

Heptavalent pneumococcal conjugate vaccine (PCV7)

Claes C, Reinert RR, Vauth C, Greiner W

Introduction

The bacteria *Streptococcus Pneumoniae* (pneumococcus) is one of the most frequent causes of invasive (e.g. meningitis) and non-invasive (e.g. otitis media) infections world-wide. Young children, children with an insufficient immune system as well as seniors are particularly at risk for a pneumococcal related disease.

With market approval of the heptavalent pneumococcal conjugate vaccine (PCV7) for the European market by the European Agency for the Evaluation of Medicinal Products (EMA) in February 2001, there is for the first time a treatment available, which provides a reliable protection for children under two years old.

With effect from July 1st, 2001 the German Standing Commission on Vaccination (STIKO) recommended the vaccination for children at special risk for pneumococcal related diseases. This recommendation was broadened further in July 2006 to all children under the age of two.

With the latest German health care reform act (Gesetz zur Stärkung des Wettbewerbs in der Gesetzlichen Krankenversicherung) in 2006, all vaccination programs regardless of the disease that already have been recommended by the STIKO in the past were included within the standard statutory health insurance benefit package starting from 2007. The highest decision-making entity of the self-governing statutory health insurance scheme is the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA), that defines mandatory treatments and the extent to which they are to be reimbursed by the insurances. They usually base their decisions on recommendations from the STIKO. A first decision on reimbursable vaccinations was made June 30th, 2007, where all vaccinations recommended by the STIKO became standard benefits. Hence, also vaccination with PCV7 was included in the package. However, the G-BA made the amendment that they reserve themselves the right to again look at and evaluate the available evidence in the case of PCV7.

Objective

This Health Technology Assessment report analyses the existing evidence on the effectiveness of a general vaccination recommendation with PCV7 with regard to individuals and the society and examines the transferability of international results to the present German situation. In addition this report will focus on data about the cost-effectiveness of PCV7 with inclusion of the expected effects due to herd immunity.

Methods

In order to identify the relevant literature a systematic literature search including clinical and epidemiological studies of pneumococci was conducted. Additionally the same procedure was applied for economic, ethical and legal publications. In a first step the results were selected based on their bibliographic data. In a second step the relevant literature was extracted on basis of the full text of relevant references and was evaluated afterwards.

The identified full health-economic evaluations were assessed with the help of structured abstracts, in order to examine the quality of the studies and their transferability to the German situation.

In a third step a cost-utility-analysis of a general vaccination program following the STIKO-recommended 3+1 dosing scheme was undertaken from the perspective of the German statutory health insurance as well as from a societal perspective.

Assessment of the epidemiology

Epidemiologic data for invasive pneumococcal disease (IPD) in the German paediatric population are available through the Pneumococcal Surveillance Network including the registry for rare paediatric diseases in Germany (ESPED), the laboratory surveillance panel of the Robert Koch Institute and by the German National Reference Centre for Streptococci. For children under 2 (5) years of age, 660 (970) cases of IPD are estimated to occur annually with 420 (680) cases induced by serotypes covered by the PCV7. For German children under the age of 5 (2) years there are 19 (14) IPD related deaths per year and 38 (29) suffer from serious complications after IPD. The serotype distribution is age-dependent. The serotype coverage of the vaccine in the age group of children under two years of age is 72 %. Based on a study of the National Reference Centre for Streptococci in Germany, the incidence of IPD in adults (after correcting for underreporting) is 16.2 cases per 100,000 in the age group of over-65-year-olds. However, the authors of the mentioned study stress that in patients with community-acquired pneumonia blood-cultures were only taken in 37 % of the cases. Moreover, blood cultures were often from patients under antibiotic therapy, so that the causative agent for the disease could not be found. Therefore, the authors concluded that the 'true' incidence of IPD in adults in Germany must be closer to 50 cases per 100,000. Additional studies in various regional states in Germany are currently underway. In several countries of South- and South-eastern Europe resistance-rates to pneumococci are >50% in both macrolides and penicillin G. In recent years the resistance-rate of pneumococci to macrolides has significantly increased while the level of resistance to penicillin G is still below 10%.

