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Serotype changes in adult invasive pneumococcal infections in Portugal did not reduce the high fraction of potentially vaccine preventable infections

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ABSTRACT

We determined the serotype and antimicrobial susceptibility of 1100 isolates responsible for adult invasive pneumococcal infections (IPD) in Portugal between 2006 and 2008. Serotypes 3 (13%), 1 (12%), 7F (11%), 19A (10%) and 14 (7%) were the most frequent causes of IPD and the two later serotypes accounted for the majority of erythromycin and penicillin nonsusceptible isolates. Serotype 1 was associated with younger adults whereas serotype 3 was associated with older adults. Despite the availability of the 23-valent polysaccharide vaccine (PPV23) in Portugal since 1996, the proportion of PPV23 preventable IPD remained stable and above 80%. Comparing with previous data from Portugal, we showed a continued decline of the serotypes included in the 7-valent conjugate vaccine (PCV7) in adult IPD and a rise of serotypes included in the 13-valent conjugate vaccine, increasing its potential coverage of adult IPD to 70% in 2008. Penicillin non-susceptibility remained stable (17%) whereas erythromycin resistance (18%) has continued to rise in the post-PCV7 years.

1. Introduction

Streptococcus pneumoniae (pneumococcus) remains a leading cause of acute otitis media, sinusitis, pneumonia, bacteremia and bacterial meningitis, causing significant morbidity and mortality throughout the world and affecting disproportionally the extremes of life. A vaccine including 23 of the 94 capsular polysaccharides known in pneumococci is licensed since 1983. Although its use is not recommended in children <2 yrs, it was advocated for older risk groups and all adults ≥65 yrs in the USA [1]. In Europe different countries have diverse recommendations regarding the use of the 23-valent polysaccharide vaccine (PPV23) in older adults, ranging from the absence of national guidelines, to recommendations of universal or risk group vaccination starting at 60 or 65 yrs [2]. The efficacy of PPV23 in the groups for which it is recommended is also a continuous matter of debate, with two recent meta-analysis reaching contradictory conclusions [3,4]. Although recommended in several European countries, in most there is a low overall uptake of PPV23 [5], possibly due in part to a general perception of poor efficacy of this vaccine. In Portugal, in spite of the availability of PPV23 since 1996, there are no official recommendations for its use outside strictly defined risk groups but medical societies have advocated the vaccination of all older adults. Still, a recent study found that the vaccine was prescribed to less than 9% of all patients ≥65 yrs followed by general practitioners in a primary care center in the north of the country [6].

The remarkable efficacy of the seven-valent conjugate vaccine (PCV7) against the serotypes included in its formulation resulted in a sharp decline in the vaccinated age groups of the proportion of invasive pneumococcal infections (IPD) caused by the serotypes targeted by the vaccine [7–11]. The effects of PCV7 in the USA where not restricted to the vaccinated age group, but were felt across the entire population [10], resulting in marked reductions of the incidence of IPD, particularly among older adults [10,12]. This "herd effect" is attributed to reduced colonization of children by PCV7 serotypes, due to mucosal immunity provided by conjugate vaccines that in turn leads to reduced adult colonization with PCV7 serotypes [13]. In Europe, although there were epidemiological changes in the serotypes causing IPD in the non-vaccinated population in all countries where the vaccine was administered, the large reduction in the overall number of invasive infections in adults observed in the USA was not replicated in countries such as Spain or the Netherlands [11,14,15].

The effect of PCV7 on antibiotic resistance in Europe was also variable. While a decrease in penicillin non-susceptibility was noted in all countries among isolates responsible for pediatric IPD in the post-PCV7 period [7,9,15,16], such a decline was not

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apparent in adults in Portugal and Spain [14–16]. These variations can be due to differences in the impact of PCV7 in colonization since it was shown that in Portugal vaccination with PCV7 was not associated with diminished colonization with antibiotic resistant isolates [17].

It was anticipated that the initial benefits of PCV7 would be at least partially offset by the emergence of serotypes not included in the vaccine that would replace the declining PCV7 serotypes. Such replacement has indeed been observed, although its magnitude was highly variable – being modest in North America [8,10] and much more significant in Spain [9,14,15]. Although serotype 19A has consistently been identified as a dominant non-vaccine serotype, other emerging non-vaccine serotypes differ among the various geographic locations and also between age groups [7,8,10,16]. Even within serotype 19A, different genetic lineages emerge in different geographic locations [18]. Taken together, these data highlight the importance of the characteristics of the local pneumococcal population and of local selective forces in conditioning the outcomes of vaccination [19].

On the other hand, it is known that serotypes responsible for IPD may have significant temporal variations in the same geographic region as documented in Spain and Denmark [20,21], even with limited antibiotic selective pressure and in the absence of PCV use, so that changes in the proportion of vaccine preventable IPD can be expected to occur with time in the same region. In addition, the divergent prevalence of the various serotypes in different geographic regions also conditions the potential benefits of vaccination. Significant heterogeneity exists among European countries [11,15,16,20,22] and a much higher prevalence of serotype 1 IPD is documented in Europe than in the USA [7,10,16]. Although serotype 1 is frequently associated with outbreaks and significant yearly variations of the proportion of IPD caused by this serotype are documented, a considerable fraction of IPD was consistently caused by this serotype in the last decades in Europe [20,21].

