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Secular trends (1990–2013) in serotypes and associated non-susceptibility of *S. pneumoniae* isolates causing invasive disease in the pre-/post-era of pneumococcal conjugate vaccines in Spanish regions without universal paediatric pneumococcal vaccination

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ABSTRACT

This study analyzed temporal trends of non-susceptibility/serotypes in invasive pneumococci from Spanish regions where pneumococcal conjugate vaccines (PCVs) were not included in paediatric immunization programmes. All invasive pneumococcal isolates voluntarily sent to the Spanish Reference Laboratory for Pneumococci (January 1990–December 2013) from hospitals located in target study regions were analyzed by age group. The PCV estimated coverage in children <24 months was correlated with 13-valent PCV (PCV13) serotypes trends. A total of 28,124 invasive isolates were analyzed: 3138 (11.2%) from children <24 months, 2161 (7.7%) from children 24–59 months, 781 (2.8%) from children 5–14 years, and 22,044 (78.4%) from adults. The estimated coverage increased from 17.6% (2002) to around 40% (2010–2013). The percentage of PCV13 serotypes among all isolates over time followed a cubic significant trend ($R^2 = 0.884$), with an increasing trend up to 2001 followed by a decrease (more prominent from 2010 onwards). The estimated PCVs coverage was significantly correlated with the decrease in the percentage of PCV13 isolates in children <24 months ($r^2 = 0.824$) and in adults ($r^2 = 0.786$), mainly due to decreases in serotypes 1 and 7F in adults, and in serogroup 6 and serotypes 7F and 19A in children <24 months. None of the non-PCV13 serotypes stood out with substantial increases in the last period. This study showed that the different serotypes (and its associated non-susceptibility trends) were not equally affected by low PCVs disposition. Lack of impact in certain serotypes as serotype 1 (in children 24–59 months), 6C (in all age groups), and 19A (in adults) suggests the need for increasing vaccine coverage in the target vaccine population to increase direct and indirect protection.

1. Introduction

Q2 In Spain the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) in 2001 in the private market reversed the increase in PCV7 serotypes and in antibiotic non-susceptibility related to antibiotic consumption in the 1980s and 1990s [1]. However, the decrease in the incidence of invasive pneumococcal disease (IPD) by PCV7 serotypes was minored by an increase in non-PCV7 serotypes as serotype 19A [1]. The introduction of new pneumococcal conjugate vaccines (PCVs) has markedly changed the distribution of serotypes causing invasive disease in Western countries [2–5]. In Spain the 10-valent (PCV10) and the 13-valent (PCV13) PCVs were introduced in May 2009 and June 2010, respectively, for immunization of healthy children, but in contrast to most European countries, they were not included in universal immunization programmes except PCV13 in two Spanish regions, Madrid and Galicia. Although a steady increase in privately purchased PCV uptake has been assumed, PCV7 reached <50% coverage in children <24 months in 2006 [6], with absence of published data on PCV coverage in Spain at present time. PCV coverage is critical for indirect effect not only among unvaccinated children but also

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for aged adults that may benefit from children vaccination. In this sense, ≥75% community's children vaccination has been postulated as required for herd immunity with respect to colonization [7].

The selective pressure by vaccine-induced host immunity may affect non-susceptibility in two ways: (a) increasing its prevalence within each serotype and (b) increasing the prevalence of serotypes with high non-susceptibility prevalence [8,9]. Prior to PCV7 introduction, 83% penicillin (PEN) non-susceptible pneumococci received at the Spanish Reference Laboratory for Pneumococci (SRLP) belonged to some serotypes included in PCV7 (6B, 9V, 14, 19F and 23F) [10], with high PEN-erythromycin (ERY) co-non-susceptibility among them [11]. In parallel to redistribution of serotypes after PCV7 introduction, a reduction in PEN and ERY non-susceptibility was observed [1]. However, further rebound of antimicrobial non-susceptibility due to the increase in serotypes not included in PCV7 as serotype 19A [12] could be expected.

In this context, the objective of the present study was to analyze temporal trends of serotypes and non-susceptibility in different age populations in Spanish regions not including PCVs in their vaccination calendar, and the correlation of the trend of PCV13 serotypes with PCV estimated coverage in children <24 months.

2. Material and methods

2.1. Strains and microbiological and molecular methods

The SRLP receives pneumococcal isolates from Spanish hospitals through a passive surveillance system with minimal required information accompanying isolates (hospital and city, sample, age of the patient and date of isolation). The present study included all IPD isolates sent to the SRLP between January 1990 and December 2013 from hospitals located in all regions of the country where PCVs were not included in their paediatric immunization programmes. Serotyping was performed with the quellung reaction, dot blot assay [13], and/or real-time PCR [14]. Susceptibility to PEN and ERY over the whole period and that to levofloxacin (LVX) from 2002 onwards were determined by the agar dilution technique [15] in accordance with the criteria of the Clinical and Laboratory Standards Institute (CLSI) [16]. Intermediate and fully resistant isolates were considered non-susceptible. Breakpoints for non-susceptibility were those defined by the CLSI [17]: PEN, ≥0.12 μg/ml; ERY, ≥0.5 μg/ml; and LVX, ≥4 μg/ml.