Medical Assessment

Results

The heptavalent pneumococcal conjugate vaccine (PCV7) is the first pneumococcal vaccine, which is able to induce a sufficient immune response in children under the age of two. The conjugation of the polysaccharide to a protein carrier changed the nature of the vaccine antigen significantly. A T-cell independent antigen was transformed into a T-cell dependent antigen, which consequently has the ability to be used in young children. PCV7 contains the polysaccharide of serotypes 4, 6B, 9V, 14, 19F, and 23F and the oligosaccharide of serotype 18C. In the study submitted to the FDA (American Food and Drug Administration) for licensure of PCV7 the vaccine was given to 37,868 children at two, four, six and twelve to 14 months of age in a double-blind 1:1 randomized trial. A meningococcal serogroup C vaccine was given to the control group. The efficacy against serotype-specific IPD was 97 % in fully vaccinated children (95 % confidence interval: 94 to 100).

Data on cross-protection of PCV7 (protection against infections caused by pneumococci of serogroups included in the vaccine) is scarce. There is some evidence that this cross-protection may partially exist within the serogroup 6. For serogroup 19, however, a significant cross-protection cannot be assumed on basis of data for immunogenicity, efficacy, and effectiveness. After the introduction of PCV7 in the USA adverse events have only rarely been reported, so that there are no major safety issues after the usage of several million doses of this vaccine. Post-marketing surveillance in the USA for the first two years after the introduction of PCV7 showed one adverse event in 7,576 vaccinations. In the same time 31.5 million

doses of the vaccine were sold. In more than 50 % of the cases these adverse events turn out to be local tenderness, swelling or mild fever.

PCV7 can be administered concomitantly with other licensed paediatric vaccines of the National Immunization Program (STIKO) in Germany. This is documented by numerous studies on concomitant use. There is neither a clinically relevant reduction of the immunogenicity of PCV7 or other vaccines nor a significant increase in the rate of adverse events when PCV7 is used together with currently marketed hexavalent combination vaccines or other vaccines used in the second year of life. The concomitant use with MenC vaccines is not recommended due to missing data in the second year of life.

Notwithstanding the current 3 + 1 scheme with 3 primary vaccinations in the first year of life followed by one booster dose in the second year of life, PCV7 is used in some European countries in a different (2 + 1) scheme (Belgium, Denmark, Italy, Norway, UK, and Switzerland). Data on the immunogenicity of this 2 + 1 scheme is not conclusive and effectiveness data collected in the mentioned countries is still pending.

In patients with the clinical diagnose of pneumonia an efficacy of 11.4 % was documented in 1,309 patients. If the patients received a chest x-ray the efficacy increased to 13.8 % and in the case of a chest x-ray that is typical for pneumococcal pneumonia the efficacy was 33 %. In a more recent study from the Nationwide Inpatient Sample, which is the largest inpatient database available in the US, data was analyzed with an interrupted time-series analysis that used pneumonia (all causes and pneumococcal) admission rates as the main outcomes. Monthly admission rates estimated for the years after the introduction of PCV7 vaccination (2001 to 2004) were compared with expected rates calculated from pre-PCV7 years (1997 to 1999). At the end of 2004, all-cause pneumonia admission rates had declined by 39 % (95 % CI 22 - 52) for children younger than two years, who were the target population of the vaccination program. A Finnish study enrolled 1,662 infants in a randomized, double-blind efficacy trial of PCV7. At the age of two, four, six, and twelve months the children received either the vaccine under study or a hepatitis B vaccine which served as control. The bacteriologic diagnosis was based on a culture of middle-ear fluid obtained by myringotomy. The vaccine reduced the number of episodes of acute otitis media from any cause by 6 %, culture-confirmed pneumococcal episodes by 34 %, and the number of episodes due to the serotypes contained in the vaccine by 57 %, whereas the number of episodes due to all other serotypes increased by 33 %. In the US acute otitis media was listed among the vaccine indications, whereas in Europe the EMEA added this indication in the year 2007. Data on recurrent otitis, that is available in the literature, is not conclusive.

For the health economic assessment of PCV7 the indirect effects (herd immunity) of vaccination programs require special attention. After the introduction of PCV7 into the National Immunization Program of the US an unexpected and significant reduction in the incidence of IPD in non-vaccinated age groups could be documented. A study of the CDC (Centers for Disease Control and Prevention) showed that for persons aged >5 years, vaccine serotype disease decreased 62 % from 1998/1999 to 2003, with the largest absolute rate reduction occurring among those aged >65 years (absolute rate difference: 21.7 cases per every 100,000 [decline from 33.6 in 1998/1999 to 11.9 in 2003]).

