Effects and costs of pneumococcal conjugate vaccination of Belgian children

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Federaal Kenniscentrum voor de gezondheidszorg
Centre fédéral d'expertise des soins de santé
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FOREWORD

Vaccinations are an extremely successful chapter in the history of medicine Since the first experiments performed by Jenner in the late 18th century with cowpox, many serious infectious diseases have been combated through vaccinations. In 1980 the world could even be declared 'free from smallpox'. Part of this success was explained through a unique feature of vaccination as a technique, the fact that also non-vaccinated individuals are protected since the germ becomes less prevalent in the environment, the so-called *'herd immunity'*.

Vaccination used to be save, efficient and cheap and the number of infectious diseases for which vaccination became routine has grown in recent years. Consequently, questions about the advisability of the introduction of new vaccinations were seldom asked: if it did the job it needed to be done.

Streptococcus pneumoniae (pneumococcus) are bacteria that are often present in the upper airways in children and adults and that do not necessarily lead to disease. They can, however, cause serious diseases such as pneumonia, meningitis or sepsis but more often they will lead to less serious disorders such as ear- or upper respiratory tract infections. But, the less frequent severe infections are potentially lethal and can occasionally lead to serious neurological damage. The incidence of pneumococcal disease is strongly age-dependent and at risk are mainly children up to the age of 5 and adults aged 65 and over.

At the moment a pneumococcal vaccine for young children came to the market in Belgium, the question was raised whether this should be included into routine vaccination schedules. The vaccine might be efficient but is also expensive. At this moment the complete vaccination scheme with 4 injections costs over 250 € per child, a cost paid by the parents or partly reimbursed by the sick fund.

To evaluate whether universal vaccination of newborns would be appropriate usage of available means, and how this vaccination should be implemented, the KCE was asked to conduct a health technology assessment (HTA). The outcome of this evaluation was uncertain: earlier economic evaluations disagreed, local determinant had to be included as was the effect of 'herd immunity', and to obtain reliable estimates for Belgium using local data was essential.

This report is the result of an intensive cooperation of several partners and was conducted under important time constraints. These constraints, however, were not allowed to interfere with quality. Considering the anticipated arrival of several new vaccines in the near future this report might be a trendsetter. We hope this report will help policymakers to use available resources effectively, using a rational health economic approach.

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Effects and costs of pneumococcal conjugate vaccination of Belgian children

SUMMARY OF THE REPORT

OBJECTIVE

The objective of this report is to determine the cost-effectiveness of universal vaccination in young children (under the age of 2) with the currently available seven-valent conjugated pneumococcal vaccine (PCV7), taking into account direct benefits for the immunized children and indirect benefits (herd immunity effects) for the population at large.

A second objective is to determine the optimal vaccination schedule to achieve those benefits cost-effectively.

KEY RESULTS

We have reviewed the international published and unpublished literature, and collected and analyzed a wide range of Belgian epidemiological and cost data. A simulation model was developed, parameterised and fitted by using scientifically validated data, as much as possible from Belgian sources. Simulations were performed to estimate how effective and cost-effective universal PCV7 vaccination of Belgian children would be.

We conclude the following from our baseline calculations:

- At € 9869 per *Quality Adjusted Life Year* (QALY) gained in the baseline, PCV7 vaccination using a 2+1 schedule with injections at 2,3 and 15 months of age is cost-effective compared to other widely accepted interventions in Belgian health care.
- At € 155,619 per QALY gained in the baseline (using already more pessimistic assumptions for the 2+1 than the 3+1 schedule), the *incremental cost-effectiveness* of a 3+1 schedule (2,3,4, 15 months) versus a 2+1 schedule (2,3 and 15 months) compares unfavourably to other widely accepted interventions in Belgian health care.

UNCERTAINTIES

Sensitivity analyses showed the **first conclusion** to be very robust to various plausible changes in input parameters, as well as in multivariate probabilistic sensitivity analysis, in which all parameters were varied simultaneously according to (as much as possible) data driven distributions. It was also shown to be consistently robust to more implausible scenarios, such as ignoring the occurrence of herd immunity effects altogether (when the incremental cost-effectiveness increases to € 44,984 per QALY gained). Overall, it is important to remember that the baseline calculations were as realistic as possible, yet conservative where information is currently lacking. The model ignores any positive impact PCV7 vaccination may have on the long-term incidence of antibiotic resistant pneumococcal strains. Furthermore, herd immunity effects observed in the US were used only net of negative changes in non-vaccine type incidence in invasive pneumococcal disease. That is, herd immunity effects taken into account in this analysis, were always reduced to allow for (what are likely) serotype replacement effects observed over the first 5 years in the US program. Furthermore, since this first conclusion remained valid if herd immunity is completely ignored, it is bound to remain valid under scenarios of large serotype replacement effects (whereby non-vaccine types take over from vaccine types) over time. Of note is also that there are several multivalent pneumococcal conjugate vaccines (9 and 11-valent) likely to be marketed within 5 years from now, which would provide at least partial solutions to such serotype replacement effects. Additionally, the use of the 23-valent polysaccharide vaccine (which is currently not licensed in Belgium for children under 2 years of age), as a potential booster vaccine at age 15 months (instead of PCV) needs also to be further investigated, as it may provide an effective remedy for serotype replacement effects in children.

The **second conclusion** is more uncertain. Its validity depends on the difference in effect the extra interspersed dose (at 4 months) may have on long term (beyond 30 years hence) direct protection against clinical disease in vaccinees, as well as the extent of herd immunity immediately inferred to non-vaccinated people. In the USA, where due to serious vaccine shortages over the first 3 years of the program, eligible children received only an average of 2.7 doses (and only 35% received a full 3+1 schedule), no significant differences in effectiveness between both schedules could be detected. Furthermore in clinical trials, immunogenicity induced for the seven serotypes did not differ significantly between the two schedules In the analyses presented in this report we pessimistically assumed there would always be at least a difference in direct vaccine protection. Yet only when this difference is assumed to be large and long lasting would the additional effectiveness of the extra dose at 4 months warrant the extra costs that it would take. There is currently no evidence that a 3+1 schedule evokes greater herd immunity than a 2+1 schedule. Yet, we have assumed this to be the case in sensitivity analyses (reasonably bounded by data from the US), and still could not demonstrate a clear-cut case for the 3+1 schedule.

Indeed, given a willingness to pay of € 40,000 per QALY gained, we find in multivariate sensitivity analysis, that infant immunisation with PCV7 is always cost-effective. Using the same criterion for cost-effectiveness, the incremental cost-effectiveness of the 3+1 versus the 2+1 schedule was only in 5% of the simulations acceptable, when herd immunity is the same under both schedules (which seems the most likely assumption, given current evidence), and was acceptable in about 60% of simulations when we take an optimistic view of the difference in herd immunity between both schedules. Given a willingness to pay of € 200,000 per QALY gained, these percentages increased to about 60% and 80%, respectively.

IMPLEMENTATION

Additional elements that plead for the use of a 2+1 schedule are related to overcrowding of the schedule, and the knowledge that more new vaccines are expected to become available for introduction soon. The introduction of these new vaccines may be deterred by a lack of existing vaccination opportunities on the schedule, and additional high introduction costs if new vaccination opportunities need to be created.

It is important to remember that in this analysis, the introduction of PCV7 was assumed not to affect the uptake of other vaccines in the program. Clearly, since many of the existing vaccinations are for severe, and highly prevalent diseases (in the absence of vaccination), any negative interference with vaccine uptake of other vaccines could be detrimental to the attractiveness of PCV7 introduction. Therefore, in practice it is important that other due vaccinations are not postponed for the benefit of receiving a PCV7 injection.

The current situation in Belgium, whereby parents and their insurers pay private market prices for a four-dose schedule is likely to be very cost-ineffective from a societal perspective. Indeed, current uptake seems too low to yield large herd immunity effects, whereas private vaccination costs are about 45% higher than they could reasonably be expected to be with a public program. From a societal perspective, i.e. when all costs and benefits are accounted for no matter whom incurs or receives them, the present situation is much more costly and less effective than what could be achieved by a public program. Furthermore, an overall increase in PCV7 uptake will reduce inequities in health expectations (for those who are currently unable to receive the vaccine for medical reasons (eg, those aged under 2 months), and those who cannot afford it), an aspect which was also observed in the USA.

RECOMMENDATION

Based on those results the KCE recommends the introduction of universal childhood vaccination with the seven-valent conjugated pneumococcal vaccine using a 2+1 vaccination schedule with injections at 2, 3 and 15 months. This recommendation might not apply to children at increased risk due to co-morbidity and we invite advice from the Superior Health Council on this.

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Scientific summary

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INTRODUCTION

In 2000, a seven-valent pneumococcal conjugate vaccine (PCV7) produced by Wyeth was conclusively shown in a large US trial to be highly effective against invasive pneumococcal disease, which was caused by the seven serotypes PCV7 covers. It was also shown to be moderately effective against pneumonia and acute otitis media. Consequently, in that same year (2000), PCV7 was added to the US national routine immunisation schedule. However, until mid-2004, the producer faced severe production problems and could not meet the desired quantities needed for the US market to administer the full four-dose schedule on time for most children.

In the mean time, in other countries, PCV7 was recommended for risk groups only. This was also the case in Belgium. As more information became available on IPD in children as well as on the effectiveness of PCV7 in healthy children, the Superior Health Council in Belgium expanded its recommendation from risk groups to all infants in 2002. Ever since that time, the Superior Health Council has advised an economic evaluation study would be required to examine the different vaccination strategies.

