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VACCINES AND IMMUNIZATION
Implementing and questioning cost-effectiveness analysis

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by

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Rokotteilla on suuri merkitys sairastapausten vähentämisessä maailmanlaajuisesti. Myös rokottamattomat yksilöt hyötyvät rokotteista pysymällä terveempinä ja elämällä pidempään. Oikein kohdennettuina rokotusohjelmat parantavat elämänlaatua, mutta toisaalta ne vievät resursseja muilta terveysinterventioilta. Vaihtoehtoiskustannusta ei voida jättää huomiotta, vaikkakin investointi rokotusohjelmiin on suhteellisen pientä verrattuna terveydenhuollon kokonaismenoihin.

Kustannus-vaikuttavuusanalyysi (KVA) on taloudellisen arvioinnin menetelmä, jota käytetään terveydenhuollossa haettaessa tehokkainta tapaa käyttää voimavaroja, myös verrattaessa rokottamisen ja rokottamatta jättämisen vaihtoehtoja keskenään. Päätöksentekijät käyttävät näitä analyysejä kansallisen päätöksenteon tukena, ja siksi onkin äärimmäisen tärkeää, että päätösten taustalla on asianmukainen aineisto.

Tutkimuksen tavoitteena on arvioida ja kyseenalaistaa kustannus-vaikuttavuusanalyysejä rokotteiden tapauksessa käyttäen esimerkkinä pneumokokkikonjugaattirokotetta (PCV7). Pyrin selvittämään, kuinka rokotteiden todellista arvoa tulisi mitata kustannus-vaikuttavuusanalyysien avulla. Tutkimusongelman ratkaisu perustuu viimeaikaiseen kirjallisuuteen taloudellisesta arvioinnista sekä numeeriseen esimerkkiin KVA:n menetelmien soveltamisesta Markov-mallin avulla.

Julkaistujen pneumokokkikonjugaattirokotteen (PCV7) kustannus-vaikuttavuusanalyysien tekotavat vaihtelevat suuresti, mikä vaikeuttaa rokottamisen todellisen kokonaisarvon määrittämistä. Jotta rokottamisen kustannuksia ja seurauksia pystyttäisiin määrittämään luotettavasti, kustannus-vaikuttavuusanalyysien kriittiset valinnat koskevat seuraavia asioita: 1) oikea mallityyppi ja –rakenne, 2) asianmukainen taloudellisen arvioinnin menetelmä ja näkökulma, 3) luotettava kliininen data, 4) epävarmuuden huomiointi ja 5) asianmukaiset vaikuttavuusmittarit.

Parhaiten soveltuvan KVA-metodin valinta on tärkeä vaihe rokotusohjelmien arvioimisessa. Keskeistä on ottaa huomioon myös maakohtaiset erot, jotta kansalliset päättäjät saisivat luotettavaa tutkimustietoa päätöksentekonsa tueksi.

ABSTRACT

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Vaccines have a major impact on the reduction of diseases worldwide. In addition to the increased amount of infections prevented, vaccinated and also susceptible individuals receive health gains by living longer and staying healthy longer. When target groups for vaccination are correctly selected, the quality of life enhances due to the implementation of vaccination programmes.

On the other hand, investing in immunization is costly, and it takes resources away from other health interventions. The opportunity cost needs to be taken in consideration, even though the investment in immunization is relatively small compared to the overall amount of health care expenditures. The cost-effectiveness analyses (CEAs) are conducted in order to assess the alternatives with and without vaccination. The decision-makers use the analyses as a support in the national decision-making, thus it is extremely important that the choices are made on the right evidence.

The objective of our study is to assess and question the CEA of vaccination with a case example of pneumococcal conjugate vaccine (PCV7). That is, we are interested in finding out, how to assess the true value of vaccines. In order to have the answer to the posed study problem, we rely on recent literature of economic evaluations and implement the cost-effectiveness analysis with a numerical example based on a Markov model.

The published cost-effectiveness analyses of PCV7 lack of consistency and it is difficult to have an overall view of the value of vaccination in these circumstances. To assess reliably the costs and consequences of vaccination the following matters should be accounted: 1) correct model type and structure, 2) appropriate economic evaluation method and perspective, 3) reliable clinical data, 4) accounting for uncertainty and 5) adequate cost-effectiveness measures.

As a consequence of appropriate CEA methods the true value of vaccines is more assessable. Still, there will remain country-specific differences, which will complicate comparison of the CEAs. Nevertheless, the decision-maker will have more adequate information to support the policy-making.

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1. INTRODUCTION

Vaccines are one of the most important health interventions which have the potential to support and increase population's health status. The medical strategy of vaccination is to prevent infectious diseases from arising on individual and community level and even among populations. All countries face the decision, which vaccines should be included in the national vaccination programmes. Vaccines' appliance to the national immunization programs should be done systematically, and it should be an unbiased and comprehensive process as well as be based on real evidence, which is applied rationally and following the schedule. From the decision-makers' point of view this means taking into consideration vaccine characteristics and presentation, vaccines' supply, administration schedule, immune response, immunogenicity and failure, efficacy issues and vaccine safety. (Piso & Wild 2009, 5924.) Especially because of the increased pressure on the health care budgets, there is an ongoing tendency to do more efficiency based economic evaluations to aide this decision-making. In addition, the economic evaluations are necessary to allocate the resources there, where they are most valued.

Economic evaluation means comparing costs and consequences usually having at least two different alternatives to choose from. In the case of vaccination related economic evaluation there are mainly two alternatives to choose from: vaccination and no vaccination. Choosing appropriate economic evaluation technique is based on the purpose and viewpoint of performed analysis. Full economic evaluation techniques in health care include cost-effectiveness (CEA), cost-utility (CUA) and cost-benefit (CBA) analysis. All costs are measured in monetary terms, but the techniques differ in their effectiveness measures of consequences. (Drummond et al. 2005, 2; 9-17.) CEA and CUA are most often used in the economic evaluations of vaccination.

The objective of our study is to depict and question the methods of evaluating the alternatives without and with vaccination. Drummond et al. (2007) posed a question: Do we fully understand the economic value of vaccines? We want to continue the topic by assessing especially the methodological challenges when undertaking the economic evaluations of vaccines. Our aim is to answer to the question, how to assess the true value of vaccines with a

case example of pneumococcal conjugate vaccine (PCV7). First, we appraise CEA in the light of theory relying on the existing vaccine related literature and recent cost-effectiveness analyses. Second, we implement the cost-effectiveness analysis in practice to depict adequate cost-effectiveness measures.

The following matters, with the focus on specific features of vaccines, should be accounted, when assessing the true value of vaccines: 1) correct model type and structure 2) appropriate economic evaluation method and perspective 3) reliable clinical data, 4) accounting for uncertainty and 5) adequate cost-effectiveness measures. The CEA of vaccination should account relevant costs and consequences as from the health care provider as also from the societal perspective. In order to depict the peculiarities of vaccination, dynamic models should be used, if possible. The used data should be reliable, and adjusted for uncertainty when necessary. The appropriate cost-effectiveness measures should be used to access the effectiveness of vaccines in short and long term.

The thesis is divided in four main sections. In the second section after the introduction, we embrace the matter of vaccines and immunization. We depict the medical strategy and consequences of immunization on a patient-level as also introduce the elements of decision analytic modelling used in the cost-effectiveness analyses of vaccination programmes. Also, we have a look at the government's role of financing vaccine expenditures as also provide relevant information of the cost-effectiveness analyses of vaccination from the societal perspective. We extend the modelling issue to a case study of pneumococcal conjugate vaccine (PCV7).

In the third section we move from the theory to the practice. We provide an overview of PCV7 in Finland, France and Italy. We assess the recent economic evaluations of PCV7 in Finland and Italy from a critical point of view and depict the key principles which should be taken into consideration when performing vaccine related economic evaluations. Also, we implement the cost-effectiveness analysis in practice by introducing an example of a Markov model. Based on the used model we depict appropriate cost-effectiveness measures, which should be used in the cost-effectiveness analyses of vaccines. In the fourth section we look at the most important findings of our study. Also, we make conclusions, whether we have found the answer to the posed question. Especially, we review the results of the study and the study constraints.

2. VACCINES AND IMMUNIZATION

"With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction…" (Plotkin et al. 2008).

The message of Plotkin et al. (2008) encompasses simultaneously the value of vaccines to the patients on individual level as well as from societal perspective comprising communities and populations. Immunization is one of the most powerful and in addition cost-effective health interventions (WHO et al. 2009). The world's first vaccination was performed in 1796 by a country doctor Edward Jenner from England. He showed by his experiments that cowpox protects from the infection of smallpox. Almost one century after the experiments of Jenner first bacterial vaccine was invented. French chemist and microbiologist Louis Pasteur invented the rabies vaccine in 1885. Since then, the word 'vaccine' started to be related to all inoculating agents, not only to cowpox. (Stern & Markel 2005, 611-613.) Nevertheless, the origin of the word is still connected to the experiments of Jenner, since the root of the word is 'vaca' that means cow in Latin. Nowadays, according to the Centers for Disease Control and Prevention (CDC 2006a, 54) vaccine is defined as a "suspension of live (usually attenuated) or inactivated microorganisms (e.g., bacteria or viruses) or fractions thereof administered to induce immunity and prevent infectious disease or its sequelae."

2.1 The value of vaccines

2.1.1 Medical strategy and impact on patients

The medical strategy of vaccination is to prevent infectious diseases from arising on individual and community level and even among populations. It is thus an opposite strategy to the wait-and-treat situation. Before introducing the vaccines to the markets and more widely to communities and populations through national vaccination programmes the vaccines are properly tested in all industrialized countries as well in most developing countries in order to meet the quality and safety standards of vaccination (WHO et al. 2009, 31-33).

Immunization has notable consequences on the population level in reducing incidence rates of different diseases. We depicted some of them stated by WHO et al. (2009, 44). Dying from

measles reduced from 2000 to 2007 by 74% worldwide; also the sickness and disability factors connected to measles were reduced. In 1988 polio paralyzed children worldwide and about 350,000 cases were detected every year. Due to the vaccination, by the end of June 2009 the number of reported cases was under 500. The cases of rubella and deaths caused by neonatal tetanus were also tremendously reduced due to the implied vaccination. According to WHO et al. (2009, 8-10) providing the vaccines according to the standard recommendations of WHO prevents nowadays more than 2.5 million deaths in children under five years old every year.

In 2005-2007, over 100 million children a year were reached by immunization, which was more than ever before. Nevertheless, in 2007, 24 millions that is 20% of children born every year didn't receive the complete immunization according to the schedule and vaccines reserved to them. The lack of immunization in addition to the other major matters of concern such as malnutrition is an increased death risk. There are approximately nine million children under five years of age dying every year of which developing countries account over 90%. Introducing vaccines against pneumococcal diseases and rotavirus would probably have a rapid impact on reducing child deaths, since pneumococcal diseases and rotavirus diarrhea are the leading causes of vaccine preventable deaths accounting together for 1.3 million deaths among children less than five years old. (WHO et al. 2009.)

On a whole, vaccination has substantial health benefit to the alternative without vaccination. The most common vaccine undesirable adverse effects don't cause serious hazard to health. Possible adverse events following immunization (AEFI) are minor and temporary, such as mild fever or sore arm. The risk related to more serious adverse events is very small, accounting between one per thousands or one per millions of doses to have more serious vaccine related adverse effects. For example in the case of measles, without vaccination, the risk in having pneumonia is 1/20, encephalitis 1/2,000, and death 1/5,000 in industrialized countries and 1/5 in developing countries. With vaccination the risk in having encephalitis or severe allergic reaction due to vaccination is 1/1,000,000. (WHO 2009.)

2.1.2 Decision analytic modelling

The selection of a decision analytic model in making the economic evaluation for infectious diseases is outstandingly important since the choice can potentially have a major impact on

the results (Briggs et al. 2008, 65). The main two categories used to predict the impact of vaccination are static and dynamic. Static models assume that the rate according to which the susceptible individuals become infected is a fixed parameter and stays constant on continuous basis. In dynamic models the rate of infection ($\lambda(t)$) depend on the number of infected individuals in the population at a given point of time $I(t)$ and the effective contact rate β between susceptible and infectious individuals. In order to count $\lambda(t)$, $I(t)$ and β are multiplied by each other. That is:

$$\lambda = \text{fixed (static model)}$$
$$\lambda(t)=\beta I(t) \text{ (dynamic model)}$$

In other words, the static models assume that the disease in question isn't infectious. In addition, static models are incapable to depict the effect of herd immunity according to which the increased proportion of vaccinated in a population reduces the incidence of infection among non-vaccinated. Herd protection occurs when sufficient amount of population is vaccinated. Because of the herd immunity effect, the rate of infectious individuals in the population will be declining and consequentially the rate at which susceptible will be infected will decline as well. The static models are incapable to depict this process, whereas dynamic models can. In addition, static models are usually applied to a single aging cohort, which might not be enough to depict all the effects of the intervention in question. Thus, the dynamic models, which are run for many years, are more realistic presentations of the consequences of vaccination, although majority of the vaccine oriented economic evaluations continue using static models. (Brisson & Edmunds 2003.)

Brisson & Edmunds (2003) name 3 distinct phases after the introduction of an infant mass vaccination based on a case example of varicella vaccination programme. Similar findings have been depicted with the presentation of measles and mumps vaccinations as well. The first phase is called "honeymoon period" when shortly after presenting the vaccine a number of susceptible individuals fall in preventing the endemic transmission of the disease. In the second phase of "post-honeymoon epidemic" the number of individuals who have not been vaccinated rises through births and the number of infections rises as well. The third phase is the post-vaccination endemic equilibrium which results in a new and lower equilibrium level of the disease compared to the case incidence before vaccination. The presented phases can be

depicted with the help of dynamic models, but not with the static models where the effect of herd immunity are underestimated and thus, might lead to decision-making based on biased results. The dynamic models should be used especially when applying a vaccination programme with high coverage rates and when there is evidence that vaccination prevents the disease in population.

Nevertheless the static models have the limitations described above they are widely used in economic evaluations when handling specific types of decision problems. A typical example is a Markov model. The idea of the model is that a patient can occupy different 'states' related to the patient's health situation at a given point of time and for a specific time periods called cycles, where the length depends on the evaluated intervention and the disease in question. According to the modelling principle patient can move between the Markov states based on a set of transition probabilities. (Drummond et al. 2005, 295.) Especially the last mentioned feature of the Markov models allows assessing the alternatives under question from more complex and more realistic viewpoint compared to the decision tree technique, where consequences of interventions are depicted as discrete pathways and reversibility between health states isn't taken into consideration. Sonnenberg et al. (1993) state that Markov models are useful when a decision problem is involving continuous risk over time, when the timing of events is important and also when there is a possibility that important events may happen more than once. Based on the factors mentioned by Sonnerberg et al. (1993) Markov models can be well applied to the vaccine-related decision problems where we aim at valuing the consequences of different vaccination strategies.

2.2 Investing in immunization

All countries face the decision what vaccines should be included in the national vaccination programmes (NVP). The process of including a new vaccine into NVP should be a systematical and comprehensive process, although the decision-making principals vary among countries. For example in Finland, the recommendations of a new vaccine should be based on public health benefit, vaccine safety on the individual as also on the population level and cost-effectiveness (Nohynek 2008, 277-278).

According to the standard WHO's recommendations the following eight vaccines should be provided: tuberculosis, diphtheria, tetanus (including neonatal tetanus through immunization

of mothers), pertussis, polio, measles, hepatitis B, and Hib. Providing these vaccines prevents more than 2.5 million child deaths every year as mentioned in section 2.1. In order to save additional child lives, a consideration must be given also to six additional vaccines: rubella, meningococcal disease, pneumococcal disease, rotavirus diarrhoea, and (in certain areas) Japanese encephalitis and yellow fever. (WHO et al. 2009, 8-10;79.) Including the new vaccines would enhance the level of immunity but on the other hand will also increase the costs of immunization and set more pressure on health care budgets.

2.2.1 Health care budgets

In Finland, health care expenditures have been constantly rising from 1995 to 2007 being €14.7 billions in 2007. Health expenditures as a share of GDP during the same time period have varied from 7.2% to 8.5% of GDP being 8.2% in 2007. (THL 2009.) In France, 11 % of GDP was allocated to the health care expenditures in 2007. The share was the second highest of the OCDE countries after the share of USA. In Italy, the health expenditures as share of GDP were 0.2 % below the OCDE average being 8.7% as a share of GDP in 2007. (OCDE 2009.)