Discussion

For all serotypes included in the PCV7 a good immunogenicity was documented. The correlate for protection according to the World Health Organisation is 0.35 µg / ml, determined one month after vaccination. The existing data on efficacy is convincing. Effectiveness data from the US, collected after the introduction of PCV7 in the National Immunization Program and additional local studies document the success of the program in the US. PCV7 led to a significant reduction in IPD (sepsis and meningitis). Moreover, a significant reduction in non-invasive disease could be documented including a reduction in the carriage rate of pneumococci in asymptomatic subjects. In addition, several studies document the

favourable immunogenicity of PCV7 in immunocompromized patients but for this group of patients further studies are still warranted. Even though the literature on the ability of PCV7 to induce mucosal immunity is not conclusive, the significant indirect effect of the vaccine may be sufficient.

The replacement phenomenon demands further detailed observation. The broad usage of the vaccine led to a significant selective pressure for the pneumococcus. The conditions for pneumococci of vaccine serotypes worsen in vaccinated populations, whereas non-vaccine serotypes receive a selective advantage and are able to increase in incidence. In the US this replacement phenomenon was mainly observed in the serotype 19A. In particular, an increasing incidence of these infections was reported from Alaska in 2007. However, as most of the predominant 19A clones currently spreading in the USA are antibiotic-resistant and often multiply resistant, the high level of antibiotic consumption in the US may contribute significantly to this selection of pneumococcal strains. From Europe, there are currently no reports on replacement available, since most of the generalized pneumococcal vaccination programs have just started in the years 2006/2007. Moreover it is questionable, if the observations from the US may be applicable to Europe as well. Nevertheless, the occurrence of the replacement phenomenon in IPD in the US emphasises the need for continuous surveillance of IPD in Germany after the introduction of PCV7 into the National Immunization Program.

Economic Assessment

Methods

For the identification of all health economic evaluations on PCV7 a systematic literature research in electronic databases was conducted. The assessment of the selected publications is done using structured abstracts, which help to examine the transferability to the German context.

In a second step a cost-effectiveness analysis of a general 3+1 vaccination program in Germany is been conducted from the perspective of the German social health insurance and from a societal perspective. For this purpose a markov model is constructed, in which a hypothetical vaccinated German cohort (base year 2005) via a steady state approach is compared to an unvaccinated cohort over 99 cycles, with each cycle representing one year.

Results from the literature review

The systematic literature research produced 457 references. 18 were added by manual literature search. Among them 22 complete health economic evaluations from thirteen different countries could be identified. The vaccination schedule is predominantly in all studies been chosen as 3+1 due to the primary clinical studies. Five studies use a 2 + 1 vaccination schedule, with effectiveness results being comparable to the 3+1 vaccination schedule. All studies comprise of a decision-analytic model. The models themselves however, differ in the time horizons applied and in the duration of the immune protection. All hypothetical target cohorts differ from the study populations of the two primary studies, and only some authors had access to primary epidemiological data sources about incidences of pneumococcal diseases, case fatality rates, rate of sequelae and pneumococcal serotype structure. Although the incorporated efficacy data of all publications was derived from the two primary studies, results varied substantially. In papers published before the mid of 2003 herd immunity could not be considered due to lack of evidence. All publications examined herd immunity effects in a sensitivity analysis. All authors used a static instead of a dynamic model, so that the transmission of pneumococcus and carriage could not be modelled. Regarding the epidemiology and the methodology the modelling of the herd immunity effect is done very differently.

With few exceptions the health states are differentiated following the localization of the infection, but in most papers not with regard to different disease severity levels. In some publications the incidences are mixed with utilisation data. Furthermore, the variation of utilisation data is not subject to any sensitivity analysis in these publications. Ten articles chose a cost-utility-analysis. The assumption of respective QALY (quality adjusted life years) or DALY (disability adjusted life years) values are literature-based. In one study an own elicitation of preference based health related quality of life utility values was undertaken. All relevant direct medical costs, except for the cost of treatment of sequelae, are considered. Cost estimates were conducted either through an expert panel and/or an analysis of secondary data (e.g. billing-, health insurance- and hospital-data). The respective authors combined data on prices and costs per unit with assumptions or sum estimates. Indirect costs are considered in eleven publications in the form of loss of working time by parents due to the illness of the child using the friction cost approach. Six articles measure indirect costs with the human capital approach in form of productivity losses due to premature deaths. Adverse vaccination effects are included in only a few publications. Discounting of future costs (with rates of 3 % to 6 %) is performed and outcomes like gained life years or QALYs (with rates of 0 % to 6 %) were chosen by nearly all authors.