In January 2005, Australia and the territories of Canada introduced universal pneumococcal conjugate vaccination. In Australia and the territory of Quebec, this is done by a reduced 3-dose schedule.

At least 6 other European countries have decided to implement universal infant PCV7 vaccination sometime in 2006. None of these countries have made these decisions without a preceding economic evaluation being available.

This report was commissioned in the last week of 2005, and the final version of the report was submitted for validation to KCE in the first week of June 2006.

The aims of this report are to:

1. review the international scientific evidence base relating to the effectiveness and cost-effectiveness and cost-utility of pneumococcal conjugate vaccines
2. document and review the pre-vaccination disease burden of pneumococcal infections in Belgium
3. analyse and compare the effectiveness, cost-effectiveness and cost-utility of feasible options for use of the currently marketed pneumococcal conjugate vaccine in Belgium

This report is organised as follows. In section 1, the general background and literature related to the first aim of this report are summarised. Extensive in-depth reviews of the effectiveness and cost-effectiveness of pneumococcal conjugate vaccines are given in appendix A and appendix B, respectively. In section 2, the data and methods for further analyses are presented and discussed. These data serve two purposes: they document aim (2) of the report, and are needed as inputs into the mathematical simulation model we developed to perform an economic evaluation of introducing publicly funded universal childhood pneumococcal conjugate vaccination in Belgium. In section 3, the baseline results and the sensitivity analyses of the economic evaluation are presented. In section 4, some of the more practical policy implications are summarised, including information on pneumococcal conjugate vaccination strategies adopted in other countries, required budget and the current vaccination schedule in Belgium.

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We also thank all referring clinical microbiologists for access to information pertaining to isolates sent from their labs on a voluntary basis.

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ABBREVIATIONS:

AB = antibiotics

AOM = acute otitis media

C = Celsius

CDC = Centers for Disease Control and Prevention

CRM = cross reacting material

CI = confidence interval

cm = centimeter

DALY = Disability-Adjusted Life-Year

d = day

DTaP = diphtheria-tetanus-acellular pertussis vaccine

DTP = diphtheria-tetanus-pertussis vaccine

DTwP = diphtheria-tetanus- whole cell pertussis vaccine

E = erythema

FinOM = Finnish Otitis Media

FU = follow up

GMC = geometrical mean concentration

GP = general practitioner

gr = grade

GSK = GlaxoSmithKline

HepA = hepatitis A vaccine

HepB = hepatitis B vaccine

Hib = Heamophilus influenzae type B vaccine

HIV = humane immune deficiency virus

I = induration

ICER = Incremental Cost-Effectiveness Ratio

IPD = invasive pneumococcal disease

IPV = inactivated polio vaccine

ITT = intention to treat

LRT = lower respiratory tract

m = month

mm = millimeter

MenC = meningococcus type C vaccine

MMR = measles-mumps-rubella vaccine

MOH = Ministry of Health

MSD = Merck Sharp & Dohme

NA = not applicable

NCKP = Northern California Kaiser Permanente

NP = nasopharyngeal

NVT = non-vaccine serotype

OME = otitis media effusion

OMPC = outer membrane proteine complex

OPV = oral polio vaccine

OR = odds ratio

P = pain

PncOMPC = 7-valent conjugated pneumococcal vaccine with OMPC as proteine carrier

PCV = conjugated pneumococcal vaccine

PCV 7 = 7-valent pneumococcal conjugate vaccine

PCV 9 = 9-valent pneumococcal conjugate vaccine

PCV 11 = 11-valent pneumococcal conjugate vaccine

PP = per protocol

PPV = pneumococcal polysaccharide vaccine

PPV23 = 23 valent pneumococcal polysaccharide vaccine

PS = polysaccharide

QALY = Quality-Adjusted Life-Year

RCT = randomized controlled trial

RR = rate ratio

SAE = serious adverse event

SP = Sanofi Pasteur

T = temperature

ref. = reference

UK = United Kingdom

URT = upper respiratory tract

US = United States

VE = vaccine efficacy

VT = vaccine serotype

w = week

WHO = World Health Organization

y = year

1 BACKGROUND AND LITERATURE REVIEW

1.1 GENERAL BACKGROUND

Streptococcus pneumoniae (or "pneumococcus") is a bacterial pathogen that affects children and adults worldwide. It is a major cause of illness in children, especially those under the age of 24 months, in whom it can cause disseminated invasive infections (including meningitis and bacteraemia), lower respiratory tract infections (including pneumonia) and upper respiratory tract infections (including otitis media and sinusitis). In children, Streptococcus pneumoniae is currently one of the leading causes of meningitis and otitis media. Treatment of pneumococcal diseases is aggravated by the emergence of pneumococcal strains resistant to penicillin and other antibiotics.

The substantial disease burden and the availability of pneumococcal conjugate vaccines (with the seven-valent vaccine (PCV7) already on the market; eight and nine-valent (PCV8 and PCV9) in end-stage phase III trials and eleven-valent (PCV11) vaccines in phase II trials) give the potential introduction of a universal childhood pneumococcal conjugate vaccination program a prominent place on the health policy agenda in many countries. The PCV7 is currently licensed in Australia, North America, most parts of Europe and Central and South America. It is also part of the US, Australian and The Netherlands's universal childhood vaccination program since 2000, 2005 and 2006, respectively.[1] Given the high investment costs associated with this program, countries considering its implementation would prefer to do so on the basis of sound assessments of its population effectiveness, budget-impact and cost-effectiveness. Given the country-specific nature of the prevalence of circulating pneumococcal serotypes, and the costs of treatment for associated clinical disease, such assessments are likely to differ from one country to the next. Furthermore, value judgements on the willingness to pay to avoid morbidity and mortality are also typically somewhat different between different societies.

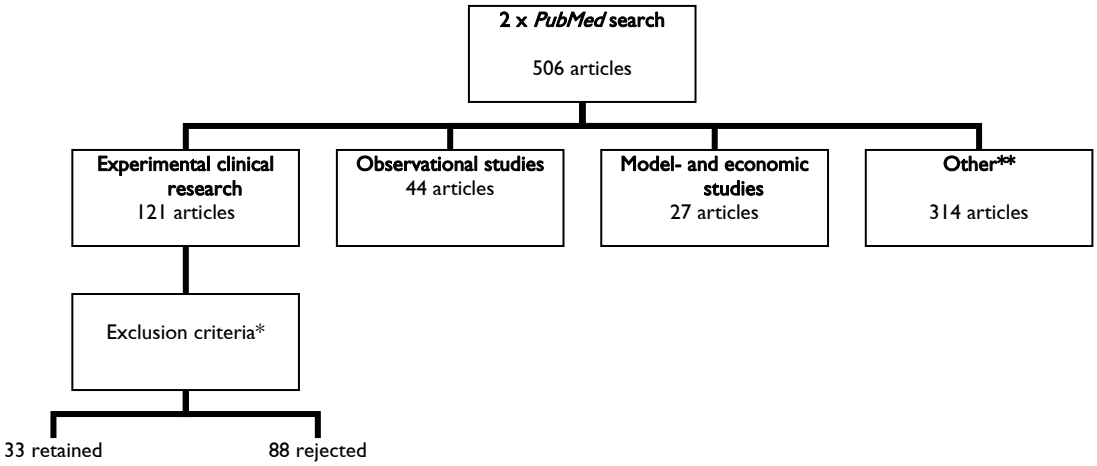
1.2 LITERATURE REVIEW METHODS

Two broad PubMed searches were performed using the Entrez search system. Each search started from 1998 because only then did the first relevant publications appear on PCVs with more than seven serotypes.

The first time, on 19-01-2006, the search term "pneumococcal conjugate vaccin* NOT review [ptyp]" was used, limited to the search field "Title/Abstract", resulting in 354 hits. Because it seemed that a number of important publications were missed using this method, another PubMed search was performed (on 13-02-2006) using the broader search term "pneumococcal AND conjugate AND vaccin* NOT review [ptyp]" with the exclusion of the articles found earlier, and limiting to "Title/Abstract", age: "All Child 0-18y" and "Humans". Another 152 publications were thus identified.

We initially categorised the studies based on abstracts (and full content if needed), as shown in Figure 1. The experimental clinical research category includes studies in which the investigators decided which participants would receive which vaccine. The only observational study included in this category is by Kayhty et al. This study differs from the other observational studies in that participants underwent immunological tests at well-defined time points before and after the administration of PCV7 doses.[2] Not every article describing clinical research states the phase of the trial, requiring inference from the methods section. In case of doubt between phase 2 and 3, we assumed that phase 3 research applies if at least 100 trial subjects take part. Nonetheless, one trial (Sigurdardottir et al.) on 160 subjects was not retained, as the information seemed to be outdated. Eight polysaccharides were conjugated to diphtheria toxoid in one vaccine and to tetanus toxoid in the other. Immunogenicity data showed a mixed carrier vaccine to be more ideal. Further testing of the original two vaccines was abandoned, and has now shifted to the mixed carrier vaccine.[3]

Figure 1: Categorisation and selection of search results



* Non PCV-studies, < phase 3, publication < 1998, duplicate publications (and follow-up studies only included if presenting additional material), adults, developing countries, risk groups (HIV-infection, sickle cell anaemia, …), outcome = antoibodies in saliva or urine, avidity of antibodies/ opsonophagocitic activity.
** biological, animal, case report, vaccine uptake, diagnostics, methodological, technical, epidemiological, theoretical impact of PCV, antimicrobial resistance, nasopharyngeal carriage, Prevnar programmatic issues, reviews, conference minutes, commentaries.