In 2006, the majority of WHO member states had a special national budget line for national vaccination purchasing as a part of their health care budgets. The special budget line increases government's awareness and transparency of used resources. It is also a signal of a long-term political commitment for allocating funds to a priority health service such immunization. In general, the contribution of governmental vaccination financing is substantially more in higher income countries (86% of vaccine expenditures) than in low income countries (38% of vaccine expenditures). (Lydon et al. 2008.) The phenomena is not surprising since the spending on health in developing countries is only 12 % of total health spending although 85% of the population lives there (WHO et al. 2009, 6).

In Finnish national budget proposition there is a special moment 33.70.20 for the supply of vaccines (*Rokotteiden hankinta*). National vaccination programmes, supply of other rare vaccines and most vaccine related supply and delivery costs are financed from the amount admitted to this moment. (Ministry of Finance 2010.) The admitted amount has been almost constantly rising from 2000 to 2010 (Figure 1).

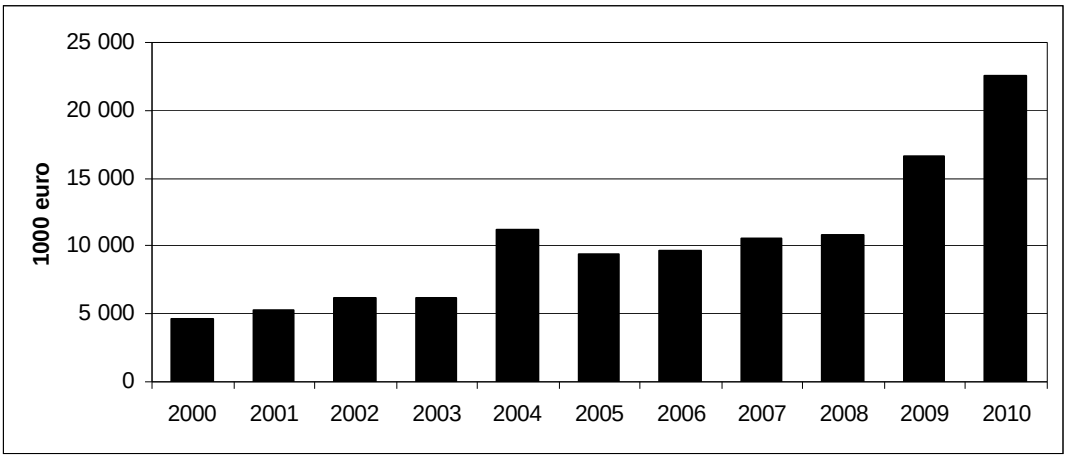

Figure 1. Vaccines' supply in Finland according to the budget propositions from 2000 to 2010 (Ministry of Finance 2010).

Especially, the amount for the purchase of vaccines increased in 2010 due to the reserved funds (€6.0 million) to start the vaccination in September 2010 with a new vaccine, pneumococcal conjugate vaccine, which will be then included in the national vaccination programme to the universal extent. The currently excepted budget proposition 2010 for the purchase of vaccines is €22.54 million, which is 0.2% of the overall amount (€11.3 billion), reserved for the Ministry of Social Affairs and Health. (Ministry of Finance 2010.)

2.2.2 CEA

Due to the increased health care expenditures together with increasing pressure on health care budgets the economic evaluations are more and more needed in order to allocate the resources to the most cost-effective health care interventions. In fact, the resources should be allocated there, where they are most valued, and the opportunity cost should be taken into consideration (Cairns 1995). The message of Cairns (1995) is that even though preventive health interventions would create health benefits to some individuals, the overall greater good of the intervention on the population level requires evidence in order to be justified on economic grounds. The matter has high relevance in the case of vaccination especially because of the emergence of new and costly vaccines. The overall value of vaccines, the costs and the consequences, should be thoroughly assessed in order to help decision-makers to choose, whether the new vaccine should be applied to the national vaccination programme, and if so,

to what extent. That is, also the target group of vaccination should be carefully selected when pursuing the greater utility to the vaccinated individuals as to the society.

Cost-effectiveness analysis (CEA) is one of the full economic evaluation techniques used in health care in order to track down the costs and the consequences of compared health care interventions. The other techniques are cost-utility analysis (CUA), which is a special case of CEA, and cost-benefit (CBA) analysis. All costs presented by the techniques are measured in monetary units, but the techniques differ in their effectiveness measures of consequences. In CEA consequences are measured using natural units of effects, such as years of life gained. Measurement unit in CUA is utility related, often quality-adjusted life year (QALY). In CBA also consequences are measured in monetary terms. (Drummond et al. 2005, 2; 9-17; Sintonen 2006, 91-93.) The mentioned full economic evaluation techniques are all applied in vaccine oriented evaluations, although CBAs are quite rare because of the challenge of measuring health improvements in monetary units (Drummond et al. 2007, 5947).

Vaccination programmes create costs and have consequences also outside the health care provider perspective, thus the cost-effectiveness analyses should be performed from the societal perspective. In this section we provide relevant, but not always assessed information of the costs and consequences related to the alternatives without and with vaccination, which should be included especially in the economic evaluations of vaccination programmes.

Productivity costs should be included in the vaccine related cost-effectiveness analyses which are made from the societal perspective. The term of productivity costs has replaced the term of indirect costs. The productivity costs are associated with lost or impaired ability to work or to engage in leisure activities due to morbidity and mortality connected to ill-health. (Sculpher 2001, 94.) The vaccination related productivity gain is one of the governments' incentives to support financially the investment process of immunization. Consequently, the cost-effectiveness analyses made from the societal perspective, should consider productivity gains, but also productivity losses due to the time taken to have the vaccination (Drummond et al. 2007, 5946).

The government has an incentive to support national vaccination programmes also because of the positive externality of vaccines we have already mentioned in Section 2.1.2: herd immunity. That is, the vaccination reduces the incidence of the infectious disease among

vaccinated individuals, but also creates indirect protection to the unvaccinated susceptible individuals. Hence, the herd effects are similar to the characteristics of public goods. Although, herd protection occurs only when sufficient amount of population is vaccinated. In order to support to reach the optimal level of vaccine coverage the national vaccination programmes are usually fully or partly funded by the governments. (Brisson & Edmunds 2003, 76.)

Routine infant vaccination programmes cause the shift in age at infection: the average age of infection rises because of the cohort and herd immunity effect. After an infant vaccination programme is introduced, the number of incidence of infectious disease in children should decrease while the proportion of adult cases rises, because the adults are not vaccinated. The effect will disappear when all cohorts are vaccinated, but until then, the effect can have an enormous impact on the overall costs and consequences of vaccination. The cohort effect can be depicted with the help of static models. Nevertheless, the dynamic models are needed to encompass the full effect of the age shift at infection. Due to the herd immunity effect the susceptible individuals tend to be older when they get the infection. Hence, the number of adult cases will rise compared to the level of the case incidence before vaccination, which can possibly lead to costly treatments, especially if the severity of the disease increases alongside with the age. This is why; even herd immunity isn't always a good thing from the societal perspective. Nevertheless, the impact of herd immunity on the incidence of adult cases and mortality depends highly on the coverage rate of vaccination. If the coverage rate of vaccination isn't sufficient in order to get the positive effects of herd immunity, the vaccination might even increase the mortality compared to the pre-vaccination level. (Brisson & Edmunds 2003.) All in all, we can declare that herd immunity has both, positive and negative impacts because of the shift of age at infection. The issue stays still rather controversial and should be carefully inspected as a part of cost-effectiveness analyses in order to define an optimal coverage rate of vaccination.

In the vaccine related literature the impact of herd immunity is more often seen as positive adverse effect of vaccination. In addition, there is evidence of a negative adverse effect of vaccination called serotype replacement. Serotype replacement occurs when, due to applied vaccination campaign, one or more vaccine strains decline in prevalence while one or more non-vaccine strains rise in prevalence (Thomasey & Martcheva 2008, 255-256). The vaccine protects the vaccinated individuals only from the strains included in vaccines, and this is why

it is very important to investigate what kind of impacts introducing a vaccine has on the strains not included in the vaccine. Martcheva et al. (2008, 7-8) point out that while vaccine coverage level increases the vaccine-included strains do decline, but the non-vaccine strains can infect the vaccinated individuals. Because the effect of serotype replacement has high value in determining whether some particular vaccine should be included in the national vaccination programme, the decision-maker should be provided with the adequate information.

2.3 Case study of pneumococcal conjugate vaccine (PCV7)

2.3.1 Reducing the burden of pneumococcal disease

Diseases caused by *Streptococcus pneumoniae* (S. pneumoniae or pneumococcus) are recognized as a major public health problem worldwide. Serious diseases caused by the infection of pneumococci include pneumonia, meningitis and febrile bacteraemia. Less serious and more common diseases are otitis media, sinusitis and bronchitis. (WHO 2007, 94.) According to Isaacman et al. (2010) *Streptococcus pneumoniae* is a major source of mortality and morbidity all over the world. The authors of the article specify one part of the diseases caused by *Streptococcus pneumoniae* as invasive pneumococcal diseases (IPD) which include meningitis, bacteremia and pneumonia with bacteremia and/or empyema. According to Beutels et al. (2007, 1362) all IPD in general include i.e. pneumococcal meningitis, bacteraemia, sepsis and peritonitis. Fletcher et al. (2006) name as predisposing factors to be infected by IPD e.g. genetic factors and chronic illnesses, HIV-infected children, age (children <2 years old and elderly >65), socioeconomic factors and thus ethnicity and geographical location and also attendance in day care centers. Fletcher et al. (2006) also point out that majority of children infected by IPD don't belong to any recognized risk groups. The laboratory diagnosis of the infections caused by *Streptococcus pneumoniae* is not always possible due to the prior use of antibiotic treatment, the improper handling and transport of specimens or inappropriate detection methods (WHO 2007, 97).

According to WHO (2007, 94) 1.6 million die every year from pneumococcal diseases, of which 0.7-1 million are children under five year old living mostly in developing countries. In developed countries children less than 2 year old and elderly people carry the major part of the disease burden. Pneumococcal diseases are the leading cause of vaccine preventable

deaths among less than 5 year old children (CDC 2006b, 512). The matter of reducing the disease burden of pneumococcal diseases has high relevancy especially with the focus on developing countries.

Pneumococcal conjugate and non-conjugate vaccines are designed to cover the serotypes which most frequently cause severe pneumococcal infections in order to reduce the burden of pneumococcal disease. The 23-valent polysaccharide vaccine is designed mainly for older children and adults who belong to the risk-groups of having pneumococcal disease (WHO 2007, 94). We took as a case example the pneumococcal conjugate vaccine which is recommended for children less than five year old. The 7-valent pneumococcal polysaccharide-protein conjugated vaccine (PCV7; Prevenar/Prevnar, Wyeth Lederle Vaccines) was first licensed in the USA in 2000. The vaccine is recommended to all 2-23 months old children and also to children belonging to the risk-groups at 24-59 months of age. Healthy children receive 3 vaccine doses at 2, 4 and 6 months of age and also 1 booster dose at 12-15 months. (De Stefano et al. 2008, 373.) Also vaccination schedule according to the 2+1 schedule is approved, according to which, children receive the vaccine doses at 3 and 5 months of age and a booster dose at 11-12 months (Beutels et al. 2006, 9). WHO (2007) states that clinical efficiency is proved also with 2week-4week-6week series. The vaccine was licensed in Europe in 2001, and by January 2009 already 24 of 32 European countries had at least decided to introduce PCV7 in their national childhood vaccination programme, either universal or risk-based implemented according to the vaccination schedules of 3+1 or 2+1 doses (De Carvalho Gomes et al. 2009, 1-2). The PCV7 covers 65-80% of serotypes associated with IPD among young children in western developed countries. Protection against IPD may exceed 90% but protection against acute otitis media is significantly lower. The proven duration of protection against invasive pneumococcal diseases is 2-3 years, although it is expected to last much longer. (WHO 2007, 94-95.) According to Salo et al. (2005, 824) the vaccine protection of PCV7 lasts to current knowledge at least 5 years.

The PCV7 is well tolerated vaccine with a good safety profile, although some adverse events following immunization (AEFI) have been detected. According to the review study of DeStefano et al. (2008) concerning safety of pneumococcal conjugate vaccines, PCV7 caused injection-site reactions as well as fever. Mild reactions were more common than severe reactions; including redness, swelling and fever at different severity rates. The vaccine dose number and age were seen as possible influential factors of increased incidence of mild

reactions, as the case incidence increased with dose numbers and the mild reaction were more common at the age of 12-15 months.

The matter of serotype replacement has now high relevancy within the research field of pneumococcal vaccination. Currently, the most comprehensive pneumococcal vaccine covers 23 serotypes of more than 90 serotypes which are connected to *Streptococcus pneumoniae* (Thomasey & Martcheva 2008, 255). A study review of Martcheva et al. (2008) showed that serotypes currently not included in the licensed vaccine of PCV7 have important pathogenic potential although according to WHO (2007, 101) it is not probable that the replacement disease would increase the overall burden of pneumococcal diseases. Still the phenomenon is an important issue, which should not be left without consideration when performing economic evaluations of the vaccine, since the unwanted effect may reduce the anticipated benefits of introducing the vaccine as a part of national immunization programmes.

In the report of Centers for Disease Control and Prevention (CDC 2005) the herd immunity and the phenomenon of serotype replacement were compared as a part of examining the consequences of including PCV7 in the national immunization programme of USA. What is surprising, the amount of IPD cases prevented in 2003 due to only herd immunity effect was more than twice as much as the IPD cases prevented directly. Although, the number of infections due to non-vaccine serotypes increased as well, but on much lower distinct compared to the IPD cases averted due to the implementation of PCV7 in the national vaccination programme. The main age groups which gained the greatest amount of health benefits as a number of IPD cases averted were children <5 years old and elderly ≥65 years old.

WHO (2007) states that the appliance of PCV7 to a national immunization programme is a priority, because of the heavy burden of pneumococcal disease occurring in young children as well because of the safety and efficacy of the vaccine in this age group. WHO considers that pneumococcal vaccine (PCV7) should be included in the national immunization programmes particularly in the countries where mortality among children under 5 years is more 50 per 1000 live births or where over 50 000 children die annually. Also populations with prevalence of increased risk having the disease should be targeted with vaccination.

Although WHO (2007) stands for introducing PCV7 to the national immunization programme, the licensed vaccine doesn't contain serotypes 1 and 5 which are responsible for substantial amount of severe disease caused by pneumococcal infection in developing countries (CDC, 2006b). PCV7 contains only the serotypes 4, 6B, 9 V, 14, 18C, 19F, and 23F. Nevertheless, serotypes 1 and 5 are included in the newly licensed 10- and 13-valent conjugate pneumococcal vaccines (THL 2010b). 10-valent pneumococcal conjugate vaccine contains serotypes of PCV7 plus additional serotypes 1, 5, and 7F; 13-valent pneumococcal conjugate vaccine contains serotypes of PCV7 plus additional serotypes 1, 3, 5, 6A, 7F, and 19A. Changing from the 7-valent to the 10-valent pneumococcal conjugate vaccine would increase the proportion of serotypes covered from 86% to 88% in the USA; from 74% to 84% in Europe; from 67% to 81% in developing countries in Africa and from 43% to 66% in parts of Asia. In addition, changing from the 10-valent to the 13-valent pneumococcal conjugate vaccine would increase the mentioned serotype coverage rates by 4%-7%. (WHO 2007, 97-102.) The 13-valent pneumococcal conjugate vaccine (PCV13) has succeeded the 7-valent pneumococcal conjugate vaccine (PCV7) especially on the basis of immunogenicity studies and PCV13 should be used to vaccinate and complete the PCV7 immunogenicity series when PCV13 is available and licensed to use (CDC 2010a; CDC 2010b).

2.3.2 Static versus dynamic model

When modelling decision problems related to infectious diseases a choice must be made: whether to use a model according to the principles of static or dynamic modelling. The choice can have a major impact on the results. (Section 2.1.2.) Herd effect and the phenomenon of serotype replacement have been often excluded also from the economic evaluations of pneumococcal conjugate vaccines. The majority of models used in the cost-effectiveness analyses are static. Nevertheless, new dynamic models have been developed in order to make the decision modelling more realistic.

We reviewed the model used by Salo et al. (KTL 2008b) in the most recent cost-effectiveness analysis of pneumococcal conjugate vaccine (PCV7) in Finland. The analysis was conducted as a part of the pneumococcal conjugate vaccine expert group report (KTL 2008a), which belonged to the Finnish decision-making process to recommend a new vaccine. Moreover, the objective of the report was to answer to the questions based on the four criteria set by the

national advisory committee for vaccination (KRAR) in order to justify financing of a new vaccine from the national health budget (Nohynek 2008, 277-278).

