EDITORIAL

Pneumococcal Conjugate Vaccine—Equally Effective for Everyone?

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Editorial to accompany the article: „The Clinical Effectiveness of Pneumococcal Conjugate Vaccines“ by Hannah Ewald et al. in this issue of *Deutsches Ärzteblatt International*

In Europe, community-acquired pneumonia (CAP) is the most common infectious disease leading to hospital admission, carrying a high morbidity and mortality. Data from the Global Burden of Disease study show 230 000 deaths (2.3%) from CAP, making CAP the fifth most frequent cause of death in Europe (1). In Germany, something over 258 000 patients with CAP were treated in hospital in 2014; hospital mortality was just below 13% (2). A prospective cohort study showed in addition that 10-year mortality is higher in patients who have experienced a CAP episode than in a control group (3), because the pneumonia is accompanied by exacerbation of other pathological conditions, especially cardiovascular disease. Since the incidence of CAP increases with age, the changing demographics worldwide mean that the rise in CAP cases is set to continue.

Vaccination the only realistic answer

Despite medical progress in recent years, CAP mortality has barely changed. The main CAP pathogens are sensitive to all conventional antibiotics; the development of pathogen resistance has not affected mortality (4). Risk factors such as age, co-morbidities, and being bedbound influence the prognosis far more than the pathogen itself. It is therefore not surprising that the development of novel antibiotics has had almost no effect on morbidity and mortality (5).

Vaccination remains the only realistic way to reduce the number of cases and hence the number of deaths from CAP in the short term. Vaccines against pneumococci (*S. pneumoniae*)—still the most common respiratory pathogen (6)—and against influenza are available. The efficacy of influenza vaccination on the burden of CAP, especially in older patients and those with co-morbidities, has already been proven (7).

There is much debate about the efficacy of pneumococcal vaccination. Two vaccines are available: the 23-valent polysaccharide vaccine (PSV23) and the 13-valent conjugate vaccine (PCV13). Because of its poor immunogenicity in infants and young children, PSV23 is not recommended as a sole vaccine in this age group. In adults, a number of randomized controlled trials (RCTs) and a few cohort and case-control studies have been carried out and showed a reduction in invasive pneumococcal disease (IPD) in over-60-year-olds, the most important group of patients owing to their high burden of disease. Regarding CAP, which is

much more common than IPD, different meta-analyses came to different conclusions (8, 9), because the numbers of patients included in vaccination studies tend to be low and the studies are extremely heterogeneous. In immunosuppressed patients, the efficacy of PSV23, even in relation to prevention of IPD, is contested: studies in HIV-positive patients at particularly high risk of IPD even showed a negative effect of PSV23 (10).

Protective effect

In this issue of *Deutsches Ärzteblatt International*, Ewald et al. present an up-to-date review of the efficacy of pneumococcal conjugate vaccines (11). The strength of this meta-analysis is that it analyzes only RCTs and includes only recent studies. Its weakness is that it treats each of the various diseases caused by pneumococci (IPD, CAP, acute otitis media) separately, but analyzes all the age groups—from infants and young children to over-60-year-olds—together. In most studies, the control with which the conjugate vaccine was compared was a placebo. In the studies in which it was compared with PSV23, the case numbers were too small to allow conclusions. In addition, vaccines with a protective effect against different numbers of serotypes (PCVs 7, 9, 10, 11, and 13) were analyzed together, even though they cannot be assumed to have the same efficacy. In their discussion of all the studies of pneumococcal conjugate vaccines, the authors conclude that their use can prevent IPD, pneumococcal CAP, and otitis media; naturally, the preventive effect was mainly shown for the serotypes contained in the vaccine. No difference in mortality was shown, but then the studies were not large enough for this endpoint.

Many unknowns

At first glance, the review findings appear to support the use of pneumococcal conjugate vaccine. I could have wished, though, that the analysis had used a slightly finer mesh. It is uncontested that PCV13 is the vaccine of choice in infants and young children because of its higher immunogenicity. Since the introduction of PCV7 vaccination in this age group, a sharp drop has been seen in IPD and in pneumococcal-related deaths in children (12). In parallel to this drop, a clear reduction has been seen in the pneumococcal disease in adults, because the pathogen is not being passed on by

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children to adults: the effect known as herd immunity. Another effect of vaccination in children was that the vaccine serotypes disappeared, being replaced by pneumococcal serotypes that until then had not been dominant (serotype shift). This effect was managed by adding new serotypes to the vaccine. As to the value of PCV13 in over-60-year-olds, the experts in the German Standing Committee on Vaccination (STIKO, Ständige Impfkommision) and the various medical societies differ in their estimates despite the fact that all their arguments rely on the same set of data.

Opponents of PCV13 vaccination in adults believe that the combination of herd immunity and serotype shift make PCV13 vaccination unnecessary in adults, because not enough cases of these serotypes will continue to occur. This assumption includes a number of unknowns, however. What effect our changing demographics will have on the way herd immunity evolves is not yet clear; nor has it been demonstrated that the serotype shift observed for PCV7 is also observed in the six additional serotypes contained in PCV13. Serotype 3, at least, is virtually unaffected by this shift. Furthermore, the effect that the migration of young, often unvaccinated people might have on serotype distribution and herd immunity is entirely unknown.

Overcoming immunization fatigue

To conclude: the review by Ewald et al. shows the high potential of pneumococcal conjugate vaccines. Unfortunately, we in Germany do not make enough of the undisputed advantages of vaccines. Although take-up of child immunization is fairly good, fewer than 20% of adults follow the immunization recommendations issued by the medical societies (13). The reasons for this are many and various, ranging from lack of understanding of the problem, through poor public education, to opposition to immunization on principle. Any health policy that aims to reduce pneumonia-related morbidity will need to overcome this “immunization fatigue.”

Conflict of interest statement

Professor Welte has received consultancy fees from Astellas, AstraZeneca, Basilea, Bayer, MSD, Novartis, and Pfizer. He has received fees from AstraZeneca, Basilea, Bayer, MSD, Novartis, and Pfizer for carrying out commissioned clinical trials related to the topic of this editorial.

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