A final update of the PubMed search was made end of April 2006, repeating the last search strategy. This produced one more article, published by Prymula et al. in 2006.[4] In addition, we included two very recent articles we became incidentally aware of, by Scheifele et al.[5] and Goldblatt et al.[6]

Published economic evaluations of conjugate pneumococcal vaccine were identified using the above search, as well as EconLit with the search terms "pneumonia", "pneumococcal", "vaccine", "cost" and "economic".

1.3 IMMUNOGENICITY, EFFICACY, SAFETY AND EFFECTIVENESS OF PNEUMOCOCCAL CONJUGATE VACCINES

Unlike the 23-valent pneumococcal polysaccharide vaccine (PPV23), Pneumococcal Conjugate Vaccines (PCV), are immunogenic in children younger than two years of age. They are formulated in the same way as the H. influenzae type b and meningococcal type C vaccines. Polysaccharides that form part of the capsule of the most commonly occurring serotypes of Streptococcus pneumoniae are conjugated to a carrier protein. This causes the immune response of what are normally weakly immunogenic polysaccharides in children to be strongly increased.[7] In February 2000 the first 7-valent PCV (PCV7) went on the market in the United States (US) (Prevnar®, Wyeth), after it had been shown to be highly effective against IPD in the Northern California Kaiser Permanente (NCKP) study. This vaccine contains serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. In the NCKP trial PCV7 was administered in a 4-dose schedule to babies at the age of 2, 4, 6 and 12-15 months. After the introduction of PCV7 into the US infant vaccination programme, a reduction in the incidence of IPD of 69% in children younger than one year, 68% in children between one and two years and 44% in children between two and three years was observed (data from 2001 compared to 1998 and 1999). No reduction was seen in children from three to four years.[8] Moreover, PCV7 was shown to be effective against pneumococcal pneumonia and otitis media.

This 7-valent PCV came onto the market in Europe in 2002. At the present time the development of PCVs against more than seven serotypes is continuing undiminished. Merck also developed a PCV7, but with another carrier protein. Wyeth is also testing a 9-valent vaccine (PCV9) and Glaxo SmithKline Biologicals an 11-valent vaccine (PCV11).

In accordance with the search methods described above, the review on the clinical and biological properties of the vaccines was written on the basis of 36 publications, and is available in appendix A. Each of the 36 publications has been described in the text as well as the tables in the appendix.

In many European countries and in the United States, the recommended vaccination schedule for the pneumococcal conjugate vaccine (PCV) requires four doses per vaccinee. The infant immunization programme in Denmark, Finland, Italy, Norway, and Sweden is based on primary vaccinations at 3 and 5 months, and a third dose at 11 or 12 months of age, whereas in most other European countries the primary immunization schedule consists of 4 doses (three <1y, and one ≥1y). The use of a simplified schedule including 3 doses of PCV7 administered concomitantly with the routine primary infant vaccinations at age 3, 5 and 11 or 12 months has been shown to confer an equivalent antibody level for any of the vaccine serotypes compared to the four-dose PCV7 scheme. [2,76] These findings are valid for both pre-term and full term infants, and confirm earlier results demonstrating that the immune response induced by PCV7 using the simplified schedule is no different from that induced by the four-dose schedule. Kayhty et al.[2] showed that the administration of two doses of PCV7 induced satisfactory antibody response, except for the serotypes 6B and 23F. However, at month 13, after the booster dose, the pneumococcal antibody concentrations were comparable with those observed with the four dose schedule.[9] Moreover, the important increase of antibody concentration after the administration of the third dose in the reduced schedule, suggests that two doses of PCV7 may induce a sufficient immunological memory. Note also that the Goldblatt et al.[6] study was specifically designed to make a direct comparison between a 2+1 and 3+1 schedule, using PCV9 of the same company that currently markets PCV7. There were no significant differences in immunogenicity levels for the serotypes contained in PCV7, both before and after boostering at age 12 months. Additional data from the United States show that a remarkable decline in invasive pneumococcal disease among young children is seen despite vaccine shortages and with only a minority of children having received a fourth dose of PCV7 vaccine.[10] Furthermore a case-control study in the USA indicates there is no significant difference in effectiveness between the 2+1 and the 3+1 schedules.[98] Another option is to postpone the final dose of PCV7 to at least age 2 years, and replace it by a dose of pneumococcal polysaccharide vaccine (as these vaccines are not effective before age 2 years). Pneumococcal polysaccharide vaccines cover more serotypes (though not all the 7 serotypes from PCV7) and are currently much cheaper than the PCV7 vaccine.

These findings provide important information for PCV7 vaccine introduction in countries routinely using three doses in the infant immunization schedule and could lead to substantial cost reductions (in terms of vaccine costs, vaccine supply and administration) at no apparent loss in effectiveness.

Full details of the literature review can be found in appendix A.

1.4 ECONOMIC EVALUATIONS OF PNEUMOCOCCAL CONJUGATE VACCINATION PROGRAM OPTIONS

Abstracts of journal articles were reviewed to retrieve full economic evaluations (as defined in Drummond et al.[11]). Only the articles published between August 2002 and February 2006 were selected, because a review article of economic evaluations on the same topic up to August 2002 had already been published by the current first author, and the rapidly changing insights make the more recent analyses much more relevant than older ones.[12,13] Our search identified 15 new studies,[14-28] each of which was systematically reviewed in terms of methodology, assumptions, results and conclusions.

Given the lack of consensus between the studies' results for both the perspectives of the payer and society, it is difficult to draw solid conclusions about the cost-effectiveness of universal infant vaccination with a PCV7. It seems unlikely, however, that PCV7 vaccination will be cost saving for the health care payer (though this is not a criterion for rejection as long as its incremental cost-effectiveness is of an acceptable magnitude). A key assumption determining the economic attractiveness of universal PCV7 vaccination is the cost of the vaccine. Indeed, given its large budget impact, all studies have identified the cost of the vaccine as one of the most influential variables determining the efficiency of PCV7 vaccination. Some studies have also reported that a substantial reduction in the cost of the vaccine could bring the ICERs within an acceptable range. For example, without herd immunity impact, the price of the PCV7 would have to be reduced to a third of its current value for the ICER to be lower than the £30,000 (€44,000) per QALY

gained threshold for acceptable interventions in England and Wales.[24] Note that a previous review of PCV7 economic evaluations published before August 2002 concluded, in line with the current findings, that the attractiveness of PCV7 vaccination hinges on the potential for price reductions and the willingness for decision makers to adopt a societal perspective.[13]

Many studies have also pointed out the difficulty of assessing with much precision the efficiency of PCV7 vaccination due to uncertainties related to the current burden of pneumococcal disease, the duration of vaccine protection and the long-term effects of vaccination on the epidemiology of pneumococcal disease. Indeed, pneumococcal conjugate vaccines have the potential to decrease nasopharyngeal carriage, thereby reducing transmission of pneumococci by herd immunity in the pediatric and adult population. Such indirect protection of the population with infant pneumococcal conjugate vaccination has been observed in Northern California,[10] and the USA in general.[29,30] This could potentially also have an impact on the cost-effectiveness of the current pneumococcal vaccination strategies in adults (using PPV). However, after the introduction of the vaccination, non-vaccine serotypes may well replace vaccine serotypes, leading to a smaller reduction in disease burden over time. This raises various questions related to the potential long-term population effects.

The possible effect of herd immunity and of substitution of vaccine serotypes with non-vaccine serotypes on the cost-effectiveness of PCV7 universal vaccination was investigated by Melegaro et al.[24] As expected, their base-case cost-utility ratio (€87,913 per discounted QALY gained) decreased dramatically when indirect protection to the unvaccinated was included (€7,352 per discounted QALY gained). But the inclusion of complete serotype replacement increased substantially this ratio (€39,132 per discounted QALY gained, still substantially lower than the base-case ratio). As was noted by these authors, there is as yet little quantified information on the magnitude of herd immunity and serotype replacement effects (i.e., the extent to which replacement occurs, and the severity of disease caused by non-vaccine types as opposed to vaccine types). At least two other studies have explicitly considered the impact of herd immunity, and concluded that PCV7 vaccination in childhood would be cost-effective. McIntosh et al.[26] concluded that four doses of PCV7 at €6,394 per life-year gained would be "highly cost-effective" in the UK, whereas Beutels et al.[31] found (at A$14,645 (about € 8500) per DALY averted in the baseline) three doses of PCV7 to be of comparable or better cost-effectiveness as routine meningococcal C conjugate vaccination in Australia, for varying time spans and assumptions regarding herd immunity and serotype replacement.

At the time of finalising this report, a new economic analysis was published for the US.[32] This analysis, like the three analyses cited above, also included the herd effects that have been observed 5 years into the US program, and compared it with another US analysis that had been made before the program was introduced,[33] and which did not account for herd effects (as these were too speculative to predict at the time, and indeed it was not known yet whether PCV7 would be able to induce herd immunity effects at all). It is therefore not surprising that the updated analysis reaches a much more favourable conclusion than the previous analysis (in the basecase $US7500 (~ € 6000) per life-year gained versus $US80,000-110,000 (~ € 64000-87000) per life-year gained).

