Pneumococcal conjugate vaccine for adults: "It's tough to make predictions, …"

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Do the results of the CAPITA study justify the general vaccination of adults with PCV13?
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"… especially about the future." This frequently used Yogi Berra quote also holds true for the paper by Mangen *et al.* [1] from the Netherlands, which modelled the cost-effectiveness of a potential vaccination programme for elderly adults using the 13-valent pneumococcal conjugate vaccine.

The 13-valent pneumococcal conjugate vaccine (PCV13) was licensed for adults in 2011. Data from the largest randomised controlled trial (RCT) on a pneumococcal vaccine published to date (the CAPITA study) show a vaccine efficacy of 45.6% for pneumonia caused by the 13 vaccine serotypes, including 45.0% for non-bacteraemic pneumonia [2]. Do these data justify the general use of PCV13 in adults? Mangen *et al.* [1] conducted economic modelling mainly based on the data of the CAPITA study that showed that PCV13 in adults is highly cost-effective. However, vaccination of infants, the main reservoir of pneumococci, with conjugate vaccines has resulted in herd protection effects, *i.e.* also decreased prevalence of the serotypes contained in vaccine in adults.

So the question remains, are the results of Mangen *et al.* [1] are transferable to countries that have implemented PCV13 in infants?

Undoubtedly, community-acquired pneumonia (CAP) is a major public health topic, including in developed countries. Its morbidity and mortality increase with age [3]. Most studies have found *Streptococcus pneumoniae* to be the most frequent pathogen in CAP [4]. Therefore, an effective vaccine against *S. pneumoniae* for elderly adults would be a breakthrough for CAP prevention. However, *S. pneumoniae* is a smart pathogen: its main virulence factor is a polysaccharide capsule that prevents recognition by phagocytes. Not only are polysaccharides are of limited immunogenicity when used as vaccine antigens, there are also 94 known different capsular types with no or very limited cross-immunity [5].

Earlier vaccination strategies against *S. pneumoniae* involved administering large amounts of pure polysaccharide. The 23-valent polysaccharide (PPV23) vaccine contains the polysaccharides of 23 out of the 94 serotypes. However, its efficacy was not convincing, probably because polysaccharides are primary B-cell antigens and therefore vaccination does not induce a T-cell response, resulting in a lack of both memory cells and mucosal immunity [6, 7]. In addition, this vaccine could not be used in younger infants, because their immature immune system did not properly respond to this vaccine. However, several meta-analyses of RCTs have shown that PPV23 has a efficacy of up to 75% against pneumococcal bacteraemia [8, 9]. Interestingly, we found the same efficacy in our CAPNETZ (German Network for community-acquired pneumonia) cohort, which was not included in these meta-analyses [10].

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However, the majority of pneumococcal pneumonia is non-bacteraemic, *i.e.* noninvasive, and except for some older studies in younger adults from developed countries [11, 12] and one study of Japanese nursing home residents, PPV23 had no effect against noninvasive CAP [13]. Therefore, several countries such as the Netherlands did not implement PPV23 in their national vaccination recommendations.

The conjugate pneumococcal vaccine uses a different approach by conjugating each individual polysaccharide to a highly immunogenic carrier protein like the tetanus toxoid, which is a very effective T-cell stimulant. This conjugation results in T-cell support with consecutive mucosal immunity and memory cells [6]. This vaccine was primarily developed for infants. Due to technical challenges it initially contained only seven serotypes. The implementation of the conjugated vaccine in children resulted in tremendous herd protection effects. Numerous reports from countries that implemented the conjugate vaccine reported a sharp decrease in invasive pneumococcal diseases caused by the seven serotypes not only among vaccinated children but also in non-vaccinated adults [14–18]. However, the remaining invasive pneumococcal diseases were caused more and more frequently by the non-vaccine serotypes, which seem to replace the seven serotypes. Therefore, in 2010 a 10-valent and, later, a 13-valent vaccine were licensed for infants. The 13-valent replaced the 7-valent vaccine, because the same manufacturer produced both vaccines. In 2011, the license for PCV13 was extended to adults, resulting in a dilemma: should we use the smaller PCV13 with probably better efficacy or the broader PPV23 with inferior immunogenicity? To date, there has been no head-to-head comparison between both vaccines, and such a trial would be of limited use as we will outline later.

In order for national immunisation committees to come to the best decision two important questions need to be addressed. 1) Does PCV13 protect from the majority of pneumococcal CAPs, *i.e.* noninvasive CAP? 2) Will the herd protection effects resulting from vaccination of infants entirely eradicate those 13 serotypes, so that additional vaccination of adults is meaningless? [19]. Answers to both questions are the basic information required for a valid cost-effectiveness estimation, which is today increasingly used by national vaccination committees to rationalise their decisions.