In the study (KTL 2008b) the applied model was a static cohort model (Figure 2). In the original study modelling was performed using WinBUGS-computer program. The authors considered two following alternatives: 'no vaccination' and 'vaccination'. The actual Markov states were the diseases caused by the pneumococcal infections (meningitis, bacteraemia, pneumonia treated in the special health care (SHC) and pneumonia treated in the health centers (HC) and also otitis media), death states due to a pneumococcal disease and due to other reasons and also health state without infection. Paths from meningitis, bacteraemia, pneumonia (SHC) and otitis media were describing possible complications due to pneumococcal infections. The estimates of the health states varied depending on the fact, whether the individual was vaccinated or not.

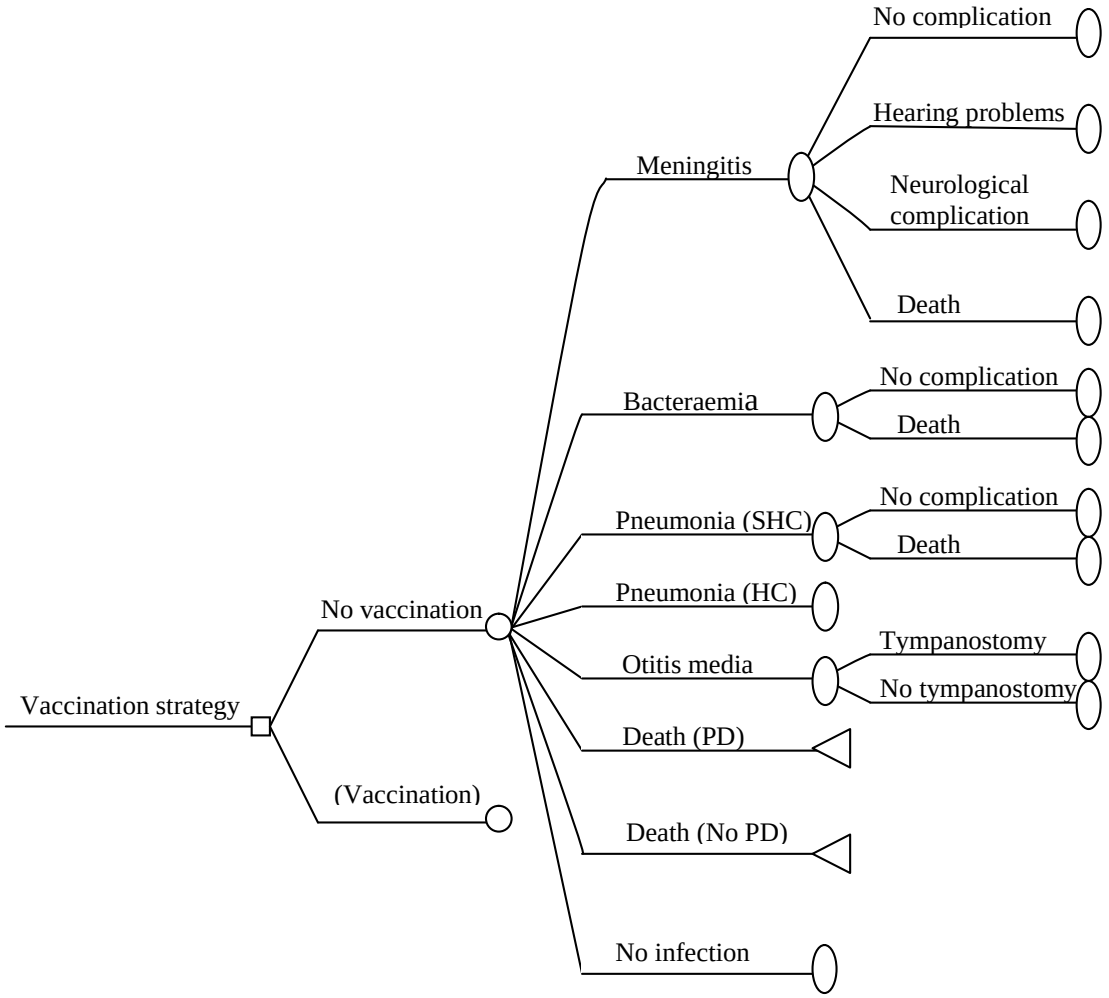

Figure 2. Schematic of the Markov model without and with vaccination (KTL 2008b).

In the study a vaccinated and unvaccinated birth cohort were followed from birth until 100 years of age. Cycle lengths were 1 month (0-6 years old) and 12 months (7-100 years old). Transition probabilities were estimated from the incidence rates for pneumococcal diseases. The burden of pneumococcal disease and related costs were modelled without vaccination and with vaccination. Cost categories included health care (treatment and vaccination) costs, travel costs due to doctor visits and productivity costs. The study was conducted from the health care provider and from the societal perspective. The societal perspective encompassed all mentioned cost categories and only direct health care costs were included in the health care provider perspective. One-way and probabilistic sensitivity analyses were performed in order to capture the uncertainty of key parameters by changing values separately and simultaneously.

In order to perform mentioned analysis study group collected age-structured epidemiologic data of pneumococcal case incidences, treatment methods and mortality rates from several national sources. The results of the case incidences were presented in the form of number of cases per 1/1,000/100,000 persons per year. In order to present the above mentioned cost categories, the study group collected information of costs related to vaccine price, vaccination, treatment, travel and work absence. In order to count the productivity costs study group collected also information of salaries and unemployment rates. The data of productivity costs was adjusted to the patient's age and to the type of pneumococcal infection, since age and infection of a patient is connected to the length of possible parental absence of work due to the child's sickness. All cost parameter were expressed in 2007 price level as mean costs €/episode. Future costs and effects were discounted at 5% discount rate. Economic evaluation was based on vaccination in 2, 4 and 11 months of age. The vaccine coverage was assumed to be 97%. In order to calculate the efficacy of the vaccine the authors relied on the published and unpublished information of the vaccine efficacy against different pneumococcal infections.

The study observed also indirect effects of vaccination programme presented as case averted among individuals ≥5 years of age. Two different scenarios were introduced. According to the scenario A the amount of invasive pneumococcal diseases would decline by 20% as a consequence of introducing the vaccination programme. According to the scenario B implementation of the vaccination programme would also reduce the amount of pneumonia

episodes treated in special care by 4%. By introducing the pneumococcal conjugate vaccine to the national vaccination programme, it would be possible to achieve cost saving in treatment costs of children under 5 years old, but also in treatment costs of older children and adults due to the cases averted in the scenarios A and B (Table 1).

Table 1.Vaccination programme costs to the health care provider and to the society (KTL 2008b, Table 9).

Health care provider perspective*	**<5 y**	**Scenario A**	**Scenario B**
Costs to the health care provider (€)	6 058 877	5 199 259	1 761 905
Costs (€) /QALY gained	76 717	18 820	5 442
Costs (€) /LYG	255 995	23 656	6 695
Societal perspective**	**<5 y**	**Scenario A**	**Scenario B**
Costs to society (€)	5 242 395	4 283 634	549 999
Costs (€) /QALY gained	66 378	15 506	1 699
Costs (€) /LYG	221 497	19 490	2 090

* including health care costs (medical costs+vaccination programme costs)
** including health care, travel+productivity costs

The vaccination programme was valued based on the quality adjusted life years (QALYs). Also incremental analysis of the changes in costs versus changes in QALYs was provided. Cost-effectiveness (costs (€) /QALY gained) was expressed with 95% credibility interval and presented using acceptability curves based on the scenarios A and B.

The greatest incidence of pneumococcal infections is among children under 5 and elderly over 65 years old. According to the estimated results without the vaccination programme there would occur 700 invasive pneumococcal diseases (IPD) and 23,000 pneumonia cases, which were potentially caused by the pneumococcal infection every year. 90 cases of IPD and 125 cases of the pneumonia cases were estimated to lead to a death state. Without the vaccination programme 100 IPD cases, 3,000 pneumonia cases (potentially caused by pneumococcal infection) and 250,000 AOM cases (only part of them is caused by pneumococcal infection) were estimated to occur among children less than 5 year of age. (KTL 2008a, 32.)

By including the pneumococcal conjugate vaccination in the national vaccination programme it was estimated to prevent 3 meningitis cases, 80 bacteraemia cases, 190 pneumonia cases, 9,600 AOM cases, 2,000 surgical ear operations and 1.2 death among under 5 year old children. In scenario A additional 100 pneumococcal infections and 19 death cases were

averted among the population ≥5 year of age. In scenario B the implementation of the vaccination programme would result as 800 pneumonia cases and 5 pneumonia related deaths averted.

The static cohort models don't take into account the herd effect because the rate of infection in the static models is fixed (Section 2.1.2). A small amount of dynamic models have been introduced to incorporate the effect as a part of the model also in the case of pneumococcal conjugate vaccination. We present an age-structured dynamic model introduced by Melegaro et al. (2010) in order to make the calculations of cost-effectiveness analyses of pneumococcal conjugate vaccine more realistic. The authors used the model in order to explore the impact of different PCV7 vaccination strategies on invasive pneumococcal diseases (IPD) and on pneumococcal serotypes. The dynamic model presented by the study group takes into account the phenomenon of serotype replacement in addition to the herd immunity effect. The model is based on the structure of Susceptible-Infected-Susceptible (SIS). The chosen structure of the model is appropriate because there is a possibility to acquire the pneumococcal disease more than once during life time. In the model, it is assumed that all infants in a cohort will get their vaccination simultaneously according to the vaccination schedule. After being vaccinated with PCV7, the individuals move to the vaccine protected group.

The authors state that the techniques can be used in order to assess the introduction of vaccination programmes in developing counties, but also in order to provide the basis for cost-effectiveness analyses. The transmission dynamic model was programmed with programme "Berkeley Madonna", and MS Excel was used, when programming the pre-vaccination model.

Melegaro et al. (2010) defined as vaccine pneumococcal serotypes (VT) 7 serotypes included in the vaccine (PCV7) and in addition serotype 6A since there is evidence that the PCV7 would reduce the burden of the disease also in the case of this serotype. All other pneumococcal serotypes were considered as non-vaccine serotypes (NVT). The structure of the dynamic model is presented in Figure 3.

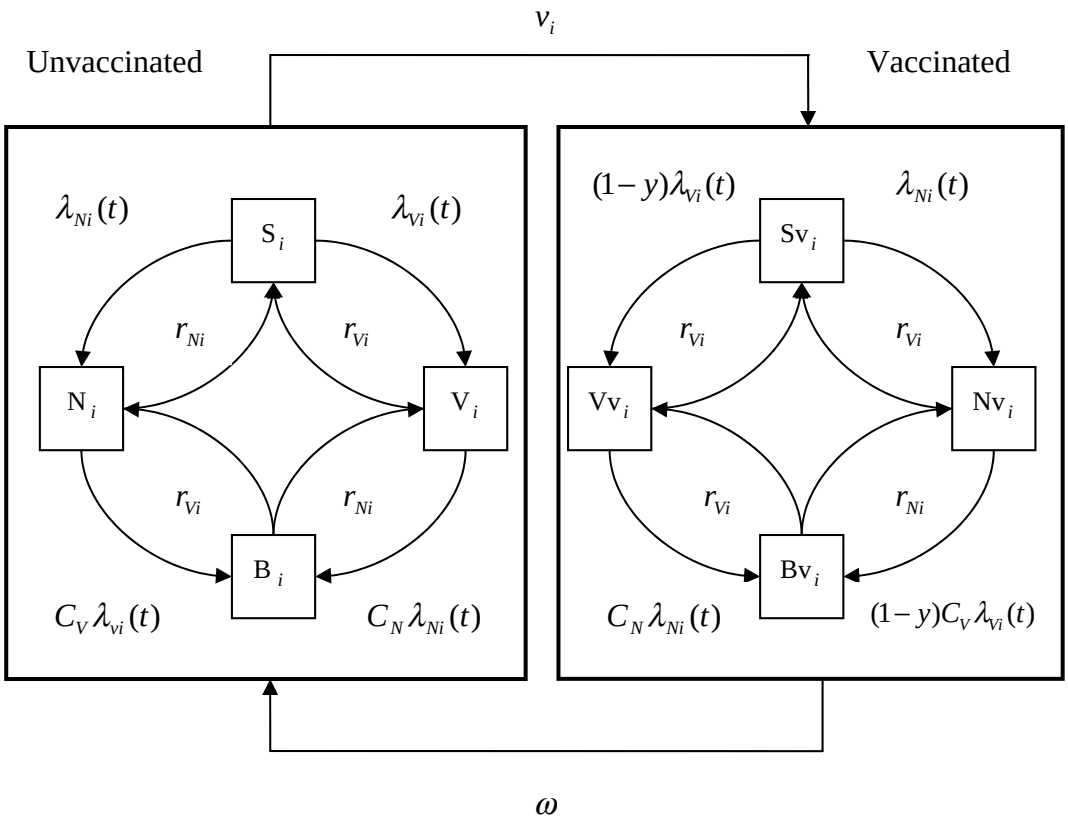

Figure 3. The structure of the dynamic model. Components of the model: S=non-carriers, V=carriers of vaccine pneumococcal serotypes, N=carriers of non-vaccine pneumococcal serotypes and B=carriers of both VT and NVT. Sv, Vv, Nv and Bv are for vaccinated individuals. (Melegaro et al. 2010.)

The unvaccinated individuals become infected at two different age- and time-specific force of infection, (λ_{Vi}) and (λ_{Ni}), depending, whether the type of caught infection is vaccine (VT/V) or non-vaccine type (NVT/N) pneumococci, respectively, as follows:

$$\lambda_{Vi}(t) = \sum_j \beta_{V,ij} \cdot \left(V_j(t) + Vv_j(t) + B_j(t) + Bv_j(t)\right)$$

$$\lambda_{Ni}(t) = \sum_j \beta_{N,ij} \cdot \left(N_j(t) + Nv_j(t) + B_j(t) + Bv_j(t)\right)$$

That is, the forces of infection varied as a function of non-vaccinated and vaccinated carriers (v) of serotypes not included in the vaccine (NVT), included in the vaccine (V) and as a

combination of N and V pneumococcal serotypes defined as B. The forces of infection varied also depending on the rate of effective contacts β_{ij} between age classes *i* and *j*, as follows:

$$\beta_{ij} = \varepsilon\beta_{ij}^{a} + (1-\varepsilon)\beta_{ij}^{p}$$

The equation parameter ε $(0 \le \varepsilon \le 1)$ was used to describe the contact patterns within and between age groups. When ε =0, contact pattern was fully proportionate, and when ε =1, the contact pattern was assumed to be fully assortative. Overall contact pattern determines the nature and effects of herd immunity connected to PCV7. The mixing between individuals was estimated to be more assortative than proportionate, what could not be derived based on a static model.

The age-specific proportions of VT and NVT pneumococcal infections, which led to developing IPD were called *Case: Carrier* ratios. The ratios depended on an infection serotype (V or NVT) and on the carrier's age. In the model, it is assumed that individuals, who have caught a vaccine type serotype pneumococci can become co-infected with the non-vaccine type serotype pneumococci. The infection rate in question is $C_N \lambda_{Ni}$, where C_N provided the basis, in order value how much VT carriage protects from being infected by NVT. Similarly, individuals with non-vaccine type serotype pneumococci can become co-infected with vaccine type serotype pneumococci at the infection rate $C_V \lambda_{Vi}$, where C_V, based on the first definition, was the estimate of valuing how much NVT carriage protects against acquisition of VT. Individuals can recover and move back to susceptible state S (V→S or N→S) or to single type of carriage (B→V or B→N) at an age-specific recovery rate r_i, which is age-depended and same for N, V and B.

The model with the option of vaccination differs from the alternative without vaccination as follows. The vaccinated individuals might get the VT infection depending on the degree of protection (*γi);* the higher the protection, the smaller the risk of having vaccine serotype pneumococci. The individuals who will get the VT infection despite the vaccination are considered as infectious as the ones without vaccination. In addition, the rate of acquiring the disease again and moving from protected state to unprotected depends on the average duration of protection δ. The waning rate *w* (=1/δ), according to which individuals can move to same

compartment as unvaccinated, is constant across all ages. The degree and duration of vaccine protection were estimated using pre- and post-vaccination data.

