Pneumococcal vaccination: time to move on?

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The search for an efficient pneumococcal vaccine has been driven by the enormous clinical impact of pneumococcal infections especially in young children. *Streptococcus pneumoniae* is the primary bacterial cause of childhood acute otitis media, bacteremia, pneumonia, and meningitis and is an important cause of mortality in the developing world [7]. The threat posed by *S. pneumoniae* is particularly high in certain risk groups: children below the age of 2 years, immune-compromised patients including HIV infection and patients with hematologic malignancies, diabetes, and severe renal failure. The spread of antimicrobial-resistant *S. pneumoniae* worldwide has added to the need for vaccine development [7, 8, 12].

Pneumococcal polysaccharide antigens are unable to generate an efficient immune response in children younger than 2 years of age; pneumococcal polysaccharide vaccines are thus not protective in this age group [17, 22]. Conjugation or ‘coupling’ the pneumococcal polysaccharide antigen to an immunogenic protein carrier converts the polysaccharide antigen to a T cell-dependent antigen and alters the response to the polysaccharide in several important ways [20]: an efficient antibody response can be generated from a young age including development of memory B cells primed and ready to respond to either the polysaccharide (as would be encountered during an infection) or to a second dose of the same vaccine antigen. The development of pneumococcal conjugate vaccines allows the prevention of pneumococcal

disease in populations that are unable to generate an adequate immune response to polysaccharide vaccines.

Initial reports of decrease in invasive pneumococcal disease (IPD) after the introduction of the 7-valent pneumococcal conjugate vaccine (PCV-7) were impressive [1, 2, 11, 23]. In 2001, 1 year after the vaccine's license, the rate of IPD in children under 2 years of age dropped from 188 to 59 per 100,000 in the US (−69%; $p<0.001$); the rate of disease caused by vaccine and vaccine-related serotypes declined by 78% ($p<0.001$) and 50% ($p<0.001$), respectively [23]. Disease rates also fell in other age group including adults, a phenomenon called herd immunity.

Because of the limited number of serotypes contained in the PCV-7 vaccine, possible serotype replacement was anticipated and active surveillance was put in place in several countries including the US. The ‘Center for Disease Control’ and several groups have documented that the number of pneumococcal infections caused by non PCV7 vaccine serotypes is increasing, primarily serotype 19A [3, 9, 13, 15, 16, 18, 19]. Moreover, multidrug antibiotic resistance among the 19A serotype isolates has become a major concern [13–16].

The study published in this issue of the European Journal of Pediatrics reports on the surveillance of pediatric invasive pneumococcal infections in a tertiary care pediatric center in Quebec (Canada) after government sponsored introduction of PCV-7 vaccine for children up to age 5 years in a 2+1 schedule for infants [5]. Other reports mainly concern 3+1 schedules. This rather small study confirms data from several other epidemiological studies on evolution of pneumococcal epidemiology underlining the value of well-performed monocentric surveillance. A weakness of this study is the absence of individual patient vaccination status as well as data on the general vaccination uptake in the province. Data are given as absolute IPD numbers and not compared with overall admission data.

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The overall reduction in IPD of 61.4% in the whole pediatric age group is similar to other reports. In the post-vaccination period, children with IPD were older (mean age of 26 months versus 18.8 months), but the percentage of children with underlying conditions was not higher. Interesting in this study is the detailed documentation of the different types of IPD. Post-vaccination, the proportion of bacteremia decreased while pneumonia increased. Meningitis remained at around 12% of all IPD, the absolute number of cases thus slightly decreasing. Although from 2008, the absolute number of IPD is again on the rise, it is still well below the pre-vaccination level. The recent increase is however mainly due to non-vaccine serotype infection, with serotype 19A as the main culprit; again, these data are in line with other reports.

In a recent publication, eight US children's hospitals report on a prospective surveillance of invasive pneumococcal infections from 1994 to 2008, vaccination being started in 2000 [10]. By 2004, there was an overall decline of 65% in IPD cases in all age groups. Compared to the period before start of vaccination ($n=400$ –500), IPD number has decreased yearly from 2001 ($n=200$) through 2004 (150), with numbers again rising from 2005 to 2008 ($n=200$). Similarly, bacteremia decreased and pneumonia increased. For the period of 2007–2008, 19A accounted for 46% of all serotypes. These results compare well to the current Canadian report, only the relative proportion of children with underlying disease was higher after vaccine introduction.

Although the PCV7 vaccine holds an inherent risk for serotype replacement, it would be an oversimplification to point to PCV-7 vaccine as the one and only cause of the worrying serotype replacement. Some serotypes including 1 and 19A were already on the rise before the vaccine was introduced as has been documented in Korea and Israel [4, 6]. A Belgian survey also documented a rise in 19A before the introduction of vaccination with a further increase post-vaccination (unpublished data, manuscript in preparation). Interestingly, in the survey of Kaplan et al., there was an association between the number of PCV7 doses received before the infection and the likelihood of 19A being responsible [10]. In the current report, however, the proportion of 19A was almost as high (40.7%) in the context of a 2+1 schedule compared to a 3+1 schedule.

So where are we now? PCV7 is immunogenic and highly protective against vaccine serotypes in a 3+1 as well as a 2+1 schedule in young children. Large scale vaccination has decreased the total number of IPD substantially. Unfortunately, for meningitis, the IPD with the highest mortality and morbidity, the vaccine has not made a big difference. Although recently the IPD incidence is rising, it is still well below the pre-vaccine level. Data are however worrying in that very virulent serotypes like 19A are on the rise, even more

so because of the high antibiotic resistance of this specific serotype. It is therefore time that the new pneumococcal vaccines become available, especially the 13 valent one since it includes the latter serotype. Further surveillance remains of utmost importance. In addition, further research towards a pneumococcal vaccine based on a common pneumococcal protein may be needed in order to obtain a consistent and lasting decrease in IPD [21].

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