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Review

Can the success of pneumococcal conjugate vaccines for the prevention of pneumococcal diseases in children be extrapolated to adults?

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ABSTRACT

Before conjugate pneumococcal vaccines (PCVs) were introduced it was estimated that *Streptococcus pneumoniae* caused 500,000 cases of pneumonia, 50,000 cases of bacteremia and 3000 cases of meningitis annually in the United States in both children and adults. After 10 years of routine use of the 7-valent pneumococcal conjugate vaccine (PCV7) the incidence of vaccine-type pneumococcal diseases (PDs) had significantly decreased in vaccinated children (direct effect) and unvaccinated subjects of all ages (indirect effect). Second generation, higher-valent PCVs, especially 13-valent (PCV13), routinely implemented since 2010, have reduced the incidence of PDs caused by the six additional non-PCV7 serotypes, in both vaccinated and unvaccinated subjects. The licence for this vaccine has recently been extended to include adults aged 18 to 49 in Europe. Although PCV13 has an indirect effect on IPD in adults, this will probably not achieve the same level of disease control in adults and the elderly (especially those at high risk) as that obtained in vaccinated children.

As highlighted in this paper, differences exist between children and adults for PD manifestations (incidence, morbidity and mortality) and serotypes isolated in nasopharyngeal carriage and diseases, so benefits from adult vaccination must be considered in this light. PCV13 induces an immune response in adults that is non-inferior for all serotypes common with the 23-valent plain polysaccharide vaccine that is currently recommended for adults and even superior for many serotypes. Although there is no evidence that this immune response translates to clinical efficacy in adults as seen in children, the results from a randomised trial in The Netherlands, expected in 2014, should provide the missing evidence. This evidence and efficient surveillance systems should provide the necessary data, essential for policy makers in their decisions on adult pneumococcal vaccination policies.

1. Streptococcus pneumoniae

The diseases and mortality associated with some *Streptococcus pneumoniae* serotypes are largely vaccine-preventable. It was estimated that *S. pneumoniae* was responsible for 500,000 cases of pneumonia, 50,000 cases of bacteremia and 3000 cases of meningitis per year in the United States in the whole population, prior to the introduction of conjugate pneumococcal vaccines [1]. The age-specific incidences of pneumococcal disease show a U-shaped distribution with the highest incidences in the younger and older populations. Pneumococcal disease mortality and case fatality rates are relative stable up to 50 years of age; they then start to increase with age.

2. Pneumococcal nasopharyngeal carriage

There is convincing evidence that pneumococcal nasopharyngeal (NP) carriage is an immediate and essential precursor for pneumococcal disease and also the source of pneumococcal transmission between people [2,3]. Pneumococcal NP carriage rate is age-dependent, starting early in the first year of life and peaking at about 55% around three years, with a steady continual decline into adulthood [4]. Although the prevalence of NP carriage in the elderly is low, frequent acquisition was reported in the elderly living in the community and institutions [5]. The average duration of

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NP carriage in adults is 19 days compared with 51 days in children <5 years [6].

In Israel, the most frequent serotypes found in NP carriage were 6B, 23F, and 19F in children and 6A, 14, 6B, 33F, 11A, 10, and 3 in adults; 23F and 19F were absent in adults and 33F, 11A, 10, and 3 were absent in children [7]. In children NP carriage is likely to be a primo-colonization, whereas in adults, it is more likely to be a recolonisation, as suggested by the results from a study in the UK, where documented NP carriage in healthy adults induced an increase in serotype-specific antibodies [8].

Although the pathogen responsible for pneumococcal diseases is the same in children and adults, many aspects differ between younger and older patients. Here we will discuss some of these and examine the role of pneumococcal vaccination in different age groups.

3. Pneumococcal serotypes associated with IPD

Prior to PCV7 introduction, serotype 14 was the most frequently found serotype in IPD in all age groups in the US and Germany although its relative frequency differed with age [9,10]. It was reported to be 33.5% in children <2 years, 25.2% in children <16 years, 16.7% in adults ≥16 years and 15.2% in adults ≥65 years. The second and third most frequent serotypes in children <2 years were 23F (7.3%) and 6B (7.7%) whereas in adults ≥16 years serotypes 3 (8.3%) and 4 (7.0%) were the second and third more frequent.

4. Clinical presentations following pneumococcal infections prior to the introduction of PCV7

Pneumococcal disease (PD) can be non-invasive such as otitis media, sinusitis, mastoiditis and non-bacteraemic pneumonia, or invasive (IPD) such as bacteraemia, meningitis, and bacteraemic pneumonia. IPD is defined by the isolation of *S. pneumoniae* from a normally sterile site (e.g. blood or cerebrospinal fluid, but not sputum).