The first question was answered by the CAPITA trial and can probably be extrapolated to other countries as well: 45% of noninvasive CAP caused by the 13 vaccine serotypes was prevented. Is 45% efficacy against 13 pneumococcal serotypes enough to recommend the widespread use of PCV13? In the CAPITA study itself, vaccine efficacy against all cause CAP was estimated to be 5.1% (95% CI −5.1–14.2). At a first glance, this seems unimpressive but Mangen *et al.* [1] estimated that the vaccine would prevent, on average, 9850 episodes of outpatient CAP, 1850 episodes of inpatient CAP, 2050 episodes of invasive pneumococcal disease and 630 deaths during the lifetime of the vaccinated cohort.

The second question is still unresolved and needs to be answered specifically for each country. The Netherlands have implemented the 10-valent conjugate vaccine (PCV10) in infants. This vaccine does not cover serotypes 3, 7 and 19A, the most frequent serotypes in adult CAP, so there are no herd protection effects that will decrease the frequency of CAP due to serotype 3, 7 and 19A. In the CAPITA study, the largest efficacy for PCV13 was found against these three serotypes. So it could be assumed that the cost-effectiveness will be greater in the Netherlands compared with countries that have implemented PCV13, covering those three serotypes. However, we do not know yet the dimension of the replacement phenomenon after introduction of PCV13 in infants: early data suggest that there is no relevant herd protection for serotype 3 [20]. Serotype 3 has a broader capsule and seems to be more frequently invasive and less frequently colonising. Also the antibody response to serotype 3 is on average lower compared with other serotypes, even after vaccination with PCV13. However, as outlined earlier, CAPITA has proven that vaccination reveals individual protection from serotype 3 pneumonia: there was a significant decrease between vaccinated subjects and controls.

Knowing these details, how would one decide, as a member of national vaccination committee, on the approach for pneumococcal vaccination in adults? Should adults be given PCV13 or PPV23, or both, or neither?

Noteworthy, the US Advisory Committee on Immunization Practices was the first major national vaccination committee to issue a recommendation for a sequential vaccination, *i.e.* PCV13 followed by PPV23 after 6–12 months, for all adults ⩾65 years of age [21].

We are convinced that cost-effectiveness should be considered before implementing vaccination programmes and country-specific epidemiology should be one basis of these models, to prevent wrong allocation of resources by the introduction of vaccines against infections with a low burden of disease. However, compared with other medical specialties, strong evidence-based decision-making is difficult in infectious diseases because the epidemiology of pathogens exhibits large regional differences and changes much faster

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than for example human susceptibility to specific diseases. Therefore, recommendations based on a high methodological standard using evidence grading and systematic literature reviews can never be long lasting.

The dynamic change of pneumococcal serotype distribution is a good example for this dilemma. Herd protection was not considered in the model by Mangen *et al.* [1], which is reasonable due to the introduction of PCV10 instead of PCV13 in infants. Instead, in sensitivity analyses, the possibility of indirect effects was addressed by an assumed factor, which reduced the incidence of PCV13-serotypes.

Nevertheless, herd protection has a substantial impact on cost-effectiveness. Therefore we believe that recommendations for specific vaccines should not only consider clinical effectiveness but also the regional epidemiological data for the time being. To make things even more sophisticated, herd protection can not only increase but may also decrease over time. The latter can be caused by immigration of non-vaccinated refugees from developing countries or war zones, like the Middle East, particularly Syria, Iraq and Libya, where the healthcare systems crashed several years ago [22]. As a consequence, the rationale for vaccine recommendations needs to be re-evaluated and modified in a scheduled manner because epidemiological data are at least as important as evidence grading based on clinical studies on vaccine efficacy, and epidemiology can change even quicker than available evidence from clinical studies.

Another question is whether a vaccine needs to be cost-effective at all. Whereas such a question may be asked regarding prevention of infections with low mortality rates like rotavirus infections in developed countries, this does not apply to (noninvasive pneumococcal disease)-CAP with a mortality between 6.4% (in patients aged 64–74 years) and 16.2% (in those aged >84 years), according to the paper of Mangen *et al.* [1], which is in line with other studies [23]. The oncology approach of defining a upper limit of costs for the so-called quality-adjusted life-years gained to decide on the implementation of expensive innovative anti-cancer treatments cannot be easily extrapolated to vaccines [24]. Whereas expensive anti-cancer treatments frequently prolong survival but do not prevent the fatal outcome, a vaccine prevents the disease occuring at all. So, if a vaccine preventing frequent infections with a considerable mortality, such as PCV13, needs to be cost-effective has to be judged on an ethical–political rather than a scientific–economic scale. Furthermore, the economic performance of a healthcare intervention is just one criterion of a multidimensional decision problem. The severity of the (prevented) disease, the lack of alternatives, the innovativeness of the intervention and ethical implications, among others, all need to be considered.

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