All publications confirm that with an introduction of PCV7 morbidity may be decreased. The incremental cost-effectiveness ratios are close to or exceed common societal willingness-to-pay thresholds. But the consideration of herd immunity moves the cost-effectiveness-ratio close forward to a cost neutrality. The immune protection of individuals leads to an average compensation of the vaccination costs by 25.2 %. Including herd immunity this value increases by an additional 47.3 %. Four studies analyzed the cost-effectiveness of different catch-up strategies, but the results are not conclusive.

The following three cross-national limitations occur to a certain extent in all reviewed modelling studies: a) exclusion of other pneumococcal related diseases (e.g. arthritis, sinusitis, endocarditis, and peritonitis), b) serotype replacement, and c) antibiotic resistance.

An intermediate result at this point is that by assessing existing literature no final conclusions about the cost-effectiveness of PCV7 for the German can be drawn. Therefore a revision of the German evaluation, taking into account the herd immunity effect, the structure of the German population, German serotype distribution, vaccine uptake, and QALY is necessary.

Results from the health economic evaluation

A general 3+1 vaccination recommendation and an uptake of 70 % in Germany could avoid approximately 232,000 pneumococcal related infections, 35 paediatric deaths, 1,834 premature adult deaths, and 83 cases of paediatric sequelae annually. Incorporation of the vaccination program would cost the German health insurances around 133 million Euro annually, which would be refinanced to 116 % in form of savings of medical costs by avoiding pneumococcal related diseases as described. Altogether for each Euro spend on vaccination 0.77 Euro are saved as a result from avoidable treatments in children and savings of 0.39 Euro as a result from herd immunity effects in adults. Each life year gained costs -640 Euro and each QALY -567 Euro. Looking at these outcomes the vaccination strategy is dominant. In addition, each Euro spent in PCV7 refinances itself with further 1.13 Euro in avoided productivity losses measured with the human capital approach.

Discussion

The sensitivity analysis shows that a) the aging German population, b) a 2 + 1 vaccination recommendation, and c) a disproportionately high decline in hospitalization due to pneumonias will have a favourable effect on the cost-effectiveness of PCV7. The herd immunity derived from the Active Bacterial

Core Surveillance leads to a similar cost-effectiveness as the evidence from the Northern California Kaiser Permanente study. The costs of inpatient care for pneumonias have a strong effect on the cost-effectiveness. The break-even of the G-DRG lump sum for pneumonia is 1.42 times higher than the Germany-wide average cost of the G-DRG in 2005.

Overall medical and economic conclusions

Based on the documented and discussed data, the health economic assessment and the sensitivity analyses the authors recommend the continuation of the general recommendation of PCV7 according to the 3 + 1 schedule as an obligatory service within the German Statutory Health Insurance for all children under 2 years of age. The favourable outcome of the health economic assessment of PCV7 is highly dependent on a high rate of children receiving the booster dose in their second year of life. The significant role of these booster doses in establishing herd immunity and the indirect effects of the vaccine need to be emphasized. Furthermore it should be underlined that within the vaccine program monitoring for vaccine uptake should be established. The continuous surveillance by the Pneumococcal Surveillance Network including the Panel for rare paediatric diseases in Germany, by the laboratory panel of the Robert Koch Institute and by the surveillance of the German National Reference Center for Streptococci must be mandatory. In the future special attention is required on serotype replacement. As demonstrated a reduction in the number of vaccine shots results in a positive effect on the cost-effectiveness ratio of PCV7. However, before a change is made, a critical analysis of effectiveness data from countries applying the 2 + 1 scheme, and here preferably from the UK is required. Of particular importance for such an analysis would be country specific differences (e.g. vaccine compliance).

The full version is only available in German

under

http://gripsdb.dimdi.de/de/hta/hta_berichte/hta202_bericht_de.pdf