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Epidemiology of *Streptococcus pneumoniae* causing acute otitis media among children in Southern Catalonia throughout 2007–2013: Incidence, serotype distribution and vaccine's effectiveness

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ABSTRACT

Objective: This study investigated incidence and serotype distribution of *Streptococcus pneumoniae* causing acute otitis media (AOM) in Catalonian children, evaluating vaccination effectiveness in the current era of extended valency pneumococcal conjugate vaccines (PCVs).
Methods: Population-based surveillance study that included all AOM cases with isolation of pneumococcus (from otic fluids/otorrea) identified among children ≤14 years in the region of Tarragona (Southern Catalonia, Spain) from 01/01/2007 to 31/12/2013. Prevalence of infections caused by serotypes covered by the different PCVs formulations were calculated for the periods before and after 30/06/2010 (date of PCV7/PCV13 replacement). The indirect cohort method was used to estimate PCV7/13 effectiveness against vaccine-type infections.
Results: A total of 78 children with a pneumococcal AOM were identified across study period, which meant an incidence rate of 23 cases per 100,000 population-year. Thirty-six cases (46.2%) occurred within the late PCV7 era and 42 cases (53.8%) during the early PCV13 era. Overall, the most common serotypes were type 19 A (21.7%), type 3 (13.3%) and type 15B (6.7%). Prevalence of cases caused by serotypes included in PCV7 did not substantially change between the first and the second study period (from 10.3% to 12.9%), whereas prevalence of cases caused by PCV13 serotypes showed a decreasing trend between both periods (from 65.5% to 48.4%). The aggregate PCV7/13 effectiveness against vaccine-type infections was 72% (95% confidence interval: −26 to 94).
Conclusion: Pneumococcal conjugate vaccination appears an acceptable preventive option to prevent pneumococcal AOM in infants. However, its serotype coverage and clinical effectiveness are not optimal.

1. Introduction

Middle ear infections are a very common otologic problem in children. Indeed, most of infants have suffered acute otitis media (AOM) at three-years of age [1]. Multiple microorganisms can be implicated in AOM cases, but *Streptococcus pneumoniae* (together with *Haemophillus influenzae*) remains as a major bacterial agent [2,3].

An earlier seven-valent pneumococcal conjugate vaccine (PCV7) was licensed for pediatric use in 2000 [4]. Although vaccination was primarily introduced to protect young children against invasive pneumococcal infections (such as meningitis and pneumonia), it was also recommended to prevent recurrent middle hear infections [5]. The introduction of PCV7 as routine childhood immunization showed initially excellent results in reducing the incidence of invasive pneumococcal disease due to PCV7 serotypes among both vaccinated and unvaccinated persons (herd effect) [6]. However, serotype replacement and emerging types were observed later [7,8], and extended valency vaccines (PCV10 and PCV13) were marketed in 2009 and 2010 to replace the "old" PCV7 [9,10].

If we consider AOM due to pneumococcus, there is scarce information about its epidemiology (incidence, serotype distribution, evolution of serotype-vaccine coverages, etc) among distinct

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infant populations in recent years. This is especially important considering possible epidemiological changes after new PCVs introduction. This study investigated incidence and serotype distribution of pneumococci causing AOM episodes in Catalonian children throughout the late PCV7 era (2007–2010) and the early PCV13 era (2010–2013). Secondarily, we examined vaccination effectiveness in preventing AOM cases due to PCV7/13 serotypes in the study population.

2. Methods

Population-based surveillance study conducted among the pediatric population in the region of Tarragona (a mixed residential-industrial area in the Mediterranean coast of Southern Catalonia, Spain) with an overall population of 337,289 all-age inhabitants [11]. The study was approved by the Institutional Review Boards of the Catalonian Health Institute and was conducted in accordance with the general principles for observational studies set out by the institution.

Considering pneumococcal conjugate vaccine use in the study area, the PCV7 was marketed in Spain during 2001, being later replaced by the PCV13 in June 2010. Despite PCV7/13 were not included in the publicly funded pediatric vaccination schedule in our setting (except for high-risk individuals), they have been routinely recommended throughout the private sector reaching intermediate vaccine uptakes among the pediatric population in the study area during the past years (51% for the PCV7 in 2008–2009 and 45% for the PCV13 in 2010–2011) [12].

A case was defined as a patient aged 14 years or less, living in the study area, with clinical symptoms of acute otitis (first or recurrent episode) and pneumococcus isolated from otic fluids (spontaneous otorrhea in a children with or without a tube in place). Cases were initially identified from a surveillance made in the two microbiological reference Laboratories in the study area (Joan XXIII and Santa Tecla Hospitals) from January 1, 2007 to December 31, 2013.

All presumptive cases were further validated by checking clinical records by two trained investigators whom verified clinical and microbiological data for the diagnosis. The electronic medical records of each patient (which contain administrative data together with registries of hospital and ambulatory visits, medication prescriptions, immunizations, medical conditions and chronic diseases) were used to establish the presence of chronic illnesses/underlying conditions of case patients as well as to determine vaccination status before the occurrence of the event. Patients were considered as vaccinated if they had received at least one dose of antipneumococcal vaccine (PCV7/13 in our setting) before the event date.

