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Evolution of pneumococcal infections in adult patients during a four-year period after vaccination of a pediatric population with 13-valent pneumococcal conjugate vaccine

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SUMMARY

Objectives: To describe the distribution of vaccine and non-vaccine pneumococcal serotypes from adult patients for different clinical scenarios, after the introduction of the 13-valent pneumococcal conjugate vaccine (PCV-13) for children.

Methods: This was a prospective study of pneumococcal infections in adult patients (January 2010 to April 2014) in Hospital Son Llàtzer, Mallorca (Spain). Two different periods of time were compared, the first before (first period) and the second after (second period) the introduction of PCV-13. Information related to clinical characteristics, outcomes of infection, pneumococcal serotypes, and antibiotic susceptibility was collected.

Results: We studied 407 episodes (371 patients), 201 in the first period and 206 in the second period. The majority of patients were male; the median patient age was 68 (range 15–99) years. Infections due to PCV-13 serotypes decreased from 59.7% to 47.6% ($p = 0.014$), mainly serotypes 3, 7, 18C, 19F, and 23F. In the second period, PCV-13 serotypes were the cause of pneumonia in 58.2% of cases and in 40.8% of invasive infections, but these serotypes were not related with any outcome variable. No differences in hospital or intensive care unit admission, severity, or mortality were observed between the two periods. Susceptibility to penicillin (98.2% vs. 95.1%, $p = 0.03$) and amoxicillin (96.5% vs. 91%, $p = 0.007$) was slightly higher in the first period.

Conclusions: Although a reduction in infections due to vaccine serotypes was observed, close to half of infections in adult patients were caused by PCV-13 serotypes. Even after pediatric vaccination with PCV-13, vaccine serotypes were still responsible for most pneumonia and invasive disease, underscoring the importance of implementing current guidelines and extending vaccination to other risk groups.

1. Introduction

Streptococcus pneumoniae causes upper and lower respiratory tract infections, chronic obstructive pulmonary disease (COPD) exacerbations, and community-acquired pneumonia, as well as producing invasive disease.[1] *S. pneumoniae* disease is responsible for a high proportion of morbidity and mortality around the world, mainly in young children and elderly patients.[2,3] Pneumococcal disease is the disease with an available vaccine with the highest mortality rate.[3] In early 2000, a 7-valent pneumococcal conjugate vaccine (PCV-7) was licensed in the USA for use in all infants and children under 2 years of age and in high-risk children aged 2–4 years.[4] Following the authorization of PCV-7, distribution of the vaccine through public programs began and a decline in the rate of pneumococcal disease was observed, not only in children, but also among adults, as well as a reduction in the incidence of antibiotic resistance.[4–7] As PCV-7 included polysaccharides of serotypes 4, 6B, 9 V, 14, 18C, 19F, and 23F, most of the 90 pneumococcal serotypes were not covered by this vaccine, so an increase in infections due to some non-PCV-7 serotypes was observed, mainly serotypes 1, 3, 7F, and 19A. Moreover, there was also some concern regarding the increase in severity in some cases of pneumococcal disease, since some of these serotypes are more aggressive.[8–13]

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In 2010, a 13-valent pneumococcal conjugate vaccine (PCV-13) was licensed by the US Food and Drug Administration (FDA) and recommended by the Advisory Committee on Immunization Practices (ACIP) for children aged 6 weeks through 71 months for the prevention of invasive pneumococcal disease (IPD) caused by the 13 pneumococcal serotypes included in the vaccine. In addition to the seven serotypes of PCV-7, the new vaccine contains polysaccharides of serotypes 1, 3, 5, 6A, 7F, and 19A. In Spain, PCV-13 has been available since June 2010 and vaccination is recommended for pediatric patients. However, in most provinces of Spain the vaccine is not financed by public health insurance, so it has to be financed by the parents. Although vaccine coverage for children is not universal, a decline of around 55% in the number of hospitalizations for IPD has been observed in Spain in children aged <15 years,[14] with a reduction in frequency of infections due to vaccine serotypes, mainly 19A and 1, and severe clinical forms such as complicated pneumonia with bacteremia, pleural effusion, and/or meningitis.[15–17] These changes have also been observed in other settings.[18,19]

Because of the limited data currently available on the impact of pediatric vaccination in other age groups, and since PCV-13 has been authorized for adult patients at risk of pneumococcal disease, it is important to ascertain the evolution of the different pneumococcal serotypes, their role in different clinical situations, and potential changes in severity of clinical presentation. The aim of this study was to describe the pneumococcal serotype distribution in adult patients in clinical practice since the introduction of PCV-13, the role of vaccine and non-vaccine serotypes in different clinical scenarios, and the severity and outcomes of pneumococcal infections over a 4-year period.