The detailed presentation of the model was described also with the help of ordinary differential equations. The equations were derived in the case of two possible alternatives, without vaccination and with vaccination, as follows,

Unvaccinated individuals:

$$\frac{dS_i(t)}{dt} = r_{\mathrm{Vi}} \cdot \mathrm{V_i}(t) + r_{Ni} \cdot \mathrm{N_i}(t) - S_i(t) \cdot \left(\lambda_{\mathrm{Vi}}(t) + \lambda_{Ni}(t)\right) - \pi_i(t) \cdot \mathrm{S_i}(t) + \omega \cdot \mathrm{S_{Vi}}(t)$$

$$\frac{dV_i(t)}{dt} = \mathrm{S_i}(t) \cdot \lambda_{\mathrm{Vi}}(t) - c_N \cdot \lambda_{\mathrm{Ni}}(t) \cdot \mathrm{V_i}(t) - r_{\mathrm{Vi}} \cdot \mathrm{V_i}(t) + r_{Ni} \cdot \mathrm{B_i}(t) - \pi_i(t) \cdot \mathrm{V_i}(t) + \omega \cdot \mathrm{V_{Vi}}(t)$$

$$\frac{dN_i(t)}{dt} = \mathrm{S_i}(t) \cdot \lambda_{\mathrm{Ni}}(t) - c_V \cdot \lambda_{\mathrm{Vi}}(t) \cdot \mathrm{V_i}(t) - r_{\mathrm{Ni}} \cdot \mathrm{V_i}(t) + r_{Vi} \cdot \mathrm{B_i}(t) - \pi_i(t) \cdot \mathrm{N_i}(t) + \omega \cdot \mathrm{N_{Vi}}(t)$$

$$\frac{dB_i(t)}{dt} = c_N \cdot \lambda_{\mathrm{Ni}}(t) \cdot \mathrm{V_i}(t) + c_V \cdot \lambda_{\mathrm{Vi}}(t) \cdot \mathrm{N_i}(t) - \mathrm{B_i}(t) \cdot \left(r_{Ni} + r_{Vi}\right) - \pi_i(t) \cdot \mathrm{B_i}(t) + \omega \cdot B_{Vi}(t)$$

Vaccinated individuals:

$$\frac{dSv_i(t)}{dt} = r_{\mathrm{Vi}} \cdot \mathrm{V_{V\,i}}(t) + r_{Ni} \cdot \mathrm{N_{V\,i}}(t) - S_{V\,i}(t) \cdot \left((1-\gamma) \cdot \lambda_{\mathrm{Vi}}(t) + \lambda_{\mathrm{Ni}}(t)\right) + \pi_i(t) \cdot \mathrm{S_i}(t) - \omega \cdot \mathrm{S_{Vi}}(t)$$

$$\frac{dV_{V\,i}(t)}{dt} = \mathrm{Sv_i}(t) \cdot (1-\gamma) \cdot \lambda_{\mathrm{Vi}}(t) - c_N \cdot \lambda_{\mathrm{Ni}}(t) \cdot \mathrm{V_{V\,i}}(t) - r_{\mathrm{Vi}} \cdot \mathrm{Vv_i}(t) + r_{Ni} \cdot \mathrm{Bv_i}(t) + \pi_i(t) \cdot \mathrm{V_i}(t) - \omega \cdot \mathrm{V_{Vi}}(t)$$

$$\frac{dNv_i(t)}{dt} = \mathrm{Sv_i}(t) \cdot \lambda_{\mathrm{Ni}}(t) - c_V \cdot \lambda_{\mathrm{Vi}}(t) \cdot (1-\gamma) \cdot \mathrm{Nv_i} - r_{\mathrm{Ni}} \cdot \mathrm{Nv_i}(t) + r_{Vi} \cdot \mathrm{Bv_i}(t) + \pi_i(t) \cdot \mathrm{N_i}(t) - \omega \cdot \mathrm{N_{Vi}}(t)$$

$$\frac{dBv_i(t)}{dt} = c_N \cdot \lambda_{\mathrm{Ni}}(t) \cdot \mathrm{Vv_i}(t) + c_V \cdot \lambda_{\mathrm{Vi}}(t) \cdot (1-\gamma) \cdot \mathrm{Nv_i}(t) - \mathrm{Bv_i}(t) \cdot \left(r_{Ni} + r_{Vi}\right) + \pi_i(t) \cdot \mathrm{B_i}(t) - \omega \cdot B_{Vi}(t)$$

In the equations i refers to a specific age group, v_i is for vaccine coverage in an age group i and $\pi_i(t)$ refers to the vaccination program in cohort i at certain time t. Within the limitation that the authors didn't provide more information of the parameter relationships in the equations (except the signification of parameters) we don't go to the details of the equations.

3. CRITICAL ASSESSMENT OF COST-EFFECTIVENESS ANALYSES

3.1 PCV7 in Finland, France and Italy

The pneumococcal conjugate vaccine (PCV7) was included in the Finnish national vaccination programme (NVP) as risk-based in January 2009 (De Carvalho Gomes et al. 2009, 2). This year, in September 2010, the pneumococcal conjugate vaccine will be included in the national vaccination programme to the universal extent. The funds for starting the vaccination are included in the national budget 2010 (Section 2.2.1). Thus, the matter of the cost-effectiveness of the pneumococcal conjugate vaccine has high relevancy.

In Italy, PCV7 has been included in the infant vaccination schedule since 2005. The extent of the vaccination programme depends on the region where the vaccination policy is implemented. The vaccination schedule in Italy includes 2 vaccinations and 1 booster dose (2+1 schedule), and is thereby similar to the vaccination implementation schedule in Finland.

In France, the 7-valent pneumococcal conjugate vaccine (PCV7) has been included in the national immunization programme to the universal extent using 3+1 immunization schedule from June 2006. The schedule was changed to 2+1 schedule in October 2008. (De Carvalho Gomes et al. 2009, 2.). From 2003 to 2006 the PCV7 was recommended only for children under 2 years old, who are at risk of having the disease due to medical or living conditions. That is, before extending the vaccination programme to the universal level, 79-89 % children were entitled to have the vaccine under these conditions. From 2001/2002 to 2006 the case incidence of pneumococcal meningitis and bacteraemia declined by 20-25 %, but the case incidence of the mentioned diseases showed increase by 6-11% in older children and adults. The changes in the case incidence are more obvious when we observe the incidence by serotypes. In children less than 2 years case incidence of vaccine serotypes declined by 64-81% (bacteraemia from 14.8 to 5.3 cases per 100,000 and meningitis from 5.6 to 1.0 case per 100,000 individuals) and the case incidence of non-vaccine serotypes increased by 74-104% (bacteraemia from 7.0 to 12.2 cases per 100,000 and meningitis from 2.4 to 4.9 cases per 100,000 individuals). (Lepoutre et al. 2008, 1-2.) All in all, the phenomenon of serotype

replacement is highly relevant issue also in the epidemiology of pneumococcal infections in France.

Due to the scarcity of data related to the investigational 10- and 13-valent pneumococcal conjugate vaccines we appraised the recently published economic evaluations of 7-valent pneumococcal conjugate vaccine (PCV7) in Finland and Italy. At present, the vaccine schedule of PCV7 in Finland and Italy is the same, although the amount of doses in the base case analysis varied in the economic evaluations. France was left without consideration because there were no recently published full economic evaluations of PCV7.

We assessed the most recent cost-effectiveness analysis of PCV7 in Finland in Section 2.3.2. The cost-effectiveness analysis by Salo et al. (KTL 2008b) updated the most recent published economic evaluation of PCV7 by Salo et al. (2005). In this section, we appraise the published economic evaluation, and also compare some key figures of both analyses as a part of comparison of the reviewed published economic evaluations in Section 3.2.

The study of Salo et al. (2005) aimed at evaluating cost-effectiveness of pneumococcal conjugate vaccine (PCV7) in children less than 5 years old. Especially, the study was carried out in order to answer to the question, whether the health benefits achieved with the universal PCV7 were enough to justify the costs related to the programme. In the study the authors assumed a vaccination schedule consisting of 4 doses of PCV7, and a Markov cohort model was chosen to compare the alternatives without and with vaccination. Only direct effects of the vaccine were included in the calculations, although the analysis was conducted from health care provider and societal perspective. As a result of vaccinating a birth cohort of 57,500 healthy infants, it would potentially prevent around 60 cases of invasive pneumococcal diseases (IPD), over 1,400 cases of pneumococcal pneumonia, around 15,000 episodes of acute otitis media (AOM), over 3,000 otological surgery procedures and 0.9 deaths among children less than 5 years old every year. The incremental cost of the vaccination programme was €3.6 million from the societal perspective and €5.7 million from the health care provider perspective. Cost per life year gained was €210,792. The authors stated that the price of the vaccine should be 50% or 70% of the assumed price of €50.5 perdose from the health care provider and from societal perspective, respectively. (Salo et al. 2005, 821-832.)

In Italy, the economic evaluations of pneumococcal conjugate vaccine (PCV) by Giorgi-Rossi et al. (2009) and Marchetti & Colombo (2005) are the most recent published cost-effectiveness analyses of PCV7. Giorgi et al. (2009) conducted the cost-effectiveness study to assess the consequences of introducing the pneumococcal conjugate vaccine (PCV7) to the immunization plan of Lazio region. The objective was to examine the health outcomes and costs of hypothetically vaccinated and unvaccinated children from the public health service perspective. The study group chose a vaccination schedule consisting of 3 doses, where price of each dose was assumed to be 40.18 euro. As a method of comparing the alternatives without and with vaccination study group used a decision analytic model conducted in MS Excel 2003. As a result of vaccinating and based on the results of budget impact analysis, after 10 years, 5 cases of meningitis, 20 invasive pneumococcal diseases (IPD), 933 cases of pneumonia, 406 pneumonia-related hospitalizations and 3,160 otitis cases would be averted. The annual costs of vaccinating (including health care costs) were estimated to decrease over time from 5.1 million euro (after one year) to €3.5 million per year (after 10 years). The incremental cost-effectiveness per averted DALY was estimated to be €18,055 with 0% discount rate and €51,727 with 3.5% discount rate. The cost per year of life gained was estimated to be €38,729 (0% discount rate) and €111,990 (3.5 % discount rate).

Marchetti & Colombo (2005) undertook the cost-effectiveness study in order to compare the alternatives with and without universal pneumococcal vaccination. The aim of the study was to estimate the health and economic outcomes of vaccinating a birth cohort of 538,138 children with 3 doses of PCV7 in Italy. A Markov model was created in order to access the aim of the study. The authors state that universal vaccination would avert 769 invasive pneumococcal infections, 18 deaths and improve the life expectancy of the birth cohort by 1,323 life years. The universal vaccination would cost 38,286€/LYS from the NHS (National Health Service) perspective and 26,449€/LYS from the societal perspective. The authors stated that PCV7 should be implemented in Italy depending on the local epidemiology of pneumococcal disease and based on the local budgets.

3.2 Appraising the published articles in terms of well-executed economic evaluation

Performing the economic evaluation of vaccination programmes has different sources of uncertainty. According to Brisson & Edmunds (2006) the sources are the choices and

assumptions made regarding 1) the model type and structure, 2) economic methods and 3) the used parameter values. We take as an example a case of pneumococcal conjugate vaccine and appraise the articles (Section 3.1) especially focusing on the methodology checklist of economic evaluation by Drummond et al. (2005, 27-53) throughout the study reviews.

1. Was a well-defined question posed in answerable form?

Well-defined question indicates as well as relevant alternatives as a viewpoint of economic evaluation. Possible viewpoints for an analyse may be those of society, when all costs and consequences to all parties are taken in consideration, a specific provider or providing institution, a patient or groups of patients and a third-party payer, who can be private or public. Also, the viewpoint may be specified already by the decision-maker, who is requesting the study. (Drummond et al. 2005, 27-30.) Indicating the viewpoint of performed economic evaluation is important, because costs and consequences may have, and probably do have, a different meaning depending on the viewpoint.

In the study of Salo et al. (2005) the answer was well defined. The authors of Salo et al. (2005) explain the context of the study, which is set by the National Advisory Committee for Vaccination (KRAR), who created a 4-step approach in order to help decision-makers to decide whether to introduce a new vaccine into the national vaccination programme (NVP). The aim of the study was to assess whether the health benefits with universal PCV7 vaccination justify the costs of the programme in relation to its cost. The analysis was made from the health care provider and the societal viewpoint.

In the studies of Giorgi-Rossi et al. (2009) and Marchetti & Colombo (2005) the question wasn't posed in answerable form. In the economic analysis of Giorgi-Rossi et al. (2009) the context is well-defined, since the study was conducted to aid the Lazio Region's Health Authority to decide whether to implement the vaccine completely free for all in the region or for risk groups only. The main goal of the study was to examine hypothetical health outcomes and costs of introducing the pneumococcal vaccine for the infants less than 10 years of age in the Lazio region by analyzing the budget impact and cost effectiveness. The study has a clear goal of proceeding in the study, but the question should be better defined. Examining costs and benefits separately is a process, and cannot be seen as an aim in obtaining the answer to the problem, whether universal pneumococcal vaccination is worth implementing for the

infants in the Lazio region as universal basis or for risk groups only. The economic evaluation was made concentrating on the payer's perspective.

Marchetti & Colombo (2005) chose a broader view of assessing the cost-effectiveness of universal pneumococcal vaccination compared to the study by Giorgi-Rossi et al. (2009). Marchetti & Colombo took into consideration whole Italy, while Giorgi-Rossi et al. (2009) concentrated on one Italian region (Lazio). The aim of the study was to estimate the health and economic outcomes of universal infant vaccination with PCV7. The authors state that they undertook the study to compare the alternatives with and without vaccination using cost-effectiveness and decision analysis approaches. The study was performed from the government payer's and the societal perspective. The question is not well-specified because of the reasons mentioned above in the context of Giorgi-Rossi et al. (2009) study.

2. Was a comprehensive description of the competing alternatives given?
Clear statements and objectives of each specific alternative should be given in order to being able to select which analysis, CEA, CUA or CBA, should be used in the economic evaluation in question. Justifications of costs and consequences are thus required. We must be able to answer, who does what to whom, where and how often, and consequentially, what are the results. (Drummond et al. 2005, 30-31.)

In the study of Salo et al. (2005) the description of the competing alternatives is given by applying a Markov model where two separate alternatives are presented: vaccination and no vaccination. The study group followed a hypothetical vaccinated and un-vaccinated birth cohort of 57,574 from birth until 5 years of age. The model consisted of 6 discrete health states on the basis of Streptococcus pneumoniae infection: meningitis, bacteremia, pneumonia, otitis media (AOM), no pneumococcal infection and death. Also, pneumococcal-associated disease outcomes were taken in consideration. The number of vaccination doses was 4 doses, which was justified in the study by manufacturer's recommendation. When the study of Salo et al. (2005) was conducted PCV7 wasn't included at all to the national vaccination programme of Finland. In January 2009 it was introduced as a part of NVP to the risk-based extent. This is one important alternative in addition to the alternatives of universal vaccination and no vaccination, but the alternative is excluded from the analysis without explaining the reason to this decision.

The alternative of vaccinating only the risk groups is excluded also from the cost-effectiveness analysis of Giorgi-Rossi et al. (2009), although the health authorities will confront a task to decide whether to vaccinate all infants in the region of Lazio or risk groups only. The method used to assess the alternatives without and with vaccination was a decision analytic model, but the study group hasn't specified more exactly, is it a decision tree or a Markov model (Giorgi-Rossi et al. 2009, 227). Also, the study group doesn't specify the amount of infants they followed. The chosen health states were invasive pneumococcal disease (IPD), pneumonia, acute otisis media (AOM) and no pneumococcal disease (no PNC disease) in the case of PCV7. Vaccination presentation was based on three doses of conjugated pneumococcal vaccine (PCV7), which was explained by the committees' recommendations.

Marchetti & Colombo stated that the required data in order to compare the alternatives of high-risk vaccination and universal vaccination in Italy isn't available at the moment. They compared only the alternatives with and without (universal) vaccination. In order to asses the costs and consequences of vaccination Marchetti & Colombo (2005) constructed a Markov model using the programme of TreeAge Pro. The chosen health states were pneumonia, otitis, no illness, natural death, and the invasive pneumococcal diseases (IPD) were divided in three separate health states: meningitis, bacteraemia and other IPD. Other complications than death state weren't accounted. When looking only at the decision tree in the study (Marchetti & Colombo 2005, Fig. 1), one might be mistaken in the interpretation because the observed health states are in the cases of <1 year old and >14 years old. Although, in the text it is mentioned the infections were observed only until 14 years of age after which only life expectancy was modeled. Marchetti & Colombo (2005) chose the vaccination schedule of three doses based on the same reasons as in the article of Giorgi-Rossi et al. (2009).

3. Was the effectiveness of programmes or services established?

In economic evaluation studies it is not enough only to assume the effectiveness of the programmes but also the validation of such result must be given. Randomized clinical trials are often used in taking estimates of treatment effects when using decision analytic modelling. Effectiveness might be also attained simultaneously with the economic evaluation, if a clinical study is carried out at the same time. (Drummond et al. 2005, 31.)