2.2. Vaccine disposition

Details of the number of PCV7, PCV10 and PCV13 doses delivered per year in the target Spanish regions were obtained from IMS Health (Intercontinental Marketing Services, Madrid, Spain) as the total number of vaccine sales per year. Estimated vaccine coverage (assuming a 3-dose schedule) was calculated by dividing the total number of doses by the number of children under 2 years of age and expressed in units/1000 inhabitants <24 months old/year. Annual population data were obtained from the Spanish Instituto Nacional de Estadística (www.ine.es).

2.3. Statistical analysis

Number of IPD isolates, percentages of different serotypes and of non-susceptibility were analyzed overall and by dividing the 24-year study period in three time periods (1990–2000; 2001–2009 and 2010–2013) according to dates of PCVs introduction. IPD isolates were analyzed overall (all isolates, total population) and by age group: children <24 months, children aged 24–59 months, children 5–14 years old, and children ≥15 years and adults (categorized as adults for study purposes). Temporal trends of serotypes included in PCV13 (individually and in global), of serotypes not included in PCV13 (overall, and individually for the most prevalent non-PCV13 serotypes) and temporal trends of PEN and ERY non-susceptibility were calculated by linear or non-linear regression using time as independent variable. Trends were considered significant when p values were ≤0.001. The model showing the highest ratio R^2/freedom degrees was considered.

Correlations between PCVs estimated coverage in children <24 months and percentage of PCV13 isolates were determined by the non-parametric Spearman's Rho (r). Comparisons between percentages of non-susceptibility were performed using the chi-square test.

The SPSS v.14 statistical program (SPSS Inc., Chicago, IL) was used.

3. Results

3.1. Number of isolates received in the SRLP and trends over the study period

The study included a total of 28,124 IPD isolates received during the study period from hospitals located in 15 Spanish autonomous communities not having PCVs included in their childhood vaccination programmes. Hospitals voluntarily sending isolates increased from 17 in 1990 to 105 in 2013 (59 hospitals in 2000, 110 hospitals in 2010). Consequently, the number of isolates received by year increased over time from a median (range) of 496 (310–1118) in the period 1990–2000 to 1264 (923–2612) in 2001–2009 and to 1992.5 (1943–2114) in 2010–2013.

Distribution of the total number of isolates by age group was: 3138 (11.2%) from children <24 months, 2161 (7.7%) from those aged 24–59 months, 781 (2.8%) from those 5–14 years old, and 22,044 (78.4%) from adults. The group of children 5–14 years old had scarce number of isolates (<3% of total isolates) and was not considered for data presentation. Study results were similar in children <24 months and in those 24–59 months except where indicated (see below). Therefore, age groups finally considered for data presentation were: children <24 months, children ≤59 months (pooling data from children <24 months and 24–59 months) and adults.

Fig. 1 shows total number of IPD isolates, of PCV13 and of non-PCV13 isolates received in the SRLP over time, number of isolates from the three age groups considered, and disposition of PCVs. As shown in the figure, the number of IPD isolates increased over time until 2009, showing significant exponential trends both when considering all isolates (R^2 = 0.925) or PCV13 (R^2 = 0.860) and non-PCV13 isolates (R^2 = 0.922) in separate. The same pattern was found when the group of adults was analyzed, with significant increasing exponential trends ($R^2 \geq 0.856$). When considering only isolates from children ≤59 months, increases followed significant cubic trends (all isolates: R^2 = 0.749; PCV13: R^2 = 0.747; non-PCV13: R^2 = 0.815), similarly as in the group of children <24 months.

PCVs disposition markedly influenced patterns of isolates over time, with a sharp slope increase in the number of isolates received in the SRLP after licensure of PCV7 from 2001 to 2009, and a decrease from 2010 onwards, after licensure of PCV13, running in parallel to the decrease in PCV13 isolates (Fig. 1).

3.2. PCV coverage and correlation with prevalence of PCV13 serotypes

Fig. 2 shows the cubic significant trend of the percentage of PCV13 serotypes among all IPD isolates over time (R^2 = 0.884) and the estimated PCV coverage in children <24 months. The estimated coverage increased from 17.6% in 2002 to around 40% from 2010 onwards, and was due to PCV7 from 2002 to 2009 and to PCV13

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