The divergences in the studies' conclusions are showing the difficulties with obtaining reliable burden of disease data. When observed herd immunity effects from the US are included, and a three dose schedule can be assumed to be similarly effective as a four dose schedule, childhood PCV7 vaccination, at the current vaccine price, is likely to be judged as relatively cost-effective to the health care payer, and potentially cost-saving to society. At the same time, it remains to be seen whether the longer term net effects on antimicrobial use and resistance, serotype replacement and cross reactivity are detrimental or beneficial to the overall cost-effectiveness of the program. It is encouraging that current evidence from the US indicates the latter.[10, 34-36, 30] This enforces the observation, that at least in the short term, the cost-effectiveness of this program is expected to be attractive. However, the review indicates that country-specific estimates (eg, incidence of VT IPD, costs of treatment, and hospitalisation rates) can be influential for the outcomes of the analysis. This is what we aim to document more elaborately for Belgium in this report.

The full economic review is available in appendix B.

2 COST-UTILITY ANALYSIS: METHODS AND DATA

2.1 METHODS AND DATA SOURCES

2.1.1 General

Data analyses and simulations were performed using MS Excel 2000, MS Access 2000, @Risk 4.5 and S-plus 6.1.

The baseline costing perspective is that of the Belgian health care payer, which includes collective payments by the Belgian health care system, as well as co-payments for health care by patients. All cost data are expressed in Euro 2005. Our primary measure of relative efficiency is direct costs per Quality-Adjusted Life-Year (QALY), though a wider range of health outcomes is presented in incremental cost-effectiveness analyses. Time preference is accounted for by discounting costs at an annual constant rate of 3%, and effects at 1.5%. These analytical choices are in line with Belgian guidelines for economic evaluation in health care. More detailed discussions on methodological issues for the economic evaluation of vaccination programs were described previously.[37-40]

The options for vaccination were selected based on global experience with PCV7, as well as with similar conjugated vaccines (Meningococcocal serogroup C conjugate vaccine and Haemophilus influenzae type b conjugate vaccine). This indicates that the effectiveness of the schedule for PCV7 is optimised by giving the first dose as early as possible (month 2) and a booster dose during the second year of life (this last aspect has been indicated as an important factor for long lasting immunity and the generation of population-wide herd immunity effects with this type of vaccine).[41] On the routine Belgian infant vaccination schedule, currently only one injection is given at months 2,3,4 and 15 (at month 12 already two injections are foreseen, and the addition of a third one could jeopardise the program for the other vaccines)

In view of the importance of herd immunity for PCV7, the experience in the USA (see below), the literature review of vaccine efficacy in appendix A as well as its current use in Belgium based on a 3+1 schedule by private vaccination, we consider the following options in our analysis:

- Option 1: PCV7 vaccination using a 2+1 schedule with injections at 2,3 and 15 months of age
- Option 2: PCV7 vaccination using a 3+1 schedule with injections at 2,3,4 and 15 months of age

Both options are compared to a situation of no vaccination, as well as incrementally to each other.

2.1.2 Mathematical model structure

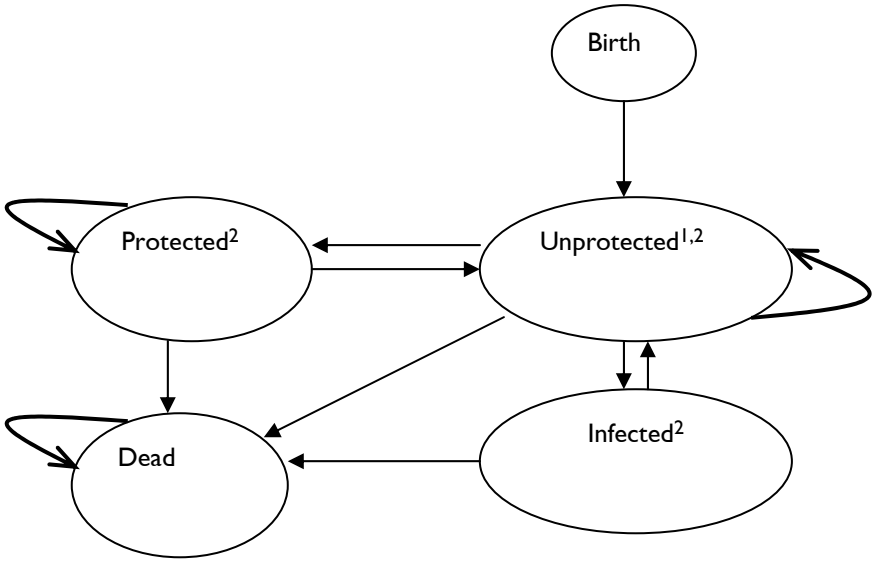
The economic analysis is by necessity based on a mathematical simulation model. We have opted for an integrated model, which combines two submodels, and can be subjected to multivariate probabilistic sensitivity analysis:

a) Static cohort model without herd immunity

An age-structured "classic" Markov model was developed in MS Excel, simulating costs and effects of pneumococcal disease and vaccination in a single closed Belgian cohort followed from birth until 100 years of age. Age-specific background mortality and life-expectancy (based on life tables from the National Institute for Statistics (NIS)) were explicitly considered.

The first 6 years of the model run in monthly cycles. The following 94 years run in annual cycles. The model is flexible in that any 1 to 4 dose schedule can be assumed over the 100 year time span, and specific in that in under 6 year olds, the timing of each dose can be focused on any month. This model is static, so it does not generate herd immunity effects, based on built-in transmission dynamics.

Figure 2: Basic structure of the static cohort model



[1] not vaccinated, or vaccinated but not (or no longer) protected
[2] Modelled in separate states (and with separate transitions from and to other states) for IPD, all-cause pneumonia and all-cause otitis media (detail not shown for clarity).

b) Static population model to assess herd immunity for PCV

Based on observations in the USA, the impact of herd immunity can be estimated (and consequences in terms of costs and effects) in a static population model (which is much like the cohort model under (a) above, modified in terms of population structure, and only assessing one year of infections over the entire population at once, instead of over an ageing cohort).

Herd immunity effects for PCV as estimated in model (b) are thus fed back as an exogenous factor into model (a), so that in fact (a) and (b) form one integrated model. This implies also that sensitivity analysis is performed on the integrated model. Scenarios of serotype replacement effects have also been built into the model, again in a static way. Note that the literature review (appendix B) revealed that no dynamic transmission model has been applied to pneumococcal conjugate vaccination yet. Only a few economic evaluations have as yet considered herd effects, all in a static way.[12,24,26,32]

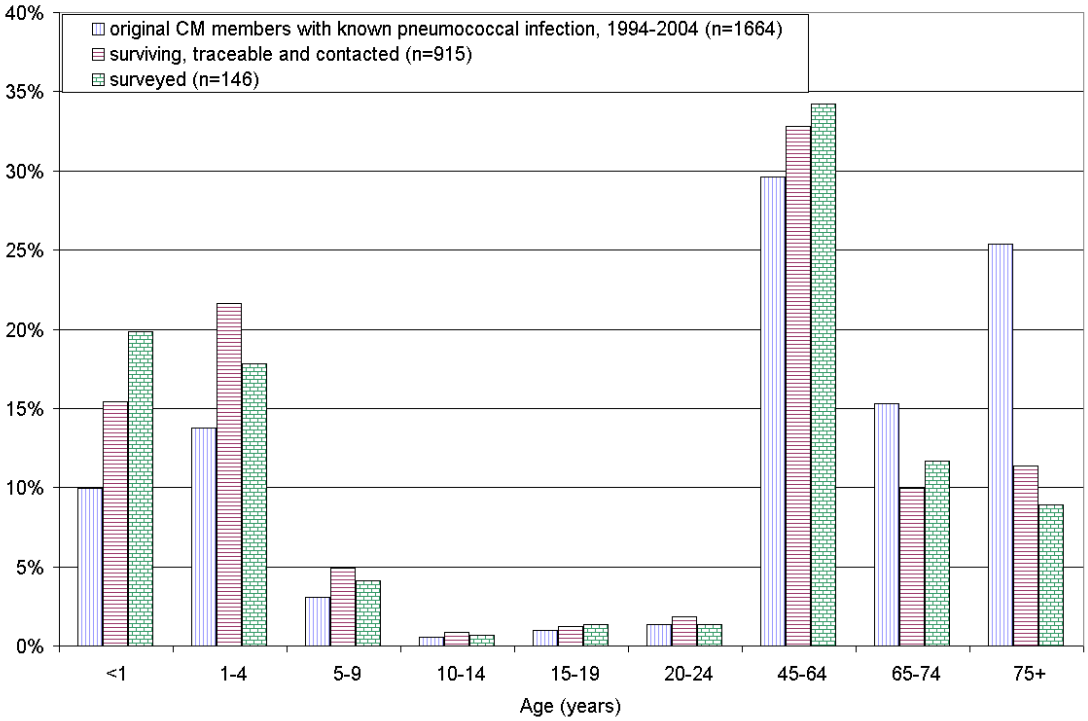
This section is organized as follows. First we describe the main Belgian data sources from which data were obtained. Second, we present data on the epidemiology of pneumococcal infections in Belgium. Third, resource use data are presented. Finally an overview is given of the input data for the simulations.