In the Salo et al. (2005, Table I) study vaccine efficacy estimates were established and validated by mentioning used trials. Efficacy estimates for invasive disease (89.1%), clinical pneumonia with a positive radiograph (17.7%) and against otological surgery procedures (20.3 %) were obtained in intention-to-treat (ITT) analyses, but for AOM (6%) study group used the per protocol (PP) efficacy estimate of FinOM Vaccine trial. The user of the economic analysis should be aware that the study group's own rationale was affecting the decision-making when choosing the efficacy measures from different available options. For example in the updated economic evaluation (KTL 2008b) different estimates were used for pneumonia treated in special care (8.9%) and for pneumonia treated in health centers (4.3%). Also, AOM estimate was counted based on the notion that averted AOM cases wouldn't reduce doctor visits due to upper respiratory tract infections in the same amount as prevented AOM cases. The efficacy estimate connected to the doctor visits due to upper respiratory tract infections was 4 %.

In the articles of Giorgi-Rossi et al. (2009) and Marchetti & Colombo (2005, Table I) vaccine efficacy and related ranges as well as were mentioned. In the article of Giorgi-Rossi et al. (2009, Table I) PCV7 vaccine efficacy measures in the studies were for invasive pneumococcal diseases IPD (88.0%), pneumonia of any aetiology (22.0%) and acute otitis media AOM (7.9%). The efficacy measures of Marchetti & Colombo (2005, Table I) were for IPD (89.1%), otitis media (6.4%) and pneumonia (17.7%). In the study of Giorgi-Rossi et al. (2009) the authors' choices of efficacy parameters lack of validation since they aren't justified without looking further in the literature. The efficacy estimates of the study of Salo et al. (2005) and Marchetti & Colombo (2005) were partly the same.

4. Were all the important and relevant costs and consequences for each alternative identified?
In a cost-effectiveness research study it is crucial to indicate all relevant costs and consequences related to the competing alternatives. According to Drummond et al. (2005, 19; 32) four categories of costs are costs to 1) health sector, 2) family / patient sector, 3) other sectors and also 4) productivity losses. These categories are straightforwardly connected to the consequences, since we are interested in depicting the savings and gains in these cost categories. According to Drummond et al. (2007, 5946) the economic evaluation of vaccination, which is conducted from the societal perspective would take into account costs due to the time being vaccinated as a part of productivity costs.

In the economic evaluation of Salo et al. (2005) the authors specified clearly the costs they thought would be relevant to include in the analysis. The direct costs included health care (medical and vaccination) costs and travel costs. The medical costs were the treatment costs of pneumococcal diseases. The vaccination costs consisted of the costs of vaccine purchase, vaccine administration and adverse effects. The adverse effects were assumed to be so mild that they wouldn't cause any substantial costs. Costs from the societal perspective included in addition to the direct costs also productivity costs, which arose from parental absence of work, premature death due to meningitis and bacteraemia and also hearing defects due to meningitis. The authors didn't account indirect effects in their cost calculations, especially a herd effect as also the effect of serotype replacement were not included in the calculations based on the fact that they were seen as uncertain population effects. Nevertheless, in the updated economic evaluation (KTL 2008b) the indirect effects were considered in two different scenarios A and B (Section 2.3.2).

The authors of the economic analysis of Giorgi-Rossi et al. (2009) took into account only health costs (vaccination and medical costs) with and without PCV7. The vaccination costs included vaccine costs as also administrative costs. The medical costs included treatment costs of pneumococcal diseases. In the study, it would be more appropriate to specify the disease types, and thus also the costs due to 'Other IPD'. Although, the study group mentioned that they didn't have reliable sources of information of IPD incidence because not all IPD were included in the infectious disease notification system in Italy. Based on the example of the study of Salo et al. (2005) it would be appropriate to include also productivity cost in the economic evaluation of Giorgi-Rossi et al. (2009). As a consequence the perspective of the analysis would become societal. Also, it would be appropriate to include the indirect effects in the analysis of the costs and consequences.

Marchetti & Colombo (2005) took into account direct and indirect costs of the pneumococcal diseases. Contrary to the articles of Salo et al. (2005) and Giorgi-Rossi et al. (2009) the authors included also costs due to PCV7 side effects, which were calculated in terms of productivity costs, but also as direct costs due to paediatrician visits. Productivity costs were valued as parental absence from work. Marchetti & Colombo (2005) didn't consider positive and negative indirect effects related to the vaccination.

5. Were costs and consequences measured accurately in appropriate physical units?

Reliable analysis cannot be performed without justifying and measuring costs and consequences accordingly in their natural and physical units. Common overhead services and related costs should be taken in consideration as well, although leaving them without consideration is a common failure in economic evaluations. (Drummond et al. 2005, 19; 32.)

According to the economic evaluation of Salo et al. (2005) the cost estimates on the use of health care resources were taken from published studies, national registers and expert panel opinion. The study group (Salo et al. 2005, Table III) presented the estimates with a more particular specification of the cost type (average, unit, total labour cost/h). Also, the administration costs of the vaccine were taken into consideration.

In the cost-effectiveness study of Giorgi-Rossi et al. (2009) it was mentioned the type of vaccination costs (price, delivery, administration) per dose and the treatment costs were specified to be average costs (€) or costs(€) per episode. In the study of Marchetti & Colombo (2005) the treatment costs were measured as costs per episode but also as a cost per patient and the birth cohort of 538,138 infants. Vaccination costs were measured as unit costs, although the authors didn't include administration costs at baseline analysis, because the vaccine was assumed to be co-administered with other vaccinations; as mentioned above, the approach is not correct.

6. Were costs and consequences valued credibly?

Valuing costs is estimating the costs used by the health programme. In order to value the consequences, preference measures, such as EuroQol EQ-5D might be used. Using the preference measures means acquiring a specific preference in numerical form to connect it to a specific health state based on the results of a patient questionnaire or general public. The results can be used to obtain required weights of quality adjusted life years (QALYs). (Drummond et al. 2005, 36-37, 173-175.) In the QALY system morbidity and mortality gains are captured in a single measure that is the gain of better quality of life and the gain of life extension are captured simultaneously. In order to count QALYs we need information about health state durations and descriptions and also related quality weights. Possible health related quality weights differ from 0(death) to 1(full health). The disability adjusted life year (DALY) is conceptually similar to QALYs, where the burden of disease is measured in comparison to an ideal healthy life of score 1.0. (Drummond et al. 2005, 14-15; 173-188.) According to the

World Health Organization (WHO) use of DALYs is the recommended approach to use in generalized cost-effectiveness analysis, although quality-adjusted-life-years (QALYs) are kept as best effectiveness measurement unit in healthcare effectiveness evaluation according to Sintonen (2006, 91-93) and according to NICE (2008, 33) QALY is appropriate measure to express health effects. Some vaccine studies use also as a measure ´cases prevented´, which is not as useful as an effectiveness measure of years of life gained (LYG), but often requires fewer assumptions (Drummond et al. 2007, 5947).

Because the matter of QALY is relative also in the economic evaluation of vaccination programmes we wanted to assess the particularity of QALY counting in the case of vaccination relying on the notions by Drummond et al. (2007, 5955-5956). The authors state that counting QALYs in the analysis of prevention intervention is more appropriate according to the utility-in anticipation concept. According to the standard approach, the utility gain from prevention an illness is the utility which would be otherwise lost when the disease would occur, but in the case of vaccination, the utility gain realises immediately after vaccination (Figure 4).

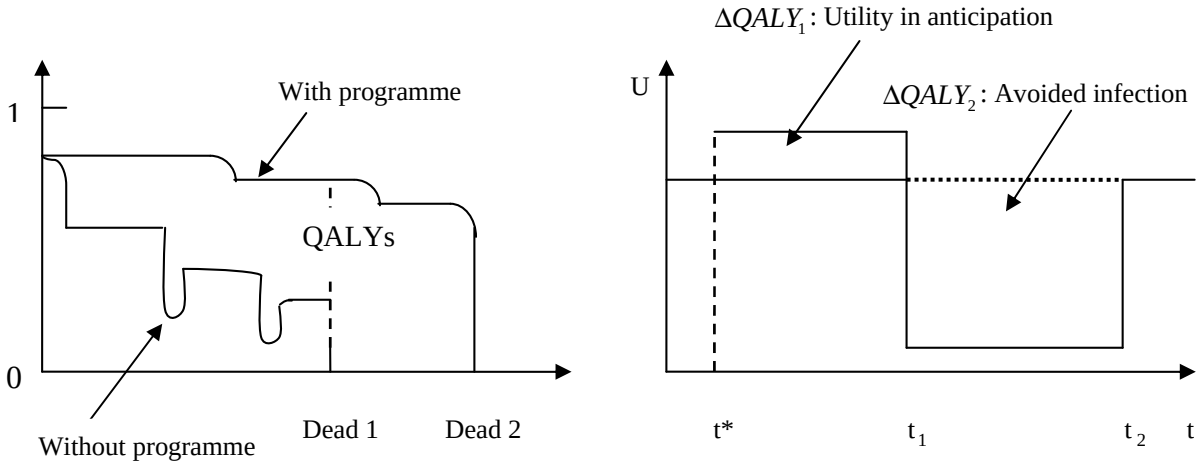

Figure 4. Standard approach of calculating QALYs (on the left) and the utility-in anticipation concept (on the right) (Drummond et al. 2005, 15 ; Drummond et al. 2007, 5956).

According to the utility-in-anticipation approach the total value of prevention is the sum of the utility-in-anticipation and the QALYs saved due to the avoided infection because of vaccination. According Drummond et al. (2007, 5956) under the standard approach QALYs

are undervalued and on the other hand, the cost per QALY –effectiveness ratio is thus overestimated.

In the study of Salo et al. (2005) all costs were updated to the 2004 price level. The sources of costs and cost types were also mentioned (Section 3.2, Question 5). The results of applying the vaccination programme were expressed in terms of the amount of averted cases of pneumococcal infections, annual incremental costs of programme, benefit-cost ratio, costs(€)/LYG and costs(€)/QALY. Due to lack of data some assumptions were made about QALY losses due to pneumococcal diseases (Salo et al. 2005, Table II).

In Giorgi-Rossi et al. (2009) study counting and estimating hospitalization and administrative costs was based both on hospital and different health service related regional databases, which were used as a source in determining related costs which were appropriately identified. Values from the administrative costs were derived from database from the Regional Health Service in the case of influenza immunization program. The results of applying the vaccination programme were expressed in terms of costs (€) averted, averted cases of pneumococcal infections, costs (€)/LYG and costs (€)/DALY (disability adjusted life year).

Although, also in the study of Giorgi-Rossi et al. (2009) it would be more appropriate to use QALYs since sensitivity analysis also is included the analysis, and also would enable better comparison between health care studies and interventions. In the Giorgi-Rossi et al. (2009, 227) article the study group explained the use of DALYs instead of QALYs because of absence of specific data and by avoiding the challenge of determination the used perspective. In addition to DALYs consequences, health benefits, were introduced separately with vaccination and without vaccination and also as the difference of the mentioned.

In the study of Marchetti & Colombo (2005) overall costs were counted based on the disease parameters (IPD, acute otitis media and pneumonia) and fatality rates, which were derived from national hospital database, recent surveillance studies and expert reports. The study group assessed the differences in costs and consequences between the alternatives in terms of cases averted, costs(€)/event averted, costs(€)/LYG, costs(€)/death averted and overall net costs (€/patient, and €/birth cohort. Thus, the study group didn’t use preference measures, although it would have been appropriate to use also utility efficacy measures as a part of expressing the cost-effectiveness results.

7. Were costs and consequences adjusted for different timing?

In economic evaluation, cost-effectiveness result should reflect the present value of costs and benefits over all existing cost and benefits over analyzed period of time. Future costs, as also consequences, should be discounted using appropriate discount rate, which is 3.5% for discounting both costs and health effects according to NICE (2008, 41-42). According to Drummond et al. (2005, 111) in the absence of any official guidance on discounting, discount rate is probably 3-5% for both costs and effects for base case analysis. In the case of preventive interventions not only chosen discount rate but also chosen procedure of discounting is important. Bos et al. (2004) propose also an alternative discounting model to be used when discounting the costs and health benefits of preventive interventions (Section 3.2, Question 8).

In the economic evaluation of Salo et al. (2005) both future cost and benefits were discounted at 3.0% discount rate. In the Giorgi-Rossi et al. (2009, 230) the cost-effectiveness, €/DALY and €/LYG, were expressed in the case of 0 % and 3.5 % discount rate. Health care cost parameters were discounted, but in the budget impact analysis (Giorgi-Rossi et al. 2009, Table 3) the costs were left without discounting and it is unclear whether the results, costs(€)/cases averted are discounted or not. Marchetti & Colombo (2005) discounted cost per event/death averted and cost per life-year saved (LYS) with 3% discount rate. Costs per patient and for the birth cohort weren't discounted.

8. Was an incremental analysis of costs and consequences of alternatives performed?

According to Drummond et al. (2005, 38-39) the additional costs that one intervention imposes over another, compared with the additional effects, benefits or utilities the programme or service deliver, is necessary to examine for a meaningful comparison. Such ratios can be illustrated also graphically. Incremental cost-effectiveness ratio (ICER) is by definition the difference of costs of two different alternatives, in our case programmes with vaccination (Sk) and without vaccination (Sj), divided by the difference of efficacy measures of the same alternatives. The formula is as follows:

$$ICER(Sj \rightarrow Sk) = \frac{Ck - Cj}{Ek - Ej}$$

ICER is expressed in monetary units per an efficacy measure, for example €cost/LYG. (Grolier et al. 2009, 49-50.) We can develop the formula adjusting it to time and by discounting the costs and the efficacy measures (Bos et al. 2004):

$$ICER(Sj \rightarrow Sk) = \frac{\sum_{0}^{\infty}\left[Ck(t) - Cj(t)\right] \bullet (1+r)^{-t}}{\sum_{0}^{\infty}\left[Ek(t) - Ej(t)\right] \bullet (1+r)^{-t}}$$

The presented formula of ICER is the standard approach of methodology of intervention Sk over intervention Sj. As we have pointed out above in the case of preventive intervention the moment of risk reduction is important since it is the time when a vaccinated individual starts gaining utility. Bos et al. (2004) propose the following formula of ICER, which focuses on the moment(s) of risk reduction:

$$ICER(Sj \rightarrow Sk) = \frac{\sum_{0}^{\infty}\left[Ck(t) - Cj(t)\right] \bullet (1+r)^{-t}}{\sum_{0}^{\infty}\left[N \bullet S(t) \bullet R(t) \bullet p \bullet RLE(t)\right] \bullet (1+r)^{-t_i}}$$

Costs are counted in similar way to the standard approach. In order to count health effects the information of population size (N), probability of risk infection (p), initial risk of infection related mortality ($R(t)$), remained life expectancy at the age t of averted death ($RLE(t)$) and probability to survive to age t ($S(t)$) are required. The new parameters are multiplied by each others and can be discounted for the timing between intervention and the occurrence of risk reduction ($-t_i$) with the social rate of time preference r; the risk reduction is the time when an individual would start developing the infectious condition without vaccination.

Graphically ICER can be illustrated as a cost-effectiveness plane with four separate quadrants with different outcomes when comparing interventions of interest S_k to the alternative S_1 (Figure 5). Horizontal axis represents the difference in effects between interventions of

interest S_k (k=2, 3, 4) and the origin depicts the alternative S_1; the vertical axis represents the difference between related costs.

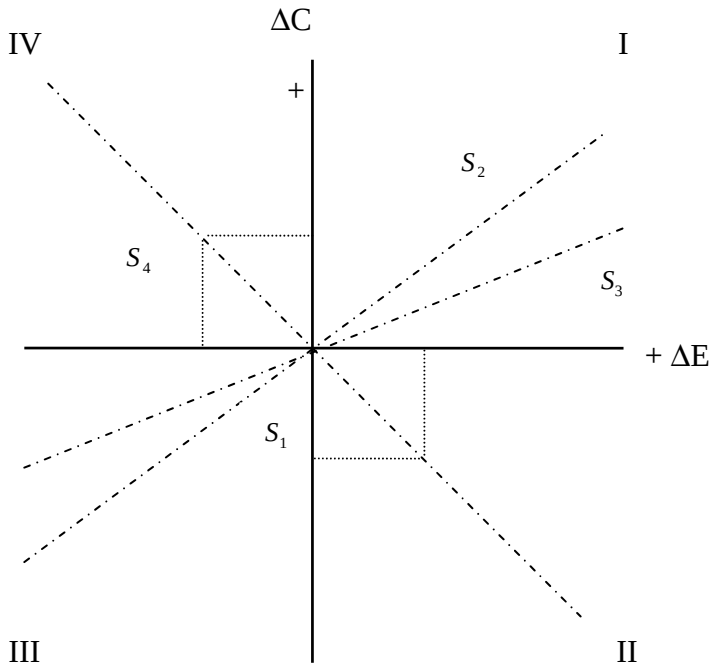

Figure 5. Cost-effectiveness plane (Drummond et al. 2005, 40; Grolier et al. 2009, 55).

