Journal of Infection (2016) xx, 1–11

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Declining mortality from adult pneumococcal infections linked to children's vaccination

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Accepted 22 January 2016
Available online ■ ■ ■

KEYWORDS
Streptococcus pneumoniae;
Pneumonia;
Serotypes;
Mortality;
Pneumococcal vaccines

Summary *Objective:* To determine changes in mortality among adults with invasive pneumococcal disease (IPD) after introducing pneumococcal conjugate vaccines (PCVs) in children.
Methods: An active surveillance of adults with culture-proven IPD in Barcelona. Serotype-specific mortality and rates of disease and death were analysed in three periods: baseline (1994–2001), PCV7 (2002–2009) and PCV13 (2010–2013).
Results: Overall, IPD caused by PCV7 serotypes was associated with increased case fatality rate (24 percent).

In patients 18–64 years (baseline vs. PCV7 vs. PCV13 periods), case fatality rate from IPD decreased (22 vs.14 vs. 12 percent), and it was associated with a decline in PCV7 serotypes (3.56 vs. 2.80 vs. 1.49 cases/10^5 person-years) and in PCV7 serotypes-specific death (0.74 vs. 0.53 vs. 0.09 deaths/10^5 person-years).

In patients ≥65 years, case fatality rate did not change (24 vs. 22 vs. 24 percent); however, there was a decline in PCV7 serotypes-specific death (4.94 vs. 3.58 vs. 2.45 deaths/10^5 person-years), and an increase in non-PCV serotype-specific death (2.55 vs. 3.70 vs. 4.09 deaths/10^5 person-years).
Conclusions: The use of PCVs for children was associated with a reduction of mortality from IPD in adults 18–64 years, through the indirect effect of herd protection. In older adults, age-related factors could play a role in IPD mortality.

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http://dx.doi.org/10.1016/j.jinf.2016.01.011
0163-4453/

Introduction

Invasive pneumococcal disease (IPD) remains a major health problem worldwide. Reducing IPD rates and mortality are two major challenges in the forthcoming years.

Streptococcus pneumoniae may be recovered from the nasopharynx of healthy people, especially young children (>50%) and less frequently adults (<10%).[1,2] Thus, young children are considered the main reservoir and often transmit the pneumococcus to other children (e.g. in day-care centres) and to adults (e.g. parents and family members).[2]

Nasopharyngeal colonization is considered the first step to produce subsequent IPD, which occurs mainly in patients with comorbidities —although it may also occur in healthy people—, which may result in pneumonia, meningitis, septicaemia and other infections.[3–8]

The prevalence of pneumococcal serotypes (>94 serotypes identified) causing colonization and IPD varies widely according to several factors such as: age, underlying host conditions, prior antibiotic therapy and the geographic area.[2,9–11]

The use of the 7-valent pneumococcal conjugate vaccine (PCV7) and more recently PCV13 in children has been associated with a decline in IPD and colonization rates by the vaccine serotypes, in children and adults because of herd protection.[12–16]

Mortality from IPD is low in immune-competent children and young adults, but increases sharply in patients with comorbidities and in older adults.[4,17,18] Several reports have investigated the role of the pneumococcal serotype as a risk factor for mortality,[19–22] but the complex interaction between host factors and bacterial factors[23,24] makes it difficult often giving discordant results. However, certain serotypes may have preference for specific hosts and different risk for death. For example, serotype 1 frequently affects healthy people and is associated with low case fatality, while serotype 3 affects either immunocompromised or healthy people and is associated with high case fatality.[4,19,20]

The objective of our study was to assess into the phenomenon of herd protection and investigate if changes in serotypes after PCVs in children could influence mortality from IPD in adults.

