunity to receive the booster dose, especially due to PCV-13-non-PCV-7 serotypes. VE was higher for PCV-7 compared to PCV-13, except for those that received the complete schedule with booster that achieved 100% of VE, which shows the relevance of the vaccines and complying with all doses scheduled.

1. Introduction

Streptococcus pneumoniae (pneumococcus) is a major cause of morbidity and mortality worldwide. It causes nearly one million deaths annually worldwide among those under five years of age [1] and can cause a wide spectrum of diseases, ranging from upper-respiratory-tract infections to severe invasive pneumococcal diseases (IPD). Epidemiological surveillance in Spain focuses on these invasive forms [2].

The incidence of IPD in industrialized countries varies widely depending on the geographic area [3]. In Europe, the incidence was 4.8 cases per 100,000 people in 2012, ranging from 0.19 in Luxembourg to 15.81 in Denmark [4].

To date, >90 different pneumococcal serotypes have been described. The highest incidence rates occur in children under two years of age and adults over 65 years of age. The case-fatality rates for IPD cases ranged between 4% and 29% among European countries in 2012 [5]. Cases presenting with bacteraemia

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and meningitis, patients with underlying conditions and the older age groups presented high case-fatality rates [6].

The most effective measure to prevent IPD is vaccination. The World Health Organization (WHO) has recommended including conjugate vaccines in childhood routine vaccination programs worldwide since 2006 [7].

In Spain, since 2001, vaccination with the capsular polysaccharide vaccine (PPV-23) is recommended for individuals more than two years old who are at high risk for pneumococcal disease, such as those presenting some chronic diseases, immunosuppression or aesplenia [8,9]. In 2005, the Community of Madrid extended the recommendations to vaccinate adults over 59 years old with PPV-23, in conjunction with the influenza vaccine [10].

In November of 2006, the Community of Madrid included the pneumococcal conjugate vaccine against seven serotypes (PCV-7 for serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) in a 3 + 1 pattern (doses at 2, 4, 6 and 18 months). Coincident with the introduction of PCV-7 in the children's routine vaccination program, the vaccine was indicated for all children under two years of age (those born on or after November 1, 2004) [11].

In June 2010, PCV-7 was replaced by the new conjugated vaccine against 13 serotypes (PCV-13), which protects against serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18 C, 19A, 19F y 23F. This change applied to children born from June 2010 and on and followed a 2 + 1 schedule (doses at 2, 4 and 15 months). The children born four months before the vaccine change got a mixture of PCV7 and PCV13.

In July 2012, PCV-13 was excluded from the funded routine vaccination program and reintroduced again (2 + 1) in December 2014. In between, vaccination in high-risk groups continued, while vaccination of infants was done privately following the recommendations with a 3 + 1 schedule (doses at 2, 4, 6 and 15 months) [12].

Pneumococcal disease was also included in February 2007 as a Reportable Disease in the Community of Madrid [13]. Serotyping was routinely performed in the Community of Madrid Regional Public Health Laboratory.

The aims of this study are to describe cases of IPD reported to the surveillance system and assess the short- and long-term vaccine effectiveness (VE) of PCV-7 and PCV-13 in the infant population targeted by the vaccination programs (infants born in 2004 and after) in the Community of Madrid.

2. Methods

2.1. Study population

This study included patients with confirmed IPD reported to the Notifiable Diseases Surveillance System, based on mandatory reporting in clinical and laboratory routine practice and covering the total resident population of the Community of Madrid:

- with an IPD onset date between January of 2007 and December of 2015;
- under 10 years old (those born in 2004 and on);
- who were residents of the Community of Madrid;
- and who had been targeted for the vaccination programs (catch-ups or routine vaccination) to receive the conjugate vaccine.

An IPD case was defined as *confirmed* when *S. pneumoniae* was isolated or antigen or DNA was detected from normally sterile sites.

2.2. Data collection

Case-based information was collected using a standardized form that included sociodemographic information, clinical data (date of onset, clinical presentation, patient evolution and high-risk factors for the development of IPD), laboratory identification, immunization status and vaccine information. Based on international recommendations, high-risk factors for the development of IPD were defined as immunodeficiency, head trauma, cerebrospinal fluid (CSF) leak, splenectomy, chronic liver disease, chronic renal disease, chronic respiratory disease, cancer, HIV, diabetes mellitus and alcoholism [3].

The most severe clinical manifestation was considered for each record if several were recorded, except for meningitis and sepsis that were described when appearing together. The existence of a high-risk factor was also described. Data were completed using the information from the electronic health records and asking questions to the attending doctors when necessary.

Additionally, data on vaccination status were completed with data from the Immunization Registry available in the Community of Madrid. This registry covers the entire resident population in the region, with data available regarding immunization since the end of 2004 [14] that is linked to Notifiable Diseases Surveillance System through the health identification code (CIPA).

Serotyping was performed at the Regional Public Health Laboratory using the latex agglutination test (Pneumo-latex) and the Quellung reaction.

2.3. Statistical analysis

A descriptive analysis of the study population was performed for all the cases meeting the inclusion criteria. Those cases with serotype or vaccination information not available were excluded from the VE analysis.

For VE analysis, we created four periods according to the vaccination program on use (Fig. 1):

1. **PCV-7 catch-up period (CU)**: Born between January 2004 and October 2006 and vaccinated during the catch-up campaign with PCV-7, with two doses for those between seven and 23 months and one dose for those over 23 months.
2. **PCV-7 within the routine vaccination program (PCV-7 WP)**: Born between November 2006 and May 2010 and vaccinated routinely within the 3 + 1 recommended vaccination program with PCV-7 (doses at two, four and six months and one booster dose at 18 months).
3. **PCV-13 within the routine vaccination program (PCV-7 WP)**: Born between June 2010 and June of 2012 or born between January and December of 2015 and vaccinated routinely within the 2 + 1 recommended vaccination program with PCV-13 (doses at two and four months and one booster dose at 15 months).
4. **PCV-13 outside the routine vaccination program (PCV-13 OP)**: Born between July 2012 and December of 2014 and vaccinated privately outside the vaccination program with PCV-13. The recommended schedule for this group was a 3 + 1 schedule (doses at two, four and six months and one booster dose at 15 months).

During PCV-7 WP and PCV-13 WP periods catch-up in children with >6 months was performed. Two doses were recommended for those vaccinated between 7 and 23 months and 1 dose for those vaccinated after 23 months of age.

Depending on the age at which the first dose was scheduled, we defined following groups: (1) vaccinated at ≤6 months; (2) vaccinated between 7 and 24 months; and 3) vaccinated at 25–59 months of age.

Depending on the vaccination status, we defined the following groups:

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