Pneumococcal isolates were sent to the reference laboratory of the National Center of Microbiology (Majadahonda, Madrid), where serotyping was performed by the Quellung reaction or dot-blot assay. According to the distinct pneumococcal vaccine formulations, each identified serotype was classified as included or not in the PCV7, the PCV10, the PCV13 and/or in the 23-valent polysaccharide vaccine (PPV23). Thus, cases were considered as: (a) Infections caused by serotypes included in PCV7 (types 4, 6B, 9V, 14, 18C, 19F and 23F); (b) Infections caused by serotypes included in the PCV10 (types 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F); (c) Infections caused by serotypes included in the PCV13 (types 1, 3, 4, 5, 6A, 6B, 7f, 9V, 14, 18C, 19A, 19F and 23F); (d) Infections caused by serotypes included in the PPV23 (types 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F).

Considering that the "old" PCV7 was replaced by the "new" PCV13 in our setting during June 2010, we defined two study periods: the "late PCV7 era" (between January, 1rst 2007 to June, 30 2010) and "the early PCV13 era" (between July, 1rst 2010 to December, 31 2013).

2.1. Statistical analysis

Incidence rates were calculated using the region population census data at the beginning of the study (7883 children <2 years; 11,830 children 2–4 years; 32,490 children 5–14 years) [11]. The 95% confidence intervals (CIs) of the rates were calculated by assuming a Poisson distribution. To compare proportions and serotype prevalence between study periods we used the chi-squared or Fisher's test as appropriate.

To estimate vaccination effectiveness (PCV7, PCV13 and aggregate PCV7/PCV13) we used the indirect cohort method [13]. Briefly, according this method, those infections caused by vaccine-serotypes are considered as "cases" for the analyses whereas those infections caused by nonvaccine-serotypes are considered as "controls"; thus, Odds Ratio (OR) is calculated and vaccination effectiveness is estimated as (1-OR)%. Statistical significance was set at $p < 0.05$ (two-tailed). The analyses were performed using Stata/SE Version 9.1. (Stata Corp.)

3. Results

3.1. Case characteristics

During the total 2007–2013 study period, 78 AOM cases due to pneumococcus were identified. Thirty-six cases (46.2%) occurred within the late PCV7 period and 42 cases (53.8%) during the early PCV13 period. Of the total 78 cases, 40 (51.3%) occurred in male and 38 (48.7%) in female. Thirty-six cases (46.2%) were less than 24 month of age, 26 (33.3%) were 24–59 months and 16 (20.5%) were 5 years or older. Overall, 23 cases (29.5%) occurred in winter, 21 cases (26.9%) in spring, 6 cases (7.7%) in summer and 28 (35.9%) in autumn. Seven patients (9%) had some comorbidities (four cases of recurrent bronchitis/asthma, one immunodeficiency, one severe heart disease and one severe neurological disorder). Eleven patients (14%) had history of prior AOM episodes. Of the total 78 AOM cases, pneumococcal vaccination status was not available in 9 cases. Of the remaining 69 patients, 34 had been vaccinated against pneumococcus (PCV7 in 20 cases and PCV13 in 14 cases) whereas 35 patients had not been vaccinated (Table 1).

3.2. Incidence rates and serotype distribution

Globally, incidence rate of pneumococcal AOM episodes was 21.4 cases per 100,000 population-year (95% CI: 17.1–26.8). By age, rates decreased significantly with increasing age: 65.2 per 100,000 (95% CI: 45.4–90.6) in children <2 years, 31.4 per 100,000 (95% CI: 20.5–46.2) in children 2–4 years and 7.0 per 100,000 (95% CI: 4.0–11.3) in children 5–14 years ($p < 0.001$).

We did not observe significant difference between overall incidence rates of pneumococcal AOM episodes comparing the two study periods: 19.7 per 100,000 (95% CI: 13.7–27.4) in the late PCV7 era *vs* 23.0 per 100,000 (95% CI: 16.4–31.3) in the early PCV13 era ($p = 0.496$).

Of the total 78 pneumococcal strains, 60 (76.9%) were serotyped. Overall, the most common serotypes were type 19A in 13 cases (21.7%), type 3 in 8 cases (13.3%) and type 15B in 4 cases (6.7%). Types 7F, 11A, 15C, 19F and 22F accounted for 3 cases each one (5%); serotypes 6A, 10A, 12F, 14, 15A and 23A accounted for 2 cases each one (3.3%); serotypes 1, 6B, 6C, 9V, 11C, 21, 31 and 33F were identified in one case each one (1.7%). In the late PCV7 era, the most dominant serotypes were types 3 and 19A. In the early PCV13 era, the most dominant serotype was type 19A followed by type 15C (Table 2).