2.1.3 Databases used

We derived data from a variety of existing databases in Belgium as well as from surveys, some of which set up specifically for the purpose of this analysis.

1. The database from the National Reference Laboratory (coordinated by Prof dr Jan Verhaegen) contains all positive pneumococcal isolates referred between 1980 and 2005. These data were analysed by year, by serogroup and by age. The strength of this dataset is that it refers to all ages, and its weaknesses, for the purpose of our study, that only serogroups (as subtyping (of serotypes) is not routine practice in Belgium) are determined, and that not all positive Belgian samples are collected (it's a voluntary, and not a mandatory referring system). Furthermore from these isolates the information regarding clinical disease is incomplete (E.g., in 2003 and 2004, the clinical diagnosis of over 45% of isolates is unknown or missing). However, since source of isolation is virtually always recorded, the most likely clinical feature of these infections can be derived. A limitation regarding the interpretability of the trends in this dataset is that the number of reporting laboratories has substantially increased over time. We will therefore focus on the data referring to the last 3 years pre-vaccination (March 2001- March 2004). Note that currently the NRL is undertaking serotyping for children <5 years of age on new samples. Retrospective serotyping was impossible as part of our study due to cost and time constraints.
2. The database from the National Christian Sickness Fund ("Christelijke Mutualiteiten", CM hereafter) contains all resource use information of members of the largest sickness fund in Belgium. The membership population of CM corresponds to 43.7% of the total Belgian population. There is a slight bias in favour of the older age groups, but this should not grossly distort the estimates based on this sickness funds. In terms of socio-economic characteristics, the unemployed are slightly underrepresented (40.6% of the unemployed are members), but, again, the overall difference is relatively limited (i.e. 43.7% versus 40.6%). Inevitably, a sizable number of these have had a positive pneumococcal isolate taken and were recorded in the National Reference Laboratory dataset, under (1) above. For the purpose of our study we focus on resource use data of the CM members, who have had a positive culture taken between 1994 and 2004. This resulted in a database of resource use by cost category of 1664 people who have had a pneumococcal infection at a known point in time between 1994 and 2004. Of these, 915 surviving members were matched in terms of municipality, age, gender and social category (based on categories and regulations for reimbursement of large risks) to unrelated CM members in other aspects, and resource use was compared, showing excess costs around the time of the first positive sample (see below). In order to be able to interpret this information better, all the 915 surviving members who could be identified, were contacted with the aim of conducting an in-depth survey on a subset of them. A comprehensive face-to-face survey of medical and non-medical resource use (complemented with the actual payments from database records for these patients) was thus carried out among 146 CM members of all ages. These patients collectively suffered from all the most prevalent forms of clinical pneumococcal disease.

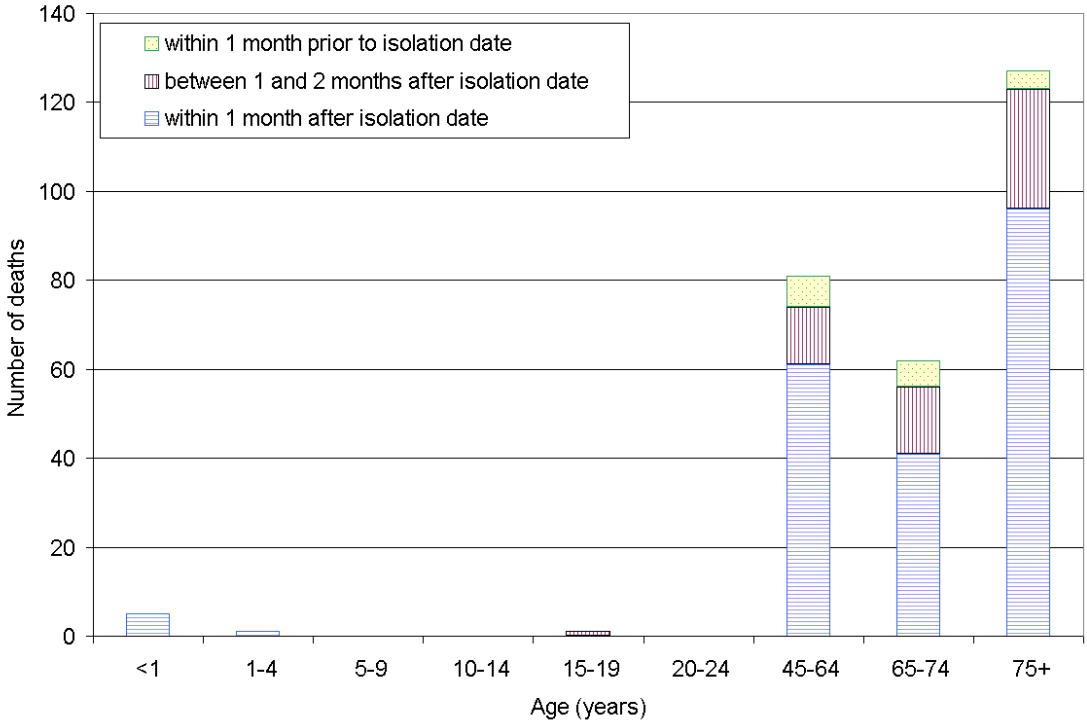
Figure 3: Age distribution of pneumococcal CM patients at different stages of analysis and data collection



The age distributions of patients at the time of diagnosis are given in figure 3 for the various stages of data analysis and surveying. Many (657, or 39.5%) of the 1664 persons in the original sample died between the time of their pneumococcal episode and 30th December 2005, often not long before or after the date of diagnosis of the isolate (see figure 4). For simplicity, the data in figure 4 were analysed by month. Of course those who have died in the month before isolation, are likely to have died only 1 or two days earlier and not 30 days. As can be seen in figures 3 and 4 only the elderly died before isolation. These data are not used to calculate case-fatality ratios, because we don't know in this dataset, which deaths are due to pneumococcus, and which due to other causes. Figure 4 merely illustrates that a significant proportion of those known to be infected with pneumococcus, died shortly after (or very shortly before) the pathogen was diagnosed from an isolate of their blood or other bodily fluids.

A full description of these selection procedures and surveying methods, which were supervised at every instance by medical advisors ("adviserende geneesheren"), is given in appendix C.

Figure 4: Age-specific number of deaths in 1664 pneumococcal CM patients (1994-2004), shortly before or after diagnosis of the isolate.



3. Raw data from a national IPD study were kindly provided by Vergison et al.[42] This database was compiled based on isolates of pneumococcus from a normally sterile body site, collected from children ≤ 59 months of age presenting to 128 pediatric hospital wards in Belgium (98.5% of all Belgian pediatric wards) between 18/03/2002 and 17/03/2003. This dataset refers to Invasive Pneumococcal Disease (IPD) cases arising over a single year pre-vaccination, based on active surveillance. It has in-depth information related to IPD cases, allowing these data to be analysed by serogroup, serotype (on 82% of patients), age, and clinical diagnosis. A limitation of this dataset for our study is that it only refers to children ≤ 5 years of age. Ideally, for the most accurate assessment of long term direct vaccine efficacy and indirect herd effects in adult age groups, this type of information would be needed over all ages.

4. National database on hospital admissions: data were obtained from the Federal Minimal Clinical Data Offices ("Federale Overheidsdienst Volksgezondheid, Minimale Klinische Gegevens (MKG)") on number of hospitalisations, average and median length of stay, and mortality by age over multiple years by ICD9-CM code (ICD 10 codes are not yet introduced in Belgian surveillance).

5. INTEGO database: data on the number of GP consultations for acute otitis media and pneumonia were obtained from the INTEGO surveillance system, which collects data from 55 GPs (in 2004), working in 47 practices, geographically spread over Flanders. To our knowledge, it is the only validated database that contains incidence data on non-hospital consultations and antibiotic prescribing for these ailments. A limiting factor is that it covers only Flanders and not Wallonia.

2.2 EPIDEMIOLOGY AND CLINICAL DATA

2.2.1 Incidence, hospitalizations, sequelae and deaths

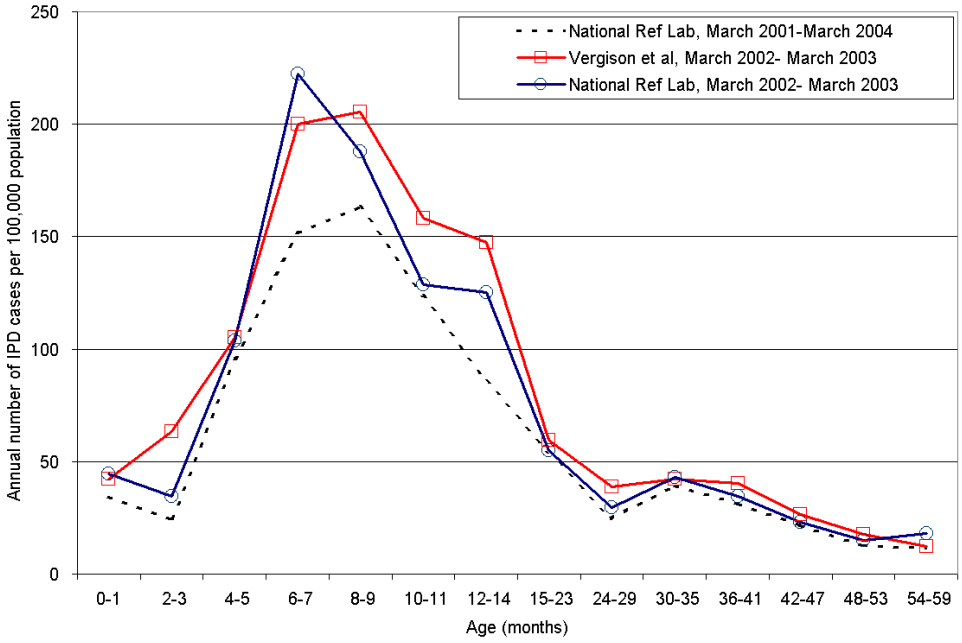
The incidence of IPD was based on the latest available Belgian data on invasive pneumococcal disease (IPD) from the National Reference Laboratory (NRL), as well as data provided by Vergison et al.[42] from their study on children < 60 months.