If we were supposed to make a rational choice between programmes allocated in quadrates II and IV, we would choose a programme of the second quadrant, since it is more effective and less costly than the others and that way it dominates other possible alternatives. The choice seems evident and it is, when we know the figures of the alternatives. Still, it is important to be aware of the possible problem of negative cost-effectiveness ratios. In Figure 5 situation is illustrated with two squares: both programmes in quadrants II and IV would realize in same ICERs, but the situations obviously do vary from each other. The choice between programmes situated in the other two quadrants, I and III, depend on the maximum cost-effectiveness ratio we are willing to accept. The choice depends, whether we are willing to accept more effective and more costly alternative or less effective and less costly alternative than S_1. (Drummond 2005, 40; 257.) That is, choosing between the alternatives depends on the decision-makers' acceptable 'threshold ratio', which represents the willingness-to-pay (WTP) for a unit of health gain. If the slope of line, that is the ICER, passing from the origin through the coordinates (ΔE, ΔC) is less than the acceptable 'threshold ratio' λ, the alternative

health programme intervention should be adopted. (Briggs 2008, 122-123.) According to NICE (2008, 58) the appropriate threshold value is the opportunity cost of programmes displaced by new more costly technologies. In monetary terms, NICE methods guide to refer to a threshold of 20 000-30 000 pounds (£) per quality-adjusted life year (QALY). According to the average of 0.79628 UK pound sterling per euro exchange rate in 2008 (European Central Bank 2010) the threshold suggested by NICE is approximately 25 100-37 700 euro per QALY gained.

In the economic evaluation of Salo et al. (2005) annual incremental cost of the vaccination programme is provided as well as from the societal (€3.6 million) as also from the health care provider (€5.7 million) perspective. Related benefit-cost ratios are 0.53 from the health care provider perspective and 0.7 from the societal perspective by what the authors refer to the relative part of medical and societal costs. As already mentioned above the main outcome of the cost-effectiveness study of Salo et al. (2005) was cost per life-year-gained (LYG), which was €210,792 from the health care provider perspective and €134,986 from the societal perspective. In addition, the discounted cost per QALY gained is €45,038 from health care provider perspective and €28,841 from the societal perspective.

In the Giorgi-Rossi et al. (2009) incremental analysis of the costs and consequences was provided. The study group observed incremental cost-effectiveness per averted DALY and cost-effectiveness per year life gained. Similar incremental cost-effectiveness ratios are used also in others childhood pneumococcal conjugate vaccination evaluations, although QALYs are much more used than DALYs (Beutels et al. 2007, 1361). In addition, study group estimated cost per case averted. In the study ICER was obtained by dividing net health care costs, that is annual savings (€), by averted DALY's: in the case of 0% discount rate cost-effectiveness was estimated to be €18,055 and in the case of 3.5% 51,727. The cost-effectiveness per LYG was estimated to be € 38,729 (0%) and €38,729 (3.5%). Cost-effectiveness results were based on the outcomes at year 10. In addition to the mentioned the authors also attended the cost per case averted (€855), per IPD (€177,591), per meningitis (€689,472) and per death (€3,907,007), although, as mentioned above it was not reported, whether the costs are discounted or not.

Marchetti & Colombo (2005) provided the incremental cost-effectiveness analysis. From the perspective of health care provider the discounted results were as follows: €671 per event

averted, €1,305,555 per IPD averted, €2,756,891 per death averted, €38,286 per life-year saved (LYS). From the societal perspective the equivalent results were as follows, €463 per event averted, €901,388 per IPD averted, €1,903,225 per death averted and €26,449/LYS.

9. Was allowance made for uncertainty in the estimates of costs and consequences?
In order to assess the possible changes of study values and parameters, economic evaluations often contain sensitivity analyses. In order to value their quality we need to look at, how the parameters are identified, why the parameters were chosen and estimated, and also, was the right kind of sensitivity analysis chosen. (Drummond et al. 2005, 42-43.)

In the economic evaluation of Salo et al. (2005) a one-way sensitivity analyses was performed to assess the uncertainties of the model. The analyses were performed on the vaccine parameters (efficacy, price, duration of protection), the incidence of pneumococcal diseases as also the discount rate was varied in the case of costs and life-years-gained. The results of the sensitivity analysis were presented in a separate table (Salo et al. 2005, Table VI). In the updated economic evaluation (KTL 2008b) in addition to the one-way sensitivity analysis also probabilistic sensitivity analysis was performed in order to find out the effects of simultaneous change of parameters from the health care provider perspective.

In the study of Giorgi-Rossi et al. (2009) one-way sensitivity analysis was performed for the ICER, in this case for the costs per DALY containing the examination of the impact of 0% and 3.5% discount rates. The sensitivity should be expanded in order to have more information of the possible result variations.

Marchetti & Colombo (2005) performed one-way sensitivity analyses by changing parameter values and tracking the changes on the discounted cost per LYS. The following parameters were accounted: discount rate, vaccination costs, the incidence of pneumococcal infections, vaccine efficacy, fatality rate, protection period, costs of pneumococcal diseases. The analysis was performed from the NHS perspective as well as from the societal perspective.

In addition, Marchetti & Colombo (2005) assessed the cost-effectiveness values in Monte Carlo analysis where the authors built the acceptability curves of universal pneumococcal vaccination from the National Health Service (NHS) and the societal perspective as a relationship between the probability of cost-effectiveness and maximum WTP for an

additional LYG. The authors pointed out with the help of acceptability curves that the greater part of simulated cases would remain below €50,000 per LYS, which the authors named as commonly accepted benchmarks for health-care interventions.

10. Did the presentation and discussion of study results include all issues of concern to users? Here the main notions are made on the presentation, interpretation and the possibility of appliance the results in some specific decision-making context (Drummond et al. 2005, 43-44). The decision-maker should be provided with relevant and sufficient information.

The authors of the economic evaluation of Salo et al. (2005) concluded their study by discussion of important issues concerning the performed analysis and the results. They claimed that in order to achieve net savings with universal PCV7 from the health care perspective the price of the vaccine should be 50% and 70% when viewed from the societal perspective compared to the price used in the base case analysis. Also, the limitation of excluding the indirect effects was mentioned. The authors confirmed the results by stating that performing the sensitivity analysis didn't change the main conclusion of the analysis. In order to compare their own results to others, the authors compared their study with 10 others recently published studies.

In the study of Giorgio-Rossi et al. (2009) the authors provided an overview of epidemiological situation in Italy in order to compare the cost savings due to possible implementation of the vaccination programme. The authors pointed out that pneumococcal vaccination program had high vaccination costs, and they don't cover in and outpatient cost savings.

Marchetti & Colombo (2005) state that based on the achieved results the universal infant pneumococcal vaccination with PCV7 is moderately cost-effective from the societal perspective. Still, the regional differences imply that the economic profile of PCV7 is quite favorable in the Italian setting, since the result of the cost per LYS has been recognized to be as low as €10,479 per LYS in the regions of Veneto and Sardinia. According to the authors the vaccine was worth implementing according to the local policies based on the epidemiology of pneumococcal disease and local budgets. This notion was made although, the study of Marchetti & Colombo (2005) had several limitations and the results don't cover all

issues of concern to the users. Especially excluding the herd immunity effect and the phenomenon of serotype replacement biases the results.

Table 2. Comparison of the published cost-effectiveness analyses.

Base case	Salo et al. 2005	Giorgi-Rossi et al. 2009	Marchetti&Colombo 2005
Model type and structure	Static Markov model	Static Decision analytic	Static Markov model
Economic method			
Study type	CEA, CUA, CBA	CEA, CUA	CEA
Perspective	Payer Society	Payer	Payer Society
Used parameters			
Duration of protection (y)	5	10	14
Vaccine effectiveness (%):			
against IPD	89.1	88.0	89.1
against AOM	6.0	7.9	6.4
against pneumonia	17.7	22.0	17.7
Number of vacc. doses	4	3	3
Vaccine cost per dose (€)	50.5	40.18	39.0
Vaccine administration costs (€)	1.6	0.8+6.16	0
Discount rate (%)	3.0	0, 3.5	3
Cost-effectiveness			
Payer's perspective	€ 210,792 per LYG € 45,038 per QALY	€ 38,729 per LYG € 51,727 per DALY	€ 38,286 per LYS
Societal perspective	€ 134,986 per LYG € 28,841per QALY		€ 26,449 per LYS
Sensitivity analysis	One-way	One-way	One-way Monte Carlo

The ways of assessing the pneumococcal conjugate vaccination programmes and related results of the cost-effectiveness analyses had great variations, which could not be explained only by the differences of country specific data. We made special notions on the used model type and structure, economic method, used parameters, cost-effectiveness results and chosen sensitivity analysis (Table 2). The variations in the ways of assessing the cost-effectiveness of programmes makes it difficult to assess the true value of the pneumococcal conjugate vaccination programme. Even when there are more reviewed articles (Beutels et al. 2007) it is difficult to make an overall statement of the cost-effectiveness of universal infant vaccination with the PCV7.

Based on our overall notions of the reviewed theory of economic evaluation throughout our study so far and based on uncertainty issues of economic evaluations stated by Brisson &

Edmunds (2006) and Beutels et al. (2006) we suggest the following issues of concern in order to appraise CEA in a proper way and thus assessing the true value of vaccines. The principles are related to the following matters: 1) model type and structure 2) appropriate economic evaluation method and perspective 3) reliable clinical data and 4) accounting for uncertainty and 5) adequate cost-effectiveness measures.

Relying on the notions throughout the text about the model type, we state that the dynamic model is more realistic way of assessing the CEA of vaccination. Although, the methods are quite new and aren't necessarily easy to assess. The appropriate economic evaluation method is CEA and CUA, although the methods of CBA can be used in order to represent the results. Reliable clinical data must be justified, and accounted for uncertainty if necessary. Further sensitivity analyses are also needed in order to investigate, what kind of impact simultaneous changing of the parameters has on the results. We assess the matter of adequate cost-effectiveness measures in Section 3.3.

3.3 Implementing cost-effectiveness results

In the case of vaccination, the decision modelling is based most often on two optional alternatives: no vaccination and vaccination. Different Markov states depend on the disease in question and the vaccine used to prevent it. According to Sonnenberg & Beck (1993, 326) a separate state must be created for each subset of cohort which accounts for distinct utility or prognosis. We provide a numerical example of a restricted Markov model consisting of five states (Figure 6). The model follows the schematic used in vaccine oriented cost-effectiveness studies, although the primary Markov-states are usually more specific disease and death states (Section 3.2). In the extended model (Figure 6) also the reversibility between health states and a death state is included in the model structure. In addition to the presented health states we could and should add an another absorbing state; another death state in order to distinct the difference between death states of natural attrition and due to infection in question. Also a state 'AEFIs' could be included in the extended model to describe the adverse events following immunization (Section 2.1.1). The AEFIs are seldom taken into account in the vaccine related cost-effectiveness analyses, which is acceptable if the adverse events are minor. However, when the adverse events cause costs from the perspectives of health care provider and society, they should not be left without consideration.

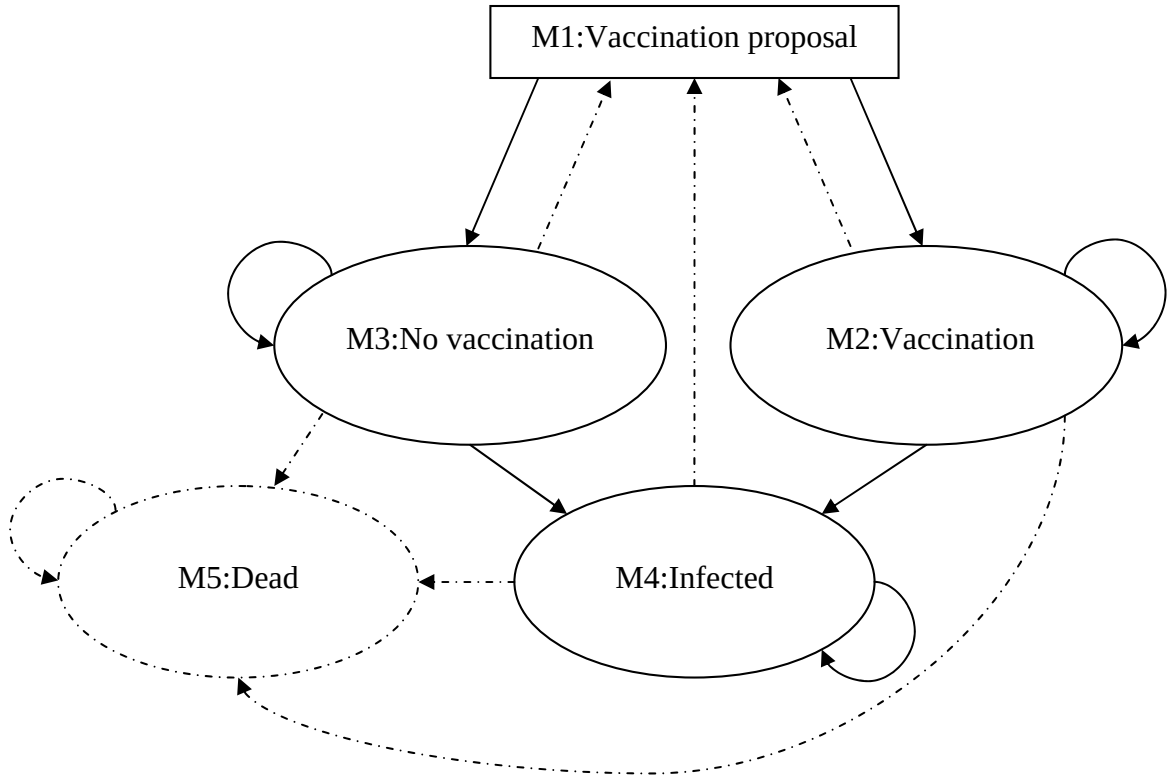

Figure 6. The structure of the Markov model in the case of (child) vaccination in general: restricted (──) and extended (- - -) model.

Based on the model structure of the extended model in Figure 6, we derived the transition probabilities between health states M1 and M5. The transition matrix is presented in Table 3.

Table 3. Transition probabilities from state M1 to state M5 based on the model structure of the extended Markov model (Figure 6).

$A_{[5,5]}$	M1:Vaccination proposal	M2:Vaccination	M3:No vaccination	M4:Infected	M5:Dead	$\sum_{j=1}^{5} a_{ij}$
M1	0	a_{12}	a_{13}	0	0	1
M2	a_{21}	a_{22}	0	a_{24}	a_{25}	1
M3	a_{31}	0	a_{33}	a_{34}	a_{35}	1
M4	a_{41}	0	0	a_{44}	a_{45}	1
M5	0	0	0	0	1	1

Although the extended Markov model is more realistic presentation of a vaccination related decision problem, we use the restricted Markov model in order to provide an example of implementing CEA and the results. That is, we assume that there are no death states and no reversibility into previous health states. Nevertheless, we assume that the individuals may stay at the health states 'vaccination' and 'no vaccination' for a longer time than just for one cycle. In our model the state 'vaccination proposal' is an entry state and the state 'infected' is assumed to be an absorbing state, from where the individuals cannot leave to other states. The assumption of using state 'infected' as the absorbing state, means that the amount of the infected individuals will increase throughout the cycles since there is no possibility of leaving the state. The transition probabilities according to the restricted model from state M1 to state M4 are presented as a transition matrix (TM) in Table 4. As an assumption in the model a patient can be even when being already vaccinated.

Table 4. Transition probabilities from state M1 to state M4 based on the structure of the restricted Markov model (Figure 6).