Two new conjugate vaccine formulations were developed and have recently become commercially available for use in children. A 10-valent formulation (PCV10) including, in addition to the PCV7 serotypes, serotypes 1, 5 and 7F that is available since March 2009 and a 13-valent conjugate vaccine (PCV13), including all PCV10 serotypes plus serotypes 3, 6A and 19A that is available since December 2009. The introduction of these vaccines into clinical practice has the potential to once again change the characteristics of pediatric IPD, eventually blunting or even reversing the rise of some of the most successful serotypes that have emerged as causes of pediatric IPD since the introduction of PCV7.

The observed benefits of conjugate vaccines in children launched a discussion about the potential benefits of vaccinating the adult population with these vaccines and several studies were performed comparing immunogenicity and protection of conjugate formulations versus PPV23 [23]. This also motivated a large study of PCV13 that is currently underway in the Netherlands comparing it to placebo for the prevention of vaccine-serotype community acquired pneumonia in adults [24]. The results of these trials may be used to support an indication for PCV13 use in adults. The potential benefits of adult vaccination with either PCV13 or PPV23 are a moving target since secular trends in pneumococcal serotypes and the herd effect provided by PCV7 and now PCV13 use in children could be expected to reduce the importance of the vaccine serotypes in adult IPD.

In Portugal PCV7 is not included in the National Vaccination Plan but, in spite of the absence of reimbursement, there has been a steady increase in vaccine uptake in the first seven years since it became available, reaching 75% of children ≤2 yrs in 2008 [16]. In previous studies, we showed that significant changes in the serotypes causing IPD in children followed PCV7 availability [7,16] and that there was evidence for a herd effect in the adult population [16]. This study aimed at documenting the continued changes on serotype distribution and antimicrobial resistance in different adult groups and evaluating the proportion of vaccine preventable adult IPD in Portugal.

2. Materials and methods

2.1. Bacterial isolates

Since 1999, the Portuguese Group for the Study of Streptococcal Infections has monitored pneumococci causing invasive infections in Portugal. This is a laboratory-based surveillance system, in which 30 microbiology laboratories throughout Portugal are asked to identify all isolates responsible for IPD and to send them to a central laboratory for characterization. A case of invasive disease is defined by an isolate of *S. pneumoniae* recovered from a normally sterile body site and does not include isolates recovered from middle ear fluid. Although the laboratories were contacted periodically to submit the isolates to the central laboratory, no audit was performed to ensure compliance, which may be highly variable in this type of study. Isolates recovered up to 2005 were previously characterized [16,25]. Only isolates recovered from adult invasive infections, i.e., recovered from patients ≥18 yrs, between 2006 and 2008 were included in the present study. Only one isolate from each patient was considered. All strains were identified as *S. pneumoniae* by colony morphology and hemolysis on blood agar plates, optochin susceptibility and bile solubility.

2.2. Serotyping and antimicrobial susceptibility testing

Serotyping was performed by the standard capsular reaction test using the chessboard system and specific sera (Statens Seruminstitut, Copenhagen, Denmark). Serotypes were classified into conjugate vaccine serotypes, i.e., those included in PCV13 (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 23F) and that comprise all the serotypes found in the lower valency vaccines PCV10 and PCV7, those included in PPV23 (all serotypes included in PCV13 except 6A and serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F) and non-vaccine serotypes (NVT). Etest strips (AB Biodisk, Solna, Sweden) were used to determine the MICs for penicillin and cefotaxime. In 2008, the CLSI changed the recommended breakpoints used to interpret MIC values [26]. Unless otherwise stated we have used the CLSI-recommended breakpoints prior to 2008 [27] as epidemiological breakpoints that allow the comparison with previous studies. According to these recommendations, intermediate level penicillin resistance was defined as MIC 0.1–1.0 μg/ml and high level resistance as MIC ≥ 2.0 μg/ml. Isolates that fell into either of these classes were designated penicillin non-susceptible. Susceptibility to cefotaxime was defined as MIC ≤ 1.0 μg/ml for non-meningitis cases and an MIC ≤ 0.5 μg/ml for meningitis cases.

Isolates were further characterized by determining their susceptibility to erythromycin, clindamycin, vancomycin, linezolid, tetracycline, levofloxacin, trimethroprim-sulfamethoxazole and chloramphenicol by the Kirby-Bauer disk diffusion technique, according to the CLSI recommendations and interpretative criteria [26].

Macrolide resistance phenotypes were identified using a double disc test with erythromycin and clindamycin according to a previously published procedure [28]. Simultaneous resistance to erythromycin and clindamycin defines the MLS_B phenotype (resistance to macrolides, lincosamides and streptogramin B) while non-susceptibility only to erythromycin indicates the M phenotype.