In order to derive estimates of the incidence of IPD from the NRL (and knowing, as outlined above, that clinical diagnosis is often missing) two general adjustments were made:

- Cultures with sources of isolation, which are unlikely associated with an invasive pneumococcal infection, were excluded. For the years 2001-2004 (the years we draw on for the cost-effectiveness analysis), the following sources of isolation were excluded (in addition to isolates for which the source was unknown (only 0.1% in 2001-2004)):"Abscess", "Bartholin glands", "pus" (general), "pus necrosis arm", "femur", "gall", "glands in neck", "nose", "eye", "ear", "middle ear", "sinus", "ulcer", "vertebral abscess", "wound fluid", "feet". Note that "femur" and "vertebral abscess" could also be considered as IPD (the medical opinions we sought to validate these exclusions, diverged on this matter). In this dataset, these categories are each related to one isolate only, and their exclusion can be considered as negligible in this analysis.
- Numbers of cases were derived from numbers of isolates. The number of isolates taken per patient with pneumococcal infection were obtained through the linkage with the CM database (1664 persons, 1994-2004). For 395 children < 60 months, 421 isolates were taken (or 1.06 per child), and for 1269 persons >59 months, 1297 isolates were taken (or 1.02 per person).

As can be seen in figure 5, and as Vergison et al.[42] also emphasise, passive surveillance yields on average a lower number of observed cases than active surveillance. However, the degree of underestimation seems to have been reduced over time, as Vergison et al.[42] reported observing twice as many cases in 2002-2003 compared to the NRL during the years 1996 – 2000 (59 versus 30 per 100,000 <5 years of age). This evolution is in accordance with the increase in the number of laboratories reporting to the NRL over time, and may partly be due to increased awareness induced by Vergison et al.[42]'s study itself. In any case, the use of the data from the NRL to infer incidence rates, constitutes a conservative approach. We use these more conservative estimates only for age groups over 5 years and only from the more recent years (2001-2004).

Figure 5: Comparison of the estimated annual age-specific incidence of Invasive Pneumococcal Disease (IPD) in children under 6 years of age from different Belgian databases



Source: National Reference Laboratory and Vergison et al.[42]

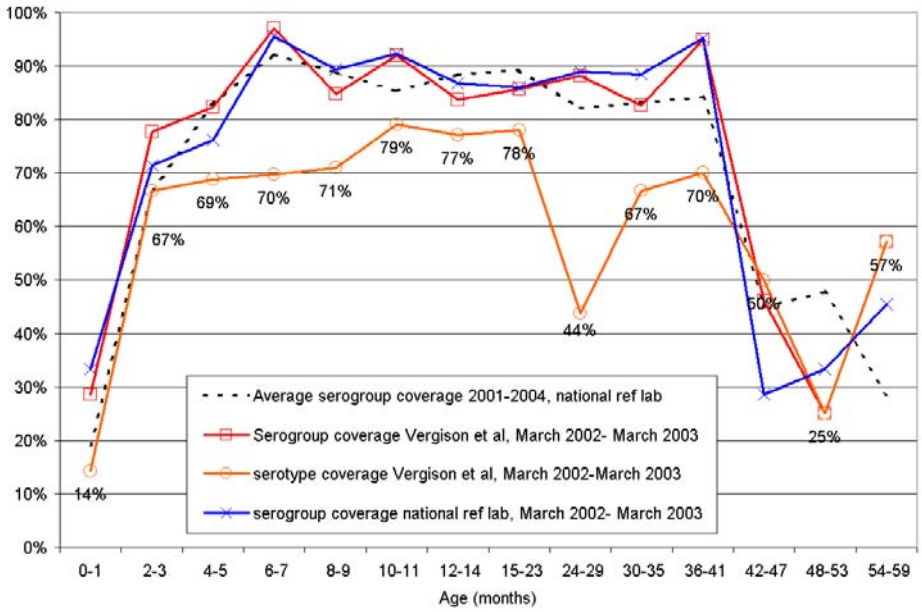
Figure 6 makes a similar comparison between estimates of the sero coverage theoretically obtainable in Belgium. It shows, for instance, that the serogroups included in PCV7 should cover close to 90% of the IPD infections in Belgian children aged 4 to 23 months.

The estimates of serotype distribution in figure 6 are all point estimates for narrow age groups over a single year, and hence uncertainty is large. However, the larger, more robust estimates from the NRL dataset (serogroup distributions accumulated over 3 years) show a similar pattern. Note that all these point estimates are varied in sensitivity analysis (according to distributions defined by the number of observations at each age).

In Vergison et al.[42], the overall PCV7 serotype coverage was 68% and 66% in <1y olds and 1-4 y olds, respectively, whereas the overall serogroup coverage was 86% and 79%, respectively. The latter two proportions are identical in the NRL dataset over the same period. Aggregated over 2001-2004, these proportions remain very similar in the NRL database, 83% and 79%, respectively.

The NRL does not undertake subtyping, and as illustrated in figure 6, the serotype coverage over the same period is substantially lower than the serogroup coverage. The average ratio of PCV7 serotype to serogroup coverage of figure 6 for ages < 5y (87%) is extrapolated to older ages, in order to derive an estimate for the serotype distribution >5y, based on the serogroup distribution recorded in the NRL database (and as shown in figure 8 below). Note that this ratio is not simply based on the comparison of the above quoted proportions, because these relate to different denominators. Indeed serotype (serogroup) coverage is calculated as the number of cases with serotype (serogroup) covered by PCV7 divided by number of cases for which serotype (serogroup) was determined. The vaccine is therefore implicitly assumed to cover those with unknown serotype (serogroup) to the same extent as those with known serotype (or serogroup), and for instance in Vergison et al.[42], serotype could not be determined in 4% of those with known serogroup.

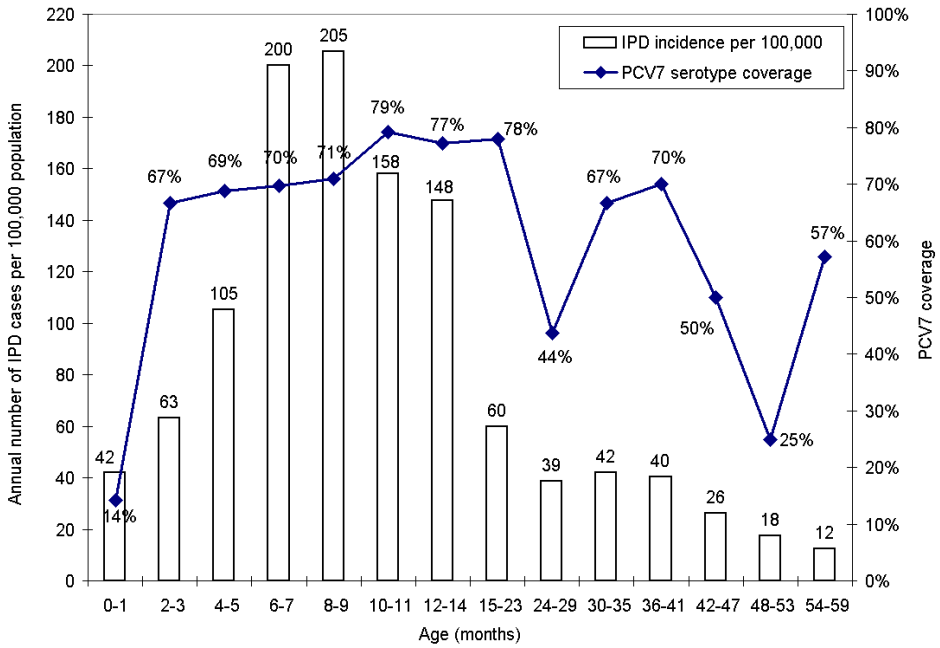
Figure 6: comparison of theoretical PCV7 serotype and serogroup coverage, derived from different Belgian sources



Source: National Reference Laboratory and Vergison et al.[42]

Figure 7 illustrates that PCV7 would cover the greatest proportion of circulating serotypes at the ages where IPD is most common amongst children.