$A_{[4,4]}$	M1:Vaccination proposal	M2:Vaccination	M3:No vaccination	M4:Infected	$\sum_{j=1}^{4} a_{ij}$
M1	0	a_{12}	a_{13}	0	1
M2	0	a_{22}	0	a_{24}	1
M3	0	0	a_{33}	a_{34}	1
M4	0	0	0	1	1

In order to present the formulas of corresponding transition probabilities of the restricted Markov model we used the following terminology:

Vcov = vaccination coverage
Veff = efficient vaccine
Vineff = inefficient vaccine
Pv = prevalence of getting the infection
SelfI = natural immunity

The transition probability a_{12} is the probability that an individual is vaccinated based on the vaccination proposal. We express the probability in terms of vaccination coverage. The transition probability a_{13} is the probability that an individual is not vaccinated, and thus, the probability is 1- *Vcov*. That is,

$$\left.\begin{aligned} a_{12} &= Vcov \\ a_{13} &= 1\text{-}Vcov \end{aligned}\right\} \quad a_{12} + a_{13} = 1$$

In the state 'vaccination' an individual is not infected (D^-). The probability of staying in the state, a_{22}, is the probability of not acquiring the disease because of an efficient vaccine or because being covered by natural immunization. Also, an individual might stay at the health state because has no prevalence in acquiring the disease, but is still vaccinated with an efficient or inefficient vaccine. The transition probability a_{24} is the probability of being infected (D^+) because of the prevalence rate and because of being vaccinated with an inefficient vaccine in the absence of natural immunity. In the first option i) we assume that there is no natural immunity and in the second option ii) we assume the existence of natural immunity. That is,

i) no natural immunity

$$\left.\begin{aligned} a_{22} &= Pv \times Pr(Veff) + (1\text{-}Pv) \times Pr(Veff) + (1\text{-}Pv) \times Pr(Vineff) \\ a_{24} &= Pv \times Pr(Vineff) \end{aligned}\right\} \quad a_{12} + a_{13} = 1$$

ii) natural immunity

$$\left.\begin{aligned} a_{22} &= Pv \times \left[Pr(Veff) + \left\{ Pr(Vineff) \times Pr(SelfI) \right\} \right] + (1\text{-}Pv) \times Pr(Veff) + (1\text{-}Pv) \times Pr(Vineff) \\ a_{24} &= Pv \times \left[Pr(Vineff) \times \left\{ 1 - Pr(SelfI) \right\} \right] \end{aligned}\right\} \quad a_{12} + a_{13} = 1$$

In the state 'no vaccination', an individual isn't vaccinated, but is neither infected. Staying at the state means not belonging to the group who is infected based on the prevalence rate or natural immunity. The transition probability of moving to the state 'infected', and acquiring the disease (D^+), a_{34}, is the probability of being infected based on the prevalence rate and

because not being protected by natural immunity. As previously, we accounted that in the option i) the individual has no natural immunity against vaccine preventable diseases and in the option ii) the natural immunity exists. That is,

i) no natural immunity

$$\left.\begin{aligned} a_{33} &= (1\text{-}Pv) \\ a_{34} &= Pv \end{aligned}\right\} \quad a_{22} + a_{24} = 1$$

ii) natural immunity

$$\left.\begin{aligned} a_{33} &= (1\text{-}Pv) + Pv \times Pr(\textit{SelfI}) \\ a_{34} &= Pv \times (1\text{-}Pr(\textit{SelfI})) \end{aligned}\right\} \quad a_{12} + a_{13} = 1$$

Based on the transition probabilities depicted above we performed a Markov cohort simulation, where we assumed a hypothetical cohort of 10 000 children, who received their vaccination belonging to a national vaccination programme. In order to count the values of cycles we used estimates relying on the existing literature of invasive pneumococcal infections (IPD) and pneumococcal conjugate vaccine (PCV). We used as an example the vaccine efficacy only against bacteraemia and meningitis excluding other invasive pneumococcal infections (Section 2.3.1). Also, in reality PCV has shown proven efficacy against other pneumococcal infections including pneumonia and acute otitis media (AOM) (Section 3.2). In order to present the mechanism of cohort evaluation, we assumed that the vaccinated individuals received only their first dose of the vaccination schedule. The evaluation of a cohort of 10 000 new born was followed over 10 cycles, and the length of one cycle was 12 months. In the economic evaluations of PCV7 the time span of the impact of vaccination has been most often 5 or 10 years (Beutels et al. 2007, 1357-1358). The vaccine protection of PCV7 lasts to current knowledge at least 3-5 years (Section 2.3.1). Since in our example the effects of the vaccination programme start to show beginning from the cycle two, we were interested in comparing the impacts of the vaccination programme to the situation without vaccination in short-term (in the end of year 6) and in long-term (in the end of year 10).

Vaccine's effectiveness against IPD was assumed to be 73% after the first dose of PCV7 (Whitney et al. 2006). Based on a review study by Beutels et al. (2007), vaccine uptake (%) is

not always reported in the economic evaluations studies of pneumococcal conjugate vaccination programmes, although values from 70% to unrealistic 100% have been used. We assumed the vaccine coverage to be 86 %, which was used by Melegaro et al. (2010) in the baseline analysis as the annual routine coverage rate for pneumococcal vaccine. According to the Finnish register of infectious diseases (THL 2010a), in 2000-2008 based on the findings of *Streptococcus pneumoniae* in blood and cerebrospinal fluid (CSF), the average annual incidence of IPD was 35.34/100,000 among children under 5 years of age. According to KTL (2008a, 10) the real incidence rate of child bacteraemia cases is probably substantially higher. We approximated the prevalence for IPD to be 100/100,000 and 10/10,000. All in all, in our first simulation i), which didn't account natural immunity, we used the following parameter estimates:

Vcov = 0.86 (86 %)
Veff = 0.73 (73 %)
Vineff = 0.27 (27 %)
Pv = 0.001 (0.1 %)

Based on the estimates mentioned above we calculated the transition probabilities for the alternative i), which didn't take into account natural immunity. The results of the calculations are presented in Table 5.

Table 5. Annual transition probabilities in the case of pneumococcal conjugate vaccine (PCV) against invasive pneumococcal diseases (IPD). The calculations are based on the restricted Markov model (Figure 6). Natural immunity against IPD is not included in the calculations.

$A_{[4,4]}$	M1:Vaccination proposal	M2:Vaccination	M3:No vaccination	M4:Infected	$\sum_{j=1}^{4} a_{ij}$
M1	0	$a_{12}=0.86$	$a_{13}=0.14$	0	1
M2	0	$a_{22}=0.99973$	0	$a_{24}=0.00027$	1
M3	0	0	$a_{33}=0.999$	$a_{34}=0.001$	1
M4	0	0	0	1	1

Based on the transition matrix (Table 5) we performed a cohort simulation. As we mentioned above, state M4 ‘Infected’ is the absorbing state. Once arrived at the state M4, the individuals (in theory) are infected again every year. Thus, the amount of treatable cases of IPD is constantly rising. The evaluation of a cohort is presented in Table 6. We accumulated the number of infected individuals in based on the amounts in the end of year 6 (cycles 0-6) and in the end of year (0-10). In the end of sixth year overall amount of infected individuals is 55/10,000 and in the end of tenth year 167/10,000 is infected. (Table 6)

Table 6. The evaluation of a cohort over 10 cycles in the case of pneumococcal conjugate vaccine against invasive pneumococcal diseases (IPD), where the existence of natural immunity is not taken in consideration.

Cycle (year)	M1	M2	M3	M4	
0	10,000				*check*
1	0	8,600.000	1,400.000	0	*10,000*
2	0	8,597.678	1,398.600	3.722	*10,000*
3	0	8,595.357	1,397.201	7.442	*10,000*
4	0	8,593.036	1,395.804	11.160	*10,000*
5	0	8,590.716	1,394.408	14.876	*10,000*
6	0	8,588.396	1,393.014	18.590	*10,000*
sum				**55.789**	
7	0	8,586.077	1,391.621	22.302	*10,000*
8	0	8,583.759	1,390.229	26.011	*10,000*
9	0	8,581.442	1,388.839	29.719	*10,000*
10	0	8,579.125	1,387.450	33.425	*10,000*
sum				**167.247**	

As we mentioned in section 2.3.1 some children belong to the risk groups and are at increased risk in acquiring a pneumococcal infection. Still, there are children who have natural immunity against the disease and thus, don’t get the infection even without vaccination. We accounted the existence of this natural immunity (*SelfI*) against pneumococcal diseases in our second cohort simulation (ii). The corresponding transition matrix is presented in Table 7. We estimated the natural immunity to be 10 %, which is only a rough estimate not relying on any specific literature.

Table 7. Annual transition probabilities in the case of pneumococcal conjugate vaccine (PCV) against invasive pneumococcal diseases (IPD). The calculations are based on the structure of restricted Markov model (Figure 6). Natural immunity against IPD is included in the calculations.

$A_{[4,4]}$	M1:Vaccination proposal	M2:Vaccination	M3:No vaccination	M4:Infected	$\sum_{j=1}^{4} a_{ij}$
M1	0	a_{12}=0.86	a_{13}=0.14	0	1
M2	0	a_{22}=0.999757	0	a_{24}=0.000243	1
M3	0	0	a_{33}=0.9973	a_{34}=0.0027	1
M4	0	0	0	1	1

Based on the transition matrix in Table 5 we performed a cohort simulation accounting the natural immunity of 10 % (Table 8). Compared to the previous simulation (Table 6), accounting the natural immunity against invasive pneumococcal infections has impact especially on the number of infected individuals.

Table 8. The evaluation of a cohort over 10 cycles in the case of pneumococcal conjugate vaccine against invasive pneumococcal diseases (IPD), where the existence of natural immunity is included in the calculations.

Cycle (year)	M1	M2	M3	M4	
0	10,000	0	0	0	*check*
1	0	8,600	1,400	0	*10,000*
2	0	8,597.91	1,398.74	3.3498	*10,000*
3	0	8,595.821	1,397.481	6.697958	*10,000*
4	0	8,593.732	1,396.223	10.04448	*10,000*
5	0	8,591.644	1,394.967	13.38935	*10,000*
6	0	8,589.556	1,393.711	16.73259	*10,000*
sum				**50.21418**	
7	0	8,587.469	1,392.457	20.0742	*10,000*
8	0	8,585.382	1,391.204	23.41416	*10,000*
9	0	8,583.296	1,389.952	26.75249	*10,000*
10	0	8,581.21	1,388.701	30.08919	*10,000*
sum				**150.5442**	

Due to including the natural immunity in the calculations, 5 (55-50) additional cases of IPD would be avoided in the end of sixth year, and 17 (167-150) additional cases of IPD would be avoided in the end of tenth year. The calculations presented above have more value when we compare the results to the alternative with no vaccination (Table 9).

Table 9. The evaluation of a cohort over 10 cycles without vaccination. The prevalence rate of invasive pneumococcal diseases (IPD) was assumed to be 0.1%.

Cycle (year)	M1	M2	M3	M4	
0	10,000				*check*
1	0	0	10,000	0	*10,000*
2	0	0	9,990	10	*10,000*
3	0	0	9,980.01	19.99	*10,000*
4	0	0	9,970.03	29.97001	*10,000*
5	0	0	9,960.06	39.94004	*10,000*
6	0	0	9,950.1	49.9001	*10,000*
sum				**149.8001**	
7	0	0	9,940.15	59.8502	*10,000*
8	0	0	9,930.21	69.79035	*10,000*
9	0	0	9,920.279	79.72056	*10,000*
10	0	0	9,910.359	89.64084	*10,000*
sum				**548.3533**	

That is, applying the vaccination programme results as 94 (149-55) IPD cases averted (no natural immunity) or 99 (149-50) IPD cases averted (with natural immunity) in the end of sixth year. In the end of tenth year, 381(548-167) IPD cases are averted (no natural immunity) or 398 (548-150) cases are averted (with natural immunity). In order to assess the impact of vaccination programme in monetary terms we created a cost matrix (Table 10). We have taken in consideration only costs from the health care provider perspective, that is vaccination and treatment costs. Performing the analysis from the societal perspective, would have required accounting also travel and productivity costs. Including indirect effects in the calculations would have required the use of dynamic model (Sections 2.12 and 3.2).

As we mentioned before, we use the restricted model as a base of our calculations. That is, there are four kinds of paths, which create costs (Table 10). Still, in our example, only two kinds of costs exist: vaccination (c_{12}) and treatment costs ($c_{24} = c_{34} = c_{44}$).

Table 10. Cost matrix related to the restricted Markov model presented in Figure 6.

$A_{[4,4]}$	M1:Vaccination proposal	M2:Vaccination	M3:No vaccination	M4:Infected
M1	0	c_{12}	0	0
M2	0	0	0	c_{24}
M3	0	0	0	c_{34}
M4	0	0	0	c_{44}

In order to calculate the expected costs of the alternatives with and without the vaccination we used cost estimates relying on the existing literature and data for invasive pneumococcal diseases (IPD) and pneumococcal conjugate vaccine (PCV7). In our example, we accounted as vaccination costs only the costs of purchasing the vaccine. Purchase price per dose was estimated to be 48 € (retail price is 84.64 €/dose) (KTL 2008b, 4). In reality, vaccination programme costs are higher due to several vaccine doses uptake and additional vaccination costs (Section 2.3.1; Beutels et al. 2007, 1357). The treatment costs were calculated based on the costs of bacteraemia and meningitis episodes and expected case incidence taken from the study of Salo et al. (KTL 2008b). Average treatment costs due to IPD were counted to be 2360€ and estimated to be 2370€ per case (0 % discount rate). It is worth noting, that in reality the costs per IPD episode are higher, because we didn't take into consideration the chirurgical procedure due to a meningitis episode when calculating the average treatment costs. Also, the overall costs without and with vaccination are greater because of travel and productivity costs, and other pneumococcal diseases (Salo et al. 2005, 827). We calculated the expected costs for each cycle of the cohort model by adding the costs of each state weighted by the proportion of individuals and by adding the costs across the cycles. We accumulated the average future costs in two cases: with vaccination (no natural immunity) and without vaccination programme (Table 11). We decided to compare the alternative without vaccination to the alternative of vaccination, where natural immunity is not included in the calculations, because of the uncertainty related to the used natural immunity estimate. The future costs were discounted using 3.5 % discount rate, which is an appropriate annual discount rate on both costs and health effects according to NICE (2008, 41-42) as we mentioned in Section 2.2.

Table 11. Calculation of expected costs for two alternatives: without vaccination and with vaccination. Vaccine price is assumed to be 48e/dose and treatment costs €2,370/IPD case. Natural immunity is not included in the calculations.

	No vaccination €		Vaccination € (one dose)	
Cycle (year)	Discount rate 0%	Discount rate 3.5%	Discount rate 0%	Discount rate 3.5%
0				
1			412,800	398,840.5797
2	23,700	22,124.2036	8,821.14	8,234.628579
3	47,376.3	42,730.70821	17,637.47615	15,907.99296
4	71,028.9237	61,897.6035	26,449.01218	23,048.78609
5	94,657.89478	79,699.40743	35,255.75179	29,684.39698
6	118,263.2369	96,207.2194	44,057.6987	35,840.96628
sum	**355,026.3554**	**302,659.1421**	**545,021.0788**	**511,557.3506**
7	141,844.9736	111,488.8671	52,854.85662	41,543.43953
8	165,403.1287	125,609.0473	61,647.22925	46,815.6183
9	188,937.7255	138,629.461	70,434.8203	51,680.20917
10	212,448.7878	150,608.9426	79,217.63346	56,158.87074
sum	**1,063,660.971**	**828,995.4603**	**809,175.6184**	**707,755.4883**

Based on the estimated costs over cycles 0-10 in Table 11 we have presented a summary of the discounted costs without and with vaccination in Table 12. The length of simulation has a great impact on the interpretation of the results.

Table 12. Discounted (3.5%) net health care costs (Table 11). Negative (-) net cost = cost saving.

	No vaccination €		Vaccination * €		Net costs €	
	≤6 y	≤10 y	≤6 y	≤10 y	≤6 y	≤10 y
Treatment costs	302,659.1	828,995.5	112,716.8	308,914.9	-189,942.3	-520,080.6
Vaccination costs	0	0	398,840.6	398,840.6	398,840.6	398,840.6
Health care costs	302,659.1	828,995.5	511,557.4	707,755.5	208,898.3	-121,240

* no natural immunity

In the end of sixth year, the cost of vaccinating a cohort of 10,000 individuals is €208,898 from the health care provider perspective. The investment of €398,841 to vaccinate a cohort would save €189,942 in treatment costs. Investing in vaccination would result as an overall cost saving of €121,240 euro in the end of the tenth year of vaccination implementation and would save then 520,081€ in treatment costs.

Salo et al. (2005, 826) estimated the reduction in the burden of disease in terms of potentially prevented cases of pneumococcal infections due to vaccinating a birth cohort. We used 'case averted' as an efficacy measure in order to count the incremental cost-effectiveness ratio (ICER) of vaccinating a cohort based on the net costs (Table 12) and the expected IPD episodes without vaccination (Table 6) and with vaccination (Table 9). In the formula of ICER, S_2 is for vaccination (without natural immunity) and S_1 is for the alternative without vaccination. That is,

$$ICER(S_1 \rightarrow S_2) = \frac{CostS_2 - CostS_1}{E_2 - E_1}$$

$$= \frac{208{,}898}{94}$$

$$= 2{,}222 \text{ €} / \text{IPD case averted}$$

Within the limitation that in our example (in the restricted model) there is no death state, we used 'QALYs gained' as the second appropriate efficacy measure and calculated the incremental cost-utility ratio (ICUR). According to the study of Salo et al. (2005, 824) QALYs lost due to pneumococcal diseases vary form 0.004 to 0.006 per case and from 0.0054 to 0.216 per year. We used as a hypothetical estimate of 0.1 QALYs lost per case of IPD. We calculated the lost QALYs for each cycle of the cohort model based on the amount of IPD cases in health state M4 'Infected' across cycles, and compared the overall sum of QALYs lost with and without vaccination. The difference was used as the efficacy measure 'QALYs gained' (Table 13).