Methods

We performed an active surveillance of adults with IPD in Baix Llobregat area of Barcelona, with a population of about 600,000 inhabitants aged18 years or older. Adult patients with IPD can attend one of two hospitals, Hospital Bellvitge or Hospital Moises Broggi. All patients with an isolation by culture of *S. pneumoniae* from a sterile site were prospectively evaluated, and data were included in an ongoing clinical and epidemiological protocol of IPD.[3,18] Clinical and microbiological variables analysed include: age, sex, smoking and alcohol habits, underlying diseases, severity of underlying diseases, source of infection, antibiotic therapy, susceptibility to penicillin and pneumococcal serotypes.

The diagnosis of culture-proven IPD was based on clinical findings and the simultaneous isolation of *S. pneumoniae* from a normally sterile body fluid such as blood, pleural fluid, cerebrospinal fluid (CSF) or peritoneal fluid. Invasive pneumonia was considered in patients with an acute onset lower respiratory tract infection with new pulmonary infiltrate on chest radiograph together with isolation of *S. pneumoniae* from blood and/or pleural fluid. Other clinical syndromes were diagnosed based on standard criteria. We used the McCabe & Jackson score to classify underlying diseases: 1 (nonfatal disease), 2 (ultimately fatal), and 3 (rapidly fatal).[25] Current smoking was considered when the patient has been smoking at least ten cigarettes per day during the last year, and alcohol abuse when the patient reported a daily alcohol intake of 80 gr. or 60 gr. for men and women, respectively, during the previous year. Antibiotic therapy was prescribed according to the hospital guidelines. Standard regimen for pneumonia included penicillin, amoxicillin—clavulanate, ceftriaxone, levofloxacin or macrolide, alone or in combination; and cases of meningitis were treated with cefotaxime with or without vancomycin. Case fatality was defined as death within 30 days of the IPD diagnosis.

S. pneumoniae strains were identified by conventional methods (optochin susceptibility and bile solubility). Pneumococci were prospectively serotyped by dot-blot assay or Quellung reaction at the Spanish Laboratory of Majadahonda, Madrid, Spain, or by PCR. All serotype 6A pneumococci were screened for serotype 6C after this new serotype was described.[26] Antimicrobial susceptibility was tested by microdilution method following the CLSI and *S. pneumoniae* ATCC 49619 was used as control.[27]

In our area, vaccination with 23-valent polysaccharide pneumococcal vaccine (PPV23) has been recommended, free of charge, for people over 65 years and for young people with immunosuppressive conditions, since 1990s; and around 60% of older adults are currently vaccinated with PPV23. Pneumococcal conjugate vaccines (PCVs) are not subsidized by the Spanish Health Service, but the uptake in children has increased since the introduction of PCV7 in June 2001[28]; and PCV7 was replaced by PCV13 in 2010. PCV13 was introduced for adults in the last trimester of 2012, but it was only for at-risk adults. Serotypes included in the PCV7 are: 4, 6B, 9V, 14, 18C, 19F, 23F, and additional PCV13 are: 1, 3, 5, 6A, 7F, 19A. In our geographic area, it has been estimated that around 60% of young children have received at least one dose of PCV7, according to data obtained from children in the public system.[29] However, since PCVs are not free of charge, some vaccines administered by private physicians may not be registered in the public system charts, and the rates of vaccination could be higher than reported.

Statistical analysis was carried out with the PASW-20. Categorical variables were analysed by Chi-square test or Fisher's exact test using two-by-k contingency tables. We used multiple logistic regression models to determine the serotype-specific mortality after adjusting for several clinical variables. We used two models, one including all IPD patients and the other including only patients with invasive pneumonia. Variables included were: pneumococcal serotype, age, sex, McCabe & Jackson score, smoking, alcohol abuse, source of infection and MICs of penicillin. In the model for invasive pneumonia, antibiotic therapy was an additional variable. We avoided including

Please cite this article in press as: Grau I, et al., Declining mortality from adult pneumococcal infections linked to children's vaccination, J Infect (2016), http://dx.doi.org/10.1016/j.jinf.2016.01.011