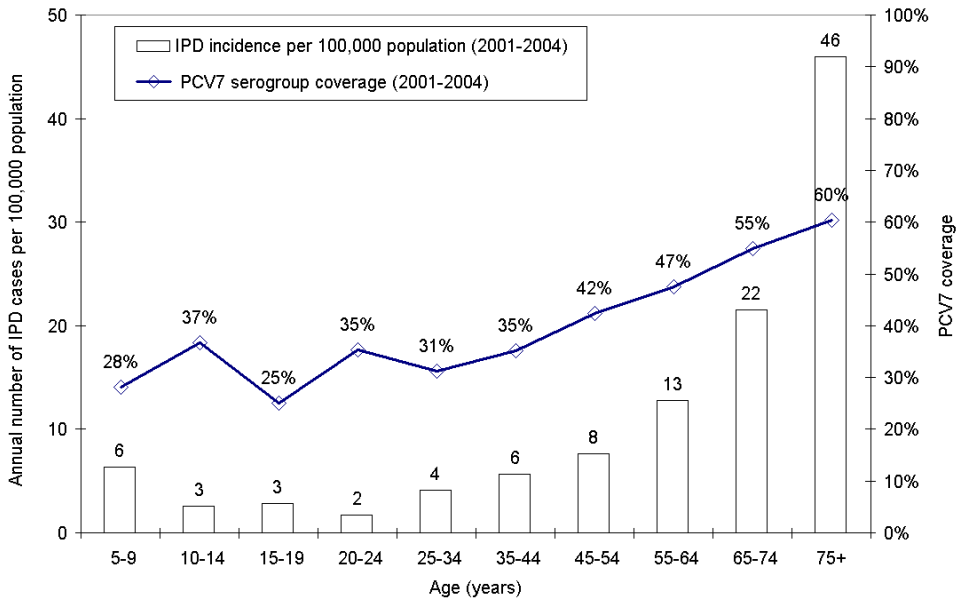
Figure 7: Annual age-specific incidence and theoretical PCV7 serotype coverage of Invasive Pneumococcal Disease (IPD) in Belgian children under 6 years of age



Source: based on Vergison et al.[42]

Figure 7 shows that, while serotype coverage with PCV7 is high for those under 2 years of age, it generally decreases with increasing age. What happens next is shown in figure 8, where serogroup coverage is shown for ages over 5 years. Serogroup coverage slowly increases from about 35% in young adults to 60% in the elderly (and corresponding estimated serotype coverage from about 30% to 50%). For the assessment of PCV7 childhood vaccination, this observation is most relevant in relation to herd immunity. Note also that there is a strong correlation between the coverage of PCV7 and the incidence of IPD in general.

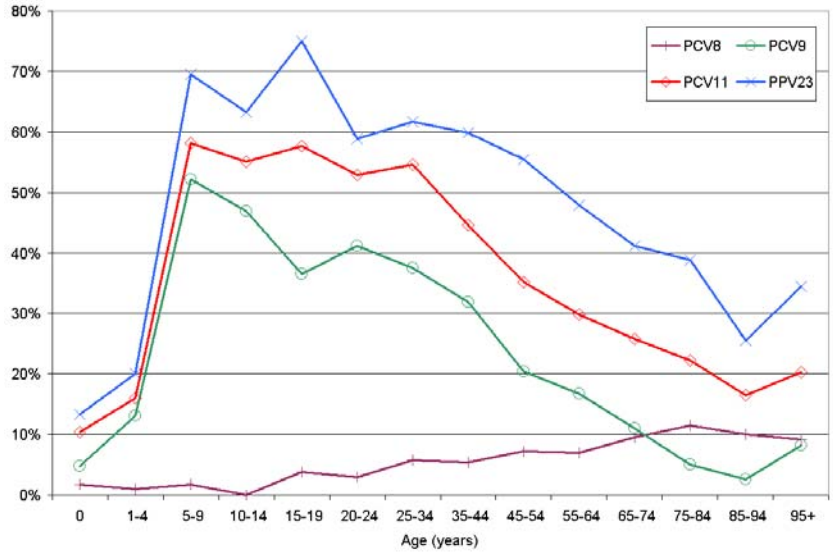
Figure 8: Annual age-specific incidence and theoretical PCV7 serogroup coverage of Invasive Pneumococcal Disease (IPD) in Belgians >5 years of age



Based on data from the National Reference Laboratory (2001-2004).

As discussed in appendix A, other vaccines against pneumococcal infections are in development, or do already exist. Figure 9 indicates what other pneumococcal conjugate vaccines, as well as the 23-valent polysaccharide vaccine (PPV23), could add over and above the protection PCV7 would offer to Belgians. PCV8 would theoretically be by far the least interesting for people under 65 (keeping in mind, though, that figure 9 shows incremental serocoverage versus PCV7). The potential of PCV11 and PCV9 vaccines seems large. At the same time, the PPV23 remains very interesting for the multitude of serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F) it covers (though it does not induce long lasting (memory –based) immunity, unless it is given as a booster after a primary series of PCV; see also appendix A).

Figure 9: Additional theoretical serogroup coverage of PCV8, PCV9, PCV11 and PPV23 versus PCV7 in Belgium (2001-2004)



Further background information on Belgian surveillance and epidemiology of pneumococcal infections is available.[43-46]

Table 1 and 2 give data on diagnosis and consequences of IPD in a study on 342 Belgian children in 2002-2003 by Vergison et al.[42]

Table 1: Clinical diagnosis and consequences of Invasive Pneumococcal Disease diagnosed in 342 Belgian children (Vergison et al.[42] 2002-2003)

	Occult bacteremia	Pneumonia	Meningitis	Pneumonia + empyema	Other	Septicemia
Number	181	84	44	18	10	5
Proportion of IPD	52.9%	24.6%	12.9%	5.3%	2.9%	1.5%
PCV7 serotype coverage	70.4%	62.0%	69.7%	28.6%	100.0%	75.0%
PCV7 serogroup coverage	91.1%	74.0%	78.4%	60.0%	100.0%	75.0%
Proportion hospitalised	95.0%	96.4%	100.0%	100.0%	100.0%	100.0%
ALOS if hospitalised	8.1	8.9	14.7	17.9	14.4	14.4
Proportion IC if hospitalised	0.6%	2.5%	56.8%	50.0%	10.0%	80.0%
ALOS in IC, if IC	1.0	5.0	6.5	11.0	2.0	13.7
Proportion complications	5.5%	13.1%	27.3%	83.3%	40.0%	20.0%
Proportion sequelae	0.0%	0.0%	25.0%	0.0%	0.0%	0.0%
Case-Fatality Ratio (CFR)	0.0%	0.0%	11.4%	0.0%	10.0%	40.0%

ALOS: Average Length of Stay (days)
IC: Intensive Care

Table 2: Age-specific clinical diagnosis of Invasive Pneumococcal Disease in 342 Belgian children (Vergison et al.[42] 2002-2003)

	Occult bacteremia	Pneumonia	Meningitis	Pneumonia + empyema	Other	Septicemia
Age (months)						
0-3	50.0%	10.0%	40.0%	0.0%	0.0%	0.0%
4-11	58.3%	15.7%	17.3%	2.4%	3.9%	2.4%
12-14	61.9%	19.0%	11.9%	2.4%	4.8%	0.0%
15-59	46.4%	35.3%	5.9%	9.2%	2.0%	1.3%
Age (years)						
<1	57.1%	15.0%	20.4%	2.0%	3.4%	2.0%
1-4	49.7%	31.8%	7.2%	7.7%	2.6%	1.0%
overall	52.9%	24.6%	12.9%	5.3%	2.9%	1.5%

From the CM database, 146 patients, whose records are also in the NRL database, were surveyed. These (former) patients can be categorized according to source of isolation in the NRL database, and clinical diagnosis based on their records and interview, as shown in table 3.

Table 3: Clinical diagnosis (based on CM survey) in relation to source of isolation (as recorded in National Reference Laboratory database) for the same persons

	Source of isolation				
Clinical diagnosis	Blood	Cerebrospinal fluid	Pleural fluid	Middle ear fluid	Total
Meningitis	1 (1%)	19 (100%)	0	0	20 (14%)
Bacteremia/ septicemia	30 (29%)	0	0	0	30 (21%)
Pneumonia	67 (65%)	0	4 (100%)	0	71 (49%)
Otitis media	2 (2%)	0	0	20 (100%)	22 (15%)
Other	3 (3%)	0	0	0	3 (2%)
Total	103 (100%)	19 (100%)	4 (100%)	20 (100%)	146 (100%)

Table 3 shows that all but one of the main four sources of IPD isolates are perfectly predictive of actual clinical diagnosis. For blood isolates the distribution of clinical diagnosis, based on the data from NRL and CM, is used in order to assign these specific clinical diagnostic categories to IPD incidence rates ≥60 months of age in the NRL dataset. The results of these distributions is given in table 4. For children <60 months of age, the clinical diagnoses in tables 1 and 2 apply (as do the proportions leading to deaths shown in table 5). Note though that for these young children the proportion of meningitis in table 4 (NRL) corresponds well with those in tables 1 and 2 (based on Vergison et al.[42]). However, there is poor correspondence between the bacteremia and pneumonia proportions, separately. An unambiguous single diagnostic category may often be difficult to define for these patients.