2. Materials and methods

2.1. Patients and study design

This was a prospective study conducted in Hospital Son Llàtzer, a teaching center with 400 beds covering a population of 225 000 inhabitants in Mallorca (Spain). All pneumococcal infection episodes from January 1, 2010 to April 30, 2014 were collected. A person with signs and symptoms of infection, respiratory or not, from whom *S. pneumoniae* was isolated was defined as having a pneumococcal infection. The quality of sputum was assessed using the Murray and Washington criteria[20] and quantitative colony counts were used for bronchoscopy samples. *S. pneumoniae* isolation in predominant culture from middle ear and sinus aspirates or conjunctival swabs was considered positive, as well as culture from blood or samples from pleural, cerebrospinal, or synovial fluid. The study was approved by the Research Commission of Hospital Son Llàtzer.

2.2. Clinical assessment and follow-up

All data were assessed by interview with the patients or their relatives and a review of hospital health records. Data were collected during and after the hospital stay once the Laboratory of Microbiology reported the isolation of *S. pneumoniae* from at least one of the referred samples. Data were recorded using a standardized, computer-assisted protocol. The following data were collected: demographic characteristics, substance use habits, receipt of pneumococcal or influenza vaccine, comorbidities, origin of the infection, clinical diagnosis, pneumococcal serotype, antibiotic susceptibility, and outcomes, including overall and infection-related hospital mortality. For time calculations, the day of admission was considered to be hospital day 0.

2.3. Definitions

Patients were considered active smokers, alcohol or drug users if the last consumption had occurred during the last year. Comorbidities were assessed with the Charlson comorbidity index. Patients were considered to be vaccinated against pneumococcus if the 23-valent polysaccharide pneumococcal vaccine, PCV-7, or PCV-13 had been administered in the 5 years before admission. They were considered to be vaccinated against influenza if the seasonal influenza vaccine had been administered during the year prior to admission. The infection was considered healthcare-associated or hospital-acquired according to accepted criteria.[21] Clinical diagnoses included the following: (1) Pneumonia, defined in the presence of compatible signs and symptoms and a new infiltrate on chest radiography. (2) COPD exacerbation or infected bronchiectasis, diagnosed depending on whether a previous or current diagnosis of COPD or bronchiectasis had been made, and in the presence of at least two of the following: fever, increased dyspnea, cough, and changes in volume or characteristics of sputum. In the absence of a diagnosis of COPD or bronchiectasis, the episode was categorized as lower respiratory tract infection. (3) Otitis, sinusitis, and bacterial conjunctivitis, defined in the presence of compatible clinical signs and symptoms and with a predominant culture of *S. pneumoniae* from middle ear or sinus aspirates and conjunctival swabs. (4) IPD, diagnosed when blood or cultures from samples of pleural, cerebrospinal, or synovial fluid were positive for *S. pneumoniae*.

The Fine score[22] was calculated for community-acquired or healthcare-associated pneumonia. Complications were defined as any untoward circumstances occurring during hospitalization. Overall mortality was defined as death from any cause during hospitalization; related mortality was evaluated according to the criteria of the research team. Hospital and intensive care unit (ICU) admission and treatment decisions were not standardized and were made by the attending physician.

2.4. Microbiological studies

Investigation of *S. pneumoniae* in each sample was performed using standard microbiological procedures. The identification of *S. pneumoniae* was performed by observation on blood agar plates of alpha-hemolytic colonies that were catalase-negative, optochin-sensitive, and bile-soluble. In the case of uncertainty, an agglutination probe with latex particles coated with specific antiserum was used (Slidex Pneumo-kit; bioMérieux, Marcy l'Etoile, France).

Susceptibility to penicillin, amoxicillin, and cefotaxime was determined by Etest (AB Biodisk, Solna, Sweden) using cut-offs for non-meningeal and meningeal isolates when indicated. Susceptibility to erythromycin, tetracycline, trimethoprim–sulfamethoxazole, and levofloxacin was determined by disk plate (Oxoid) using the 2010 Clinical and Laboratory Standards Institute criteria.[23] For serotyping, pneumococcal isolates were sent to the Pneumococcal Reference Laboratory, Centro Nacional de Microbiología, Instituto de Salud Carlos III (Madrid, Spain).

2.5. Statistical analysis

Data were analyzed using a commercially available statistical software package (SPSS 15.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics were generated for all study variables. The analysis was conducted for all patients with a documented pneumococcal infection, and also after excluding those with an unknown serotype. A comparative analysis between those with a known serotype and those with an unknown serotype was carried out to check homogeneity of the two populations. Patients aged