In the US, the main clinical manifestation was occult bacteraemia in the younger age groups and bacteraemic pneumonia in the older age groups [10]. The case fatality rate (CFR) for IPD was highest in adults aged ≥80 years (20.6%) compared with 1.4% in children <2 years. Although the incidence of meningitis was low generally, 7.5 per 100,000 in children <2 years compared with from 0.2 up to 1.9 per 100,000 in other age groups, its CFR was higher than that for pneumococcal pneumonia or bacteraemia in all age groups [10]. In The Netherlands, meningitis was more frequent in infants aged ≤1 year (44%) and decreased with age down to 7% in those aged ≥65 years; invasive pneumonia accounted for 16% of all cases of IPD in those aged ≤1 year and 83% in those aged ≥65 years [11]. Although less frequent, meningitis in those aged ≥65 years was more severe than in those aged <2 years: CFR 39% vs. 10%; ICU admission rate: 58% vs. 27%; hospital stay: median 20 days vs. 12 days, respectively [11]. Age is not the only factor that can explain these differences; there is likely to be a complex interplay of other factors, such as the frequency of comorbidities that contribute to the differences.

5. Pneumococcal serotypes, invasive power and disease severity

Not all of the more than 90 pneumococcal serotypes that have been identified based on their capsular polysaccharide antigens cause disease [12]. Among those that cause disease, not all have the same invasive potential. Serotypes that are more heavily encapsulated, with a lower invasive power and higher carriage prevalence have been reported to cause more severe disease. Serotypes 3, 6A, 6B, 9N and 19F have been repeatedly reported to be associated with an increased 30-day mortality risk in patients aged ≥5 years with IPD, a higher CFR and longer hospital stays in adults [11,13–15]. Although previously healthy individuals develop severe disease when infected with these serotypes, patients with underlying disease seemed to be more susceptible to them [15]. Serotypes 3, 6A, 6B, 8, 19F, 23F were reported to have a low invasive potential but were associated with a higher CFR and were more often isolated from adults with comorbidities [15].

The correlation between the most frequent serotypes responsible for IPD and higher 30-day mortality rate or CFR varied with age. In Denmark from 1997 to 2007, in patients ≥5 years, serotypes 31, 11A, 35F, 17F, 3, 16F, 19F, 15B, and 10A were associated with a more than 3-fold higher 30-day mortality rate than serotype 1 whereas for children <5 years, serotype 1 was the most frequently associated serotype, followed by serotypes 9V and 6B [14]. In the UK from 2002 to 2011, serotype 19F was most frequently associated with mortality in those aged ≥65 years, with a CFR of 41%, whereas it was second in those aged <5 years with a CFR of 5% (serotype 6A was first) and third in those aged 5 to 64 years with a CFR of 21% (serotypes 31 and 11A were first and second) [16].

6. Risk factors for IPD

The frequency of IPD in patients with comorbidities aged ≥50 years in the US increased significantly from 1998–1999 to 2002–2003; in patients with diabetes (from 15.3% to 21.8%), chronic obstructive pulmonary disease (from 21.7% to 25.0%), receiving recent immunosuppressive treatment (from 6.6% to 9.1%), ≥1 immunocompromising condition (from 19.5% to 23.0%) and those with other co-morbid conditions (from 53.9% to 62.6%) [17]. In the US the percentage of children <5 years with IPD with ≥1 underlying condition increased from 3% in 1998 (pre-PCV7) to 7% in 2006–2007 (post-PCV7) ($p = 0.003$), in 18–64 year-old adults the increase was from 52% to 59% ($p < 0.001$) and in those aged ≥65 years the increase was from 69% to 81% ($p < 0.001$) [18]. In The Netherlands underlying conditions were reported for 30% of the children with IPD aged 0–1 years (mostly premature birth), 19% of children aged ≥4 years and 80% of patients aged ≥65 years [11]. In addition to young age (<2 years) and ageing (≥65 years), medical risk factors, such as chronic lung disease, diabetes, chronic liver disease, chronic heart disease, chronic renal failure, splenectomy, any immunocompromised condition, also appear to be important in determining disease severity and mortality [19,20].

Community-acquired pneumonia (CAP) was more frequent in patients with underlying conditions aged ≥65 years than those aged 15–64; 70.5% vs. 29.5%, $p < 0.001$ [21]. As CAP can be caused by different pathogens, this increased frequency of underlying diseases with age may not be a specific risk factor for pneumococcal infections. In The Netherlands, the proportion of patients aged ≥65 years with immunocompromising conditions with IPD increased after PCV7 introduction, however the CFR for IPD among these patients decreased, suggesting that subjects with different risk factors (age or medical conditions) may be more susceptible to the emerging NVTs but that these were less fatal [22].

7. Pneumococcal vaccination in children: Direct and indirect effects

Conjugation of certain capsule polysaccharides to protein carriers provides a vaccine that enables children aged <2 years to mount a protective immune response against vaccine serotypes early in life. Since the introduction of a seven-valent conjugate vaccine, PCV7, containing serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, in North America, Australia and many European countries, substantial