Table 13. Estimated QALYs gained due to vaccination.

Estimated QALYs lost						
	No vaccination		Vaccination*		Difference in QALYs/y	
Discount rate	0 %	3.5 %	0 %	3.5 %	0 %	3.5 %
after 6 years	14.98001	12.77043	5.578948	4.755982	9.401062	8.014448
after 10 years	44.88021	34.97871	16.72471	13.03438	28.1555	21.94433

* no natural immunity

The incremental cost-utility ratio (ICUR) for vaccination is based on the discounted cohort simulation results in the end of sixth year (Table 12 and Table 13). That is,

$$ICUR(S_1 \rightarrow S_2) = \frac{CostS_2 - CostS_1}{\text{QALYs gained}}$$

$$= \frac{208{,}898}{8.0145}$$

$$= 26{,}065 \text{ € / QALY gained}$$

In the end of sixth year the cost per QALY gained is €26,065. In the end of year 10, ICUR is negative, -5,525 €/QALY gained. Negative ICUR implies that the vaccination would improve the quality of life as well as reduce costs compared to the alternative without vaccination.

At this point of the study we found it appropriate to include a more realistic case of the alternative of vaccination. PCV7 has been included in the national immunization programmes to the universal extent using 3+1 or 2+1 schedules (Section 3.1). In Finland, the work group set by National Health Institute (KTL 2008a) recommends including the vaccine into national immunization programme based on the vaccine uptake in 3, 5 and 12 months of age. Based on this recommendation we assumed a three-dose vaccination programme with an efficacy estimate of 0.891 to be our second base case (Base case 2). Treatment costs and prevalence rate were the same as in the previous analysis. The used efficacy estimate against IPD was proposed by Black et al. (2000) and was the same as in the work of Salo et al. (KTL 2008b) assessing the cost-effectiveness of the vaccination programme with PCV. We present the results of 'Base case 2' and use it as a reference case in the sensitivity analysis (Table 14).

Table 14. Cost-effectiveness results and sensitivity analysis.

	Net costs €		ICER (€ / case averted)		ICUR (€ / QALY)	
	≤6 y	≤10 y	≤6 y	≤10 y	≤6 y	≤10 y
Base case 1 1-dose programme and efficacy 0.73	208,898.3	-121,24	2,222.1	-318.1	26,065.2	-5,524.9
Base case 2 3-dose programme and efficacy 0.891	964,639.2	561,474.5	8,405.0	1,266.4	98,592.8	20,954.3
Prevalence 0.002	733,427.9	-69,946.1	3,200	-79.1	37,535.0	-1,308.9
Prevalence 0.003	502,886.4	-697,759	1,464.9	-528.1	17,182.5	-8,729.9

Vaccinating the cohort according to the three-dose vaccination programme tripled the vaccination costs and had a tremendous impact on the results. Consequentially, applying the three-dose vaccination programme increased the net costs from the health care provider. Based on the results (Table 14), the cost-effectiveness depends on the amount of doses of vaccine, more exactly on the price of vaccine. According to Beutels et al. (2007, 1364) the price of vaccine is a key assumption determining the economic attractiveness of universal PCV7 vaccination. In our example, also chosen time span had great influent on the results.

In addition to providing the two scenarios (≤6 y and ≤10y) of the costs we wanted to test impact of higher prevalence rates on the results based on the following remarks. Data suggests that the incidence of invasive pneumococcal diseases in developing countries among children (<5 y) is several times higher than in industrialized countries (WHO 2007, 96). In order to illustrate the impact of higher prevalence rate on the results, we approximated the prevalence of IPD to be 0.2% and 0.3%. Higher prevalence rates improved the cost-effectiveness of the vaccination, although net costs were still higher compared to the first base case analysis (Table 14).

The final decision of a policy implementation depends on the societal willingness to pay (WTP). As we have seen in Section 3.2, there exist recommendations, when the new intervention is worth implementing. Nevertheless, the WTP is not always defined on a national level. For example in Finland, at least for now, the decision-makers haven't set up the societal WTP for a vaccination programme (KTL 2008a, 35). In order to present our results on a cost-effectiveness plane (Figure 5) we used as the WTP value the cost-effectiveness results based on a rotavirus vaccine which was included in the Finnish national immunization programme in 2007. In the case of rotavirus vaccination, ICER was €25 218 per QALY gained (KTL 2008a, 35; KTL 2008b, 14). We present two different vaccination alternatives: S_2 is for vaccination a cohort of 10 000 with one vaccine dose (efficacy 0.73) and the alternative S_3 is for vaccinating a cohort of 10 000 with 3 vaccine doses (efficacy 0.891) (Figure 7). S_2 is passing from the origin through coordinates (8, 208,898*)* and the alternative S_3 is passing through the origin and coordinates (9.8, 964,639).

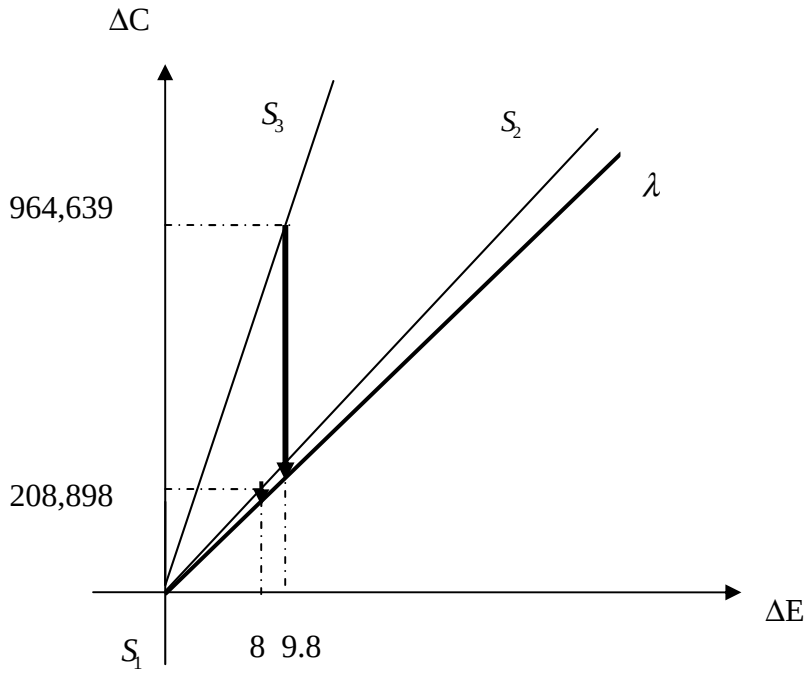

Figure 7. Implementing the results on a cost-effectiveness plane (Figure 5).

Both incremental cost-effectiveness ratios of the alternatives S_2 and S_3 are more than the acceptable threshold ratio λ (Figure 7). We depict the same result in terms of the incremental net benefit (INB). The formula of INB consists of the same parameters as the formula of ICER, but in addition also threshold ratio λ is accounted. The ratio of INB gives the value of an intervention in question in units of costs. The formula of INB is as follows (Grolier et al. 2009, 79),

$$\mathrm{INB}(\lambda)_{Sj \to Sk} = \lambda \Delta \mathrm{E}_{Sj \to Sk} - \Delta \mathrm{C}_{Sj \to Sk}$$

In Figure 7, the black arrows starting from the coordinates of the vaccination alternatives and ending on the line of threshold ratio λ represent the incremental net benefit. In our example the incremental net benefit ratios of vaccination are negative: -7,154 for the vaccination alternative S_2 and -717,503 for the vaccination alternative S_3. We present the critical values for the threshold ratio λ, witch are the values of the ICUR (Figure 8). That is, the decision-maker must be ready to invest more than €26,065 per QALY gained in order the vaccination strategy

S_2 would be accepted or more than € 98,593 per QALY gained in order to accept the vaccination strategy S_3.

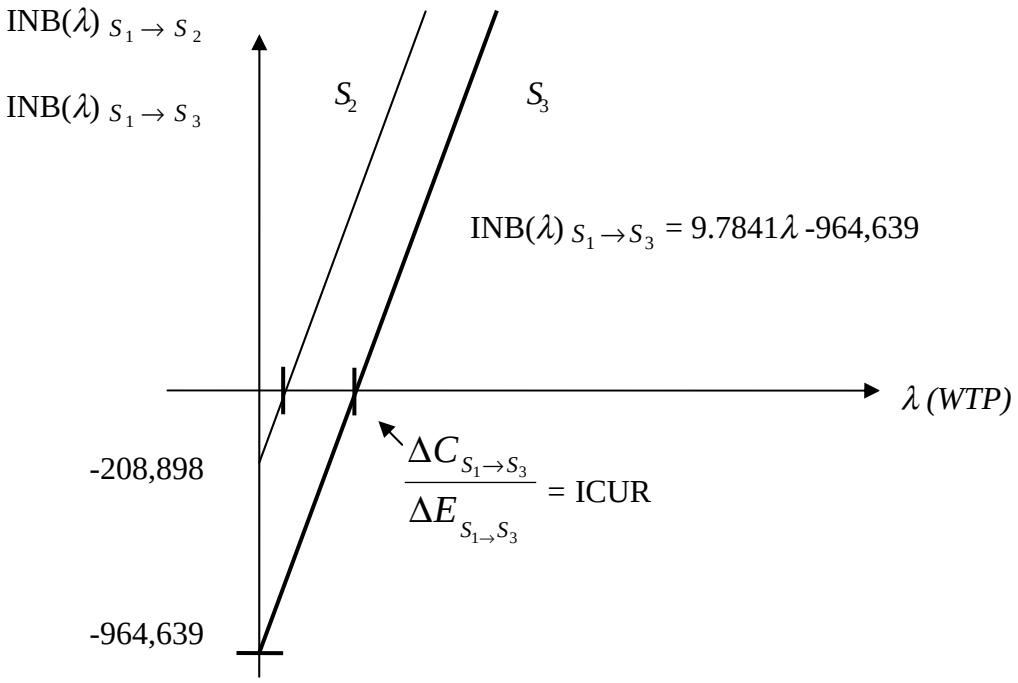

Figure 8. Implementing the results on a (λ, INB(λ))-plane (Grolier et al. 2009, 90-97). S_2 is for single-dose vaccination and S_3 is for 3-dose vaccination programme.

From the formula of INB we have the ratio of incremental net health benefit (INHB), which is the value of the alternative strategy in the units of effectiveness. The ratio has value especially to a health care unit, such as hospital. The formula of INHB is as follows (Grolier et al. 2009, 79),

$$\text{INHB}(\lambda)_{S_j \to S_k} = \Delta E_{Sj \to Sk} - \frac{\Delta C_{Sj \to Sk}}{\lambda}$$

In our example, the incremental net health benefits are negative: -0.3 for the vaccination alternative S_2 and -28.5 for the vaccination alternative S_3. The critical value of $\Delta E_{Sj \to Sk}$, when INHB(λ) accounts for zero, is counted by dividing the cost difference $\Delta C_{Sj \to Sk}$ by the threshold ratio λ. That is, the amount of QALYs gained must increase from 8 QALYs gained

at least to 8.3 QALYs gained (S_2) and from 9.8 QALYs gained at least to 38.3 before the interventions could be accepted within the limitations of the WTP.

It is important to notify, that in order to make the presented economic analysis more realistic we should extend the restricted model to the extended one as proposed in Figure 6. We should separate the state 'infected' into more specific health states, and take also other pneumococcal infections into consideration. Extending the model would give also the opportunity to use another cost-effectiveness measure, which is often used in vaccination related cost-effectiveness studies, that is costs (€)/life-year gained (LYG). In addition to the already mentioned inclusions, we should perform the analysis from the societal perspective by taking also productivity costs into consideration, and by including the indirect effects of the vaccine into our analysis. That is, the best option would be to use a dynamic model to incorporate the herd immunity effect and the effect of serotype replacement into the calculations.

4. CONCLUSIONS

Vaccines have a major impact on reducing the burden of diseases all over the world. The vaccinated individuals receive health gains from vaccines, but also the susceptible individuals benefit from vaccination through the positive indirect effect of vaccination called herd immunity. Because of the positive consequences of vaccination more people stay healthy and there are less productivity losses on population level due to the reduction of vaccine preventable diseases.

In the industrialized countries, the vaccination expenditures are mostly funded by the government. Because the government's resources are limited, the use of resources must be maximized by allocating them to the best alternatives of use. The opportunity cost shouldn't be left without consideration. In order to support the government's decision-making, and to find the target groups, where the resources are most valued, there is the need to provide the adequate information of relevant costs and consequences of the alternatives with and without vaccination.

The value of vaccines is assessed most often using cost-effectiveness analysis (CEA). CEA is a full economic evaluation technique, where the costs are measured in monetary units and the efficacy measure of consequences is a natural unit, such as life year gained (LYG). Cost-utility analysis (CUA) is a special case of CEA, where the efficacy measure is utility related, usually quality adjusted life year (QALY). In order to fully understand the value of vaccines, we must take into account the particularities of vaccines when performing the economic evaluations of vaccination.

Our aim was to answer to the study question: how to assess the true value of vaccines? To assess the true value of vaccines with the help of CEA, the following matters should be accounted: 1) correct model type and structure 2) appropriate economic evaluation method and perspective 3) reliable clinical data, 4) accounting for uncertainty and 5) adequate cost-effectiveness measures.

First of all, we need to choose an appropriate model type and structure. In order to depict the herd immunity effect in a proper way, dynamic models should be used. Second, we need to choose an appropriate economic evaluation method in order to assess the cost-effectiveness of vaccines. Moreover, the economic evaluations, in the case of vaccination especially cost-effectiveness analyses (CEA) should be performed as well as from the health care provider as from the societal perspective, when also productivity costs and indirect effects should be included in the analysis. Also special vaccine characteristics should be accounted. In the case of pneumococcal vaccination the phenomenon of serotype replacement shouldn't be left without consideration. Third, the used parameter values must be based on the real evidence and the source of the applied parameters should be properly mentioned and fourth, the uncertain parameters should be tested using sensitivity analysis. As an overall notion, the methods used should be always properly justified to be seen as reliable.

We showed the implementation of the cost-effectiveness analysis in practice with the example of pneumococcal conjugate vaccine. Although we used a simplified model compared to the decision analytic models used in the cost-effectiveness studies of pneumococcal vaccination, we found the model structure useful in order to present the principles of assessing the cost-effectiveness of vaccination programmes, and also to name adequate cost-effectiveness measures. Especially, we were able to present the results in diverse ways in terms of the incremental cost effectiveness ratio (ICER), the incremental utility ratio (ICUR), the incremental net benefit (INB) and the incremental net health benefit (INHB). The ratios define the cost-effectiveness of a vaccination programme, although INB and INHB are less frequently used in the economic evaluations of vaccination programmes. Still, the measures are very useful, and help also the decision-maker to have a better overall view of the cost-effectiveness results. In order to account the uncertainty related to the parameter values, we performed a sensitivity analysis. Based on the great variation of the results depending on the parameter values we state that sensitivity analysis should be always included in the economic evaluations of vaccination programmes.

Based on the reviews of the cost-effectiveness analyses of pneumococcal conjugate vaccination (PCV7) we saw that the cost-effectiveness analyses and related results have great variation, which complicates the decision-making based on the economic evaluations. The cost-effectiveness studies lack of transparency, which makes identifying the history behind

the figures more difficult. Also, so far, there are no published full economic evaluations of PCV with the use of dynamic model.

Our study methods have the following limitations. The amount of reviewed cost-effectiveness analyses of pneumococcal conjugate vaccines is relatively small. Taking more CEAs into consideration would assure better overview of the PCV7. Also, we implemented cost-effectiveness analysis in practice using a model with several limitations, and thus, the cost-effectiveness results based on our implementation cannot be seen reliable. The model used in our example could be extended to a more sophisticated model and possibly be developed to assess the cost-effectiveness of the newly licensed 10- and 13-valent pneumococcal conjugate vaccines. The modelling matter offers an incitement for further study. Depicting the cost-effectiveness of pneumococcal conjugate vaccination using a dynamic model is a possibility for further investigations.

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