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Impact of vaccination on invasive pneumococcal disease in adults with focus on the immunosuppressed

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Summary Pneumococcal conjugate vaccine (PCV13) has been recently added to the vaccine recommendations for immunosuppressed adults (ISP). We conducted a multicenter observational prospective study aimed to assess the evolving epidemiology of invasive pneumococcal disease (IPD) in adults, with especial focus on ISP. All IPD cases admitted from 1999 to 2014 were included. ISP was defined as patients on current cancer chemotherapy, immunosuppressive therapy for autoimmune disease, biological therapy, chronic systemic steroid use, hemodialysis, neutropenia or HIV infection. A total of 799 IPD episodes were analyzed, 198 were considered ISP. IPD incidence decreased from 20 to 8/100,000-population year ($p < 0.004$) over the study period. No changes in mortality were observed. Penicillin resistance experienced a significant decline. In 694 episodes the serotype was known. Global vaccine coverage considering the whole study period, was for PCV7 21.6% vs. 28.8% in general and in immunosuppressed population ($p = 0.04$) and for PCV13 64.5% and 56.6% respectively ($p = 0.05$). The proportion of IPD isolates included in PCV7 and PCV13 significantly decreased over time.

A reduction in the incidence of IPD in adults was seen late after the vaccine licensure, both in general population and in ISP. Coverage of PCV13 vaccine might be suboptimal for ISP in the coming years.

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Introduction

Streptococcus pneumoniae continues to be responsible for significant mortality and morbidity worldwide, causing a broad spectrum of disease including pneumonia, meningitis, bacteremia, and otitis media, and is one of the most important vaccine-preventable infections. Children under 5 years, the elderly and patients with co morbidities, particularly immunosuppressive conditions, are at highest risk of suffering invasive pneumococcal disease (IPD). In patients with immunocompromising conditions the incidence of pneumococcal infection can be as high as 342 to 2031 per 100,000 person-years.[1,2]

Until recently, the only direct prevention measure available was vaccination with the 23-valent polysaccharide vaccine (PPSV23) of older adults (licensed in 1983). Polysaccharide antigens activate only mature B cells. In contrast, conjugate pneumococcal vaccines have a T-cell immune response and are immunogenic for the immunosuppressed population.[3]

In Spain, the 7-valent (PVC7) was licensed for children in 2001 and the 13-valent conjugate vaccine (PCV13) replaced PCV7 in 2010. Mass vaccination has not been implemented. Vaccination is not funded by the government but is highly recommended by paediatricians.[4] There have not been systematic catch up recommendations for PCV13. Vaccine PCV7 uptake ranged from 4.8% in 2002, 23% in 2004 and about 50% in 2006.[5–8] At the present time, there is no available information on PCV13 uptake.

In many areas, after the implementation of children vaccination programs, a significant decline in invasive pneumococcal disease (IPD), both in children and adults, has been reported.[9] However, due to a replacement phenomenon, an increase of nasopharyngeal colonization of children of non-PCV7 serotypes was soon identified.[10] Remarkably, in some areas such as France, The Netherlands and Spain an increase of the incidence of IPD has been also reported.[11–13]

On December 2011 the FDA approved PCV13 for prevention of pneumonia and invasive disease caused by PCV13 serotypes among adults aged 50 years and older. In June 2012 the Advisory Committee on Immunization Practices (ACIP) recommended the routine use of a 13-valent pneumococcal conjugate vaccine (PCV13) for adults with immunocompromising conditions.[14,15]

On the other hand, type of disease and severity of disease have been specifically associated with some serotypes.[16] Thus, some authors have proposed that variations in serotype distributions of IPD may be accompanied by changes in the clinical presentation and severity.[17]

The aim of our study was to assess the evolving epidemiology of invasive pneumococcal disease (IPD) in adults with special focus on the immunosuppressed population (ISP), and to describe the emergence of non-vaccine serotypes and corresponding changes in the clinical presentation and severity of IPD.

Material and methods

Setting and study design

We used observational data to assess trends in IPD in adults before and after the introduction of PCV at the health district of Terrassa, province of Barcelona, between January 1999 and December 2014.

The health district includes four municipalities with a total population of 350,000 inhabitants that are served by two acute-care hospitals, Hospital Universitari Mutua Terrassa and Consorci Sanitari Terrassa.

The study was conducted in accordance with ethical principles set out in the latest version of the Declaration of Helsinki and the standard used for Good Clinical Practice. As it was an observational study, approval by the hospitals Ethics and Research Committee was not required.

Inclusion criteria and clinical variables

All adult IPD cases admitted to the participant hospitals were included. An IPD case was defined as any patient in whom *S. pneumoniae* was isolated from cerebro-spinal fluid (CSF), blood or other sterile site. Demographics, co morbidities, immunosuppressive conditions, clinical syndrome, severity of illness (measured by the presence of shock) microbiological data (site of *S. pneumoniae* isolation, antimicrobial susceptibility and serotypes) and in-hospital mortality were recorded.

The presence of immunosuppression was defined, on basis of the approved and funded indications for adult population vaccination in Spain, as patients on current cancer chemotherapy, immunosuppressive therapy for autoimmune disease, biological therapy, chronic systemic steroid use (>20 mg prednisone/day for >15 days), hemodialysis, neutropenia or HIV infection.

Microbiological studies

Blood cultures were performed with the automatic system BacT-Alert® (bioMérieux). *S. pneumoniae* strains were identified by Optochin-disk and a latex agglutination test. MICs were determined by use of the micro dilution broth method (Sensititre; Treck Diagnostic Systems) with 3% lysed horse blood. Penicillin susceptibility was defined using current meningeal CLSI breakpoints for parenteral penicillin.[18]

Serotyping was performed with specific pneumococcal antisera and the Quellung reaction at the National Microbiology Centre in Majadahonda, Madrid, Spain.

Incidence calculation and serotype trends over time

Overall adult and age-specific number of IPD episodes and global case fatality rates per 100,000 population per year were determined. Data related to demographics in the referral area were obtained from the Instituto Nacional de Estadística.[19]

Serotype distribution was compared between general and immunosupressed population according to three groups: (1) serotypes included in PCV7 (4, 6B, 9V, 14, 18C, 19F and 23F), (2) new serotypes included in PCV13 (1, 3, 5, 6A, 7F, and 19A) and (3) non-vaccine serotypes (NVS): serotypes none included in any of the available conjugate vaccines. For global coverage calculations, all serotypes included in PVC13 (4, 6B, 9V, 14, 18C, 19F, 23F 1, 3, 5, 6A, 7F, and 19A) were grouped and analyzed.