High invasiveness of pneumococcal serotypes included in the new generation of conjugate vaccines

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Abstract

The implementation of the seven-valent pneumococcal conjugate vaccine, PCV7, has resulted in significant changes in the pneumococcal population being carried and causing disease. We aimed to determine the invasive disease potential of serotypes causing invasive paediatric disease in the era of conjugate vaccines in Catalonia, Spain, and their potential coverage by the 13-valent pneumococcal conjugate vaccine, PCV13. As a secondary objective, we evaluated whether implementation of PCV7 had resulted in significant changes in the invasive disease potential of the most frequent serotypes circulating in the area. Two pneumococcal collections obtained from children admitted to the University Hospital Sant Joan de Déu (Barcelona, Spain) between 2007 and 2011 were compared: a first set of 159 invasive disease isolates, and a second set of 209 nasopharyngeal isolates recovered from healthy children admitted for minor surgery. The most common invasive serotypes were 1 (24.5%, $n = 39$), 19A (21.2%, $n = 34$), 5 (8.8%, $n = 14$), 7F (8.8%, $n = 14$) and 3 (5%, $n = 8$). The most common serotypes in carriage were 19A (10%, $n = 21$), 6C (9%, $n = 19$), 23B (8.1%, $n = 17$), 6A (7.6%, $n = 16$) and 19F (6.2%, $n = 13$). A significantly higher propensity to cause invasive disease was observed for serotypes 1, 3, 5, 7F and 19A, all of which are included in PCV13. After false-discovery-rate correction, the results were robust for serotypes 1, 5, 7F and 19A. Non-PCV13 serotypes had a low invasive disease potential. Our data reinforce the need for continuous surveillance and should encourage efforts to introduce universal vaccination with PCV13 in children in our region.

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Introduction

Streptococcus pneumoniae is a major cause of invasive disease in children and a common cause of pneumonia, meningitis and sepsis [1]. Despite being such a virulent pathogen, the main ecological niche of the pneumococcus is the nasopharynx of healthy children, which is colonized asymptomatically [2]. Although almost all children carry pneumococci during early childhood, very few develop disease. The capsule of the pneumococcus has been considered its main virulence factor and at least 94 serotypes have been described [3]. Despite this diversity, a relatively small number of serotypes are associated with most invasive disease worldwide [4].

Recent epidemiological studies in different countries have compared nasopharyngeal carriage rates of serotypes with rates of invasive pneumococcal disease (IPD) to estimate the invasive disease potential of individual serotypes and clones. The results have shown that the potential to cause invasive disease differs by serotype (and even by genotype). For example, serotypes 6B, 19F and 23F have a low disease potential while serotypes 1, 7F and 14 have a high disease potential [5–11].

The seven-valent pneumococcal conjugate vaccine (PCV7), has proven to be remarkably effective in reducing overall carriage and disease caused by PCV7 vaccine serotypes, leading to its virtual extinction in some regions [12,13]. As a result, in countries where PCV7 has been extensively used, the population and distribution of serotypes causing invasive disease and detected in nasopharyngeal carriers has changed, potentially affecting the invasive disease potential of specific serotypes.

In Spain, PCV7 was licensed in 2001, PCV10 in April 2009 and PCV13 in January 2010; however, in our community, Catalonia, these vaccines are not subsidized by the Spanish Public Health System. It is estimated that <50% of children of our geographical area were vaccinated with PCV7 during the period 2007–2009 [14].

The main goal of this study was to determine the invasive disease potential of serotypes causing invasive paediatric disease in the era of conjugate vaccines in Catalonia, Spain, and evaluate its potential coverage by the most recent conjugate vaccine. As a secondary objective we evaluated whether implementation of PCV7 had resulted in significant changes in the invasive disease potential of the most frequent serotypes circulating in the area.

Materials and Methods

Study design and sample collection

Two sample collections were compared. The first included all invasive pneumococcal isolates (n = 159) obtained from children admitted to the University Hospital Sant Joan de Déu (Barcelona, Spain) between 2007 and 2011. The second collection (n = 209) included pneumococcal isolates obtained from the nasopharynx of healthy children who attended for minor surgical procedures in our hospital during the same time period. IPD was defined as the presence of clinical findings of infection together with the isolation by culture of *S. pneumoniae* in blood, cerebrospinal fluid or any other sterile fluid. In both collections, subjects were children up to 6 years old. The mean ages of patients with IPD and carriers was 27 months (SD 19.0) and 34 months (SD 17.7), respectively.

The University Hospital Sant Joan de Déu is a tertiary teaching children's hospital that annually captures ~ 19% of all paediatric admissions recorded in Catalonia. This region has a population of around 7 million people, of which 1.2 million are <18 years of age [15].

Microbiological identification, antimicrobial susceptibility and serotyping

Pneumococcal strains were identified by standard microbiological methods that included the optochin sensitivity test and an antigenic test targeting the capsular polysaccharide (Slidex pneumo-kit; BioMérieux, Marcy-l'Etolie, France). The MICs to penicillin, cefotaxime, erythromycin, tetracycline, chloramphenicol and levofloxacin were determined by Etest (BioMérieux). Antibiotic susceptibilities were defined according to the breakpoints of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [16]. Multidrug resistance was defined as non-susceptibility to three or more antimicrobial agents.

Pneumococcal isolates were serotyped by the Quellung reaction at the National Pneumococcal Reference Centre of Majadahonda (Madrid, Spain). Since 2010, a fragment analysis technique based on fluorescent PCR and subsequent fragment analysis by capillary electrophoresis that allows the detection of 40 serotypes/serogroups (1, 2, 3, 4, 5, 6A/6B, 6C, 7C/(7B/40), 7F/7A, 8, 9N/9L, 9V/9A, 10A, 10F/(10C/33C), 11A/11D, 12F/(12A/44/46), 13, 14, 15A/15F, 15B/15C, 16F, 17F, 18/(18A/18B/18C/18F), 19A, 19F, 20, 21, 22F/22A, 23A, 23B, 23F, 24/(24A/24B/24F), 31, 33F/(33A/37), 34, 35A/(35C/42), 35B, 35F/47F, 38/25F, 39) has been implemented in our laboratory [17] and the Quellung reaction has been used as a complementary assay when the serotype cannot be determined by the PCR-based method.

Statistical analysis

Simpson's Index of Diversity was used to measure the collections' diversity through the website www.comparingpartitions.info [18].

The invasive disease potential of serotypes was estimated using ORs with 95% CI, as described by Brueggeman *et al.* [5]. The equation used for calculations of ORs was OR = $(ad)/(bc)$, where a was the number of invasive X serotypes, b was the number of carriage X serotypes, c was the number of invasive non-X serotypes, and d was the number of carriage non-X serotypes. An OR of 1 indicated that the serotype was equally likely to be recovered from invasive disease and carriage, whereas an OR >1 indicated an increased probability to cause invasive disease. OR significance was tested with the two-tailed Fisher exact test, using a cut-off p value of ≤0.05 (two-tailed) for all statistical analyses. The resulting p values were corrected for multiple testing by controlling the false discovery rate (FDR) to ≤0.05 through the Benjamini and Hochberg method as previously described [9,19].

Results

Serotype distribution in disease and colonization

Among the 159 pneumococcal strains causing IPD in young children, collected in our laboratory between 2007 and 2011, 26 serotypes were identified. The most common were