Table 4: Clinical diagnoses of IPD cases based on source of isolation for incidence estimates in the National Laboratory Database (2001-2004)

Age (years)	meningitis	Bacteremia/ septicemia	pneumonia	other
0	18.3%	24.3%	54.4%	3.0%
1-4	7.0%	27.3%	62.8%	2.9%
5-9	9.5%	25.1%	61.2%	4.2%
10-19	8.9%	25.8%	61.7%	3.6%
20-24	9.8%	26.1%	58.4%	5.6%
25-44	6.7%	27.2%	61.7%	4.3%
45-64	6.8%	27.1%	62.5%	3.5%
65-74	3.5%	28.1%	65.2%	3.1%
75+	2.6%	28.6%	65.2%	3.6%

Table 5: Age-specific highly severe consequences of Invasive Pneumococcal Disease diagnosed in 342 Belgian children (Vergison et al.[42], 2002-2003)

Age (months)	Complications	Sequelae	Deaths	Total
0-3	15.0%	5.0%	5.0%	25.0%
4-11	14.2%	7.1%	2.4%	23.6%
12-14	9.5%	2.4%	2.4%	14.3%
15-59	18.3%	0.0%	2.0%	20.3%

Table 6: Annual hospitalisation rate per 100,000 population (2001-2004) based on the National Minimal Clinical Data Set ("Minimaal Klinische Gegevens" (MKG))

Age (years)	Pneumococcal meningitis	Pneumococcal septicaemia	All-cause pneumonia	Pneumococcal pneumonia (% of all-cause pneumonia)	Acute Otitis Media (AOM)
<1	33.1	45.7	1,161	83.1 (7.2%)	339
1-4	2.9	14.3	912	75.6 (8.3%)	230
5-9	0.9	1.8	211	20.8 (9.9%)	75
10-14	0.4	0.6	63	6.4 (10.3%)	11
15-19	0.3	0.5	47	6.8 (14.3%)	3
20-24	0.5	0.4	43	4.1 (9.7%)	2
25-44	0.4	0.9	67	9.8 (14.7%)	2
45-64	0.9	1.9	145	17.4 (11.9%)	1
65-74	1.3	5.0	413	40.9 (9.9%)	2
75+	1.0	10.3	1,362	95.7 (7.0%)	1

Based on MKG, with following ICD-9 CM codes in first diagnostic field:
Pneumococcal meningitis: 320.1
Pneumococcal septicaemia: 038.2
Pneumococcal pneumonia: 481
All cause pneumonia: 481+ 482.9 + 485 + 486
Acute otitis media: 38100+38101+38102+38103+38104+38105+38151+38200+38201+38202

The annual hospitalisation and death rates recorded in the national MKG database are shown in tables 6 and 7. Note that MKG notifications in the category "pneumococcal septicemia" contain hospitalizations for occult bacteremia too, while in Vergison et al.[42] (table 1), occult bacteremia

(CFR: 0%) was reported separately from septicemia (CFR: 40%), giving an overall CFR of 1.1% in all bacteremia and septicemia combined. There were two septicemia deaths in Vergison et al.[42]'s study, one aged <1y and one aged 1-4y (while no death 1-4y was recorded for septicemia in the MKG between 2001-2004, a period overlapping with that of the Vergison study). In view of this, the case-fatalities for meningitis and "septicaemia" <60 months of age seem to correspond reasonably well to those observed in Vergison et al.[42]. Nonetheless, as for all the other IPD related data, the baseline model input data on case-fatality for < 60 month old children is derived from Vergison et al.[42]. Furthermore, as for all input data, confidence intervals generated for proportions in the model are derived from the original study numbers.

Table 7: Fatalities proportionate to hospitalised cases, of the same category (case*-fatality ratio) (MKG, 2001-2004)

Age (years)	Pneumococcal meningitis	Pneumococcal septicemia	All-cause pneumonia	Pneumococcal pneumonia
<1	6.6%	1.0%	0.04%	0.04%
1-4	11.3%	0.0%	0.00%	0.01%
5-9	4.5%	2.3%	0.02%	0.02%
10-14	0.0%	0.0%	0.13%	0.00%
15-19	12.5%	0.0%	0.00%	0.00%
20-24	7.7%	0.0%	0.18%	0.00%
25-44	6.1%	12.5%	0.30%	0.21%
45-64	10.3%	17.9%	1.38%	0.46%
65-74	17.6%	15.9%	2.43%	0.85%
75+	31.3%	27.1%	4.78%	1.16%

Based on MKG, with following ICD-9 codes in first diagnostic field:
Pneumococcal meningitis: 320.1
Pneumococcal septicaemia: 038.2
Pneumococcal pneumonia: 481
All cause pneumonia: 481+ 482.9 + 485 + 486
* note that all meningitis and septicaemia cases can be assumed to be hospitalised (see also in table 5), but not all pneumonia cases.

Reliable estimates of the incidence of AOM and pneumonia, specifically caused by pneumococcus, are not available in Belgium. The category "pneumococcal pneumonia" in the MKG (in table 6) is likely to be substantially underestimated, and the proportion of pneumonia hospitalisations caused by pneumococcus infection, as shown in table 6, serves only as an approximate estimated minimum, which is used to support assumptions regarding herd immunity analysis (see below).

Furthermore the incidence of all-cause pneumonia cases and hospital admissions, with diagnosis confirmed by a positive film (another specific diagnosis of pneumonia to link to the vaccine efficacy in the only trial that investigated protective efficacy versus pneumonia; see appendix A) is not available. Therefore, in order to estimate the impact of PCV on the disease burden of pneumonia in Belgium:

- Pneumonia cases associated with IPD (i.e. 30% of IPD cases <5 years, and 65% of the patients with positive blood isolates > 5 years, see tables 1 and 3) will be assumed to undergo the same reduction as the other forms of IPD under the influence of the vaccine. This assumption is supported by the review of the clinical trials data (see appendix A). In view of their severity, these cases of pneumonia are likely not seen by a GP first (indeed in Vergison et al.[42], 97% of these cases were admitted upon presentation at a pediatric ward).
- Other community acquired pneumonia (CAP) cases are estimated based on the frequency of unique GP diagnosis per patient in the INTEGO database (as shown in table 8). The impact of the vaccine on these cases is based on the protective efficacy observed in the NCKP trial (6% ITT, 4% PP, see appendix A) for all-cause pneumonia (clinical diagnosis not defined). This efficacy estimate is closest related to the available Belgian incidence data through INTEGO.

In sum, in view of the limitations of available epidemiological data, the basic underlying assumption that we need to make in our analysis is that there is no overlap between

- IPD (with pneumonia) cases reported to the NRL and Vergison et al.[42] by labs and pediatricians, and
- CAP incidence observed by GPs only (assumed to be all-cause pneumonia without IPD).

To the first incidence estimates, VT-corrected vaccine efficacy versus IPD applies, and to the second VE versus all-cause pneumonia (without standardised diagnosis). None of the other VE measures against pneumonia from the trials seems to apply to Belgian data.

Table 8: Incidence of all cause acute otitis media (AOM) and all cause pneumonia* per 100,000 population, based on INTEGO (2004)

Age (years)	AOM	All-cause pneumonia
0-4	13,563	1,557
5-14	4,363	208
15-24	1,194	156
25-44	733	267
45-64	668	361
65-74	468	690
75+	135	1,053

*Based on non-standardised clinical diagnosis (i.e. confirmation by X-ray is not standard, and it is not known by which frequency it occurs for this diagnosis in INTEGO, or Belgium in general)

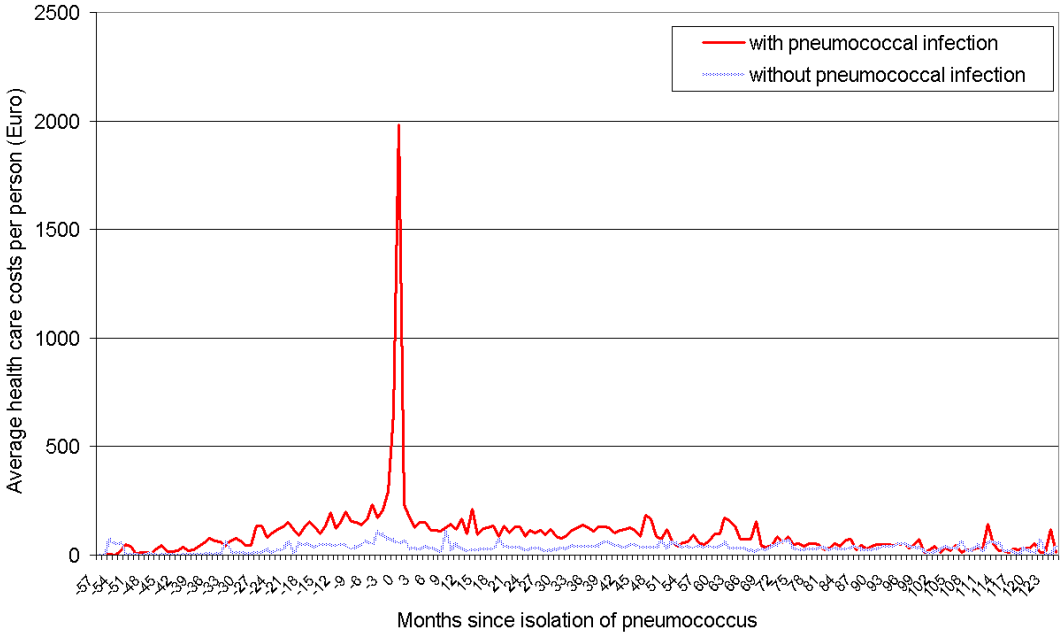
Finally the incidence of AOM is also based on the INTEGO database (cf. table 8), and the impact of the vaccine is matched accordingly using the main observations from the trials (8% in the baseline, see appendix A).

2.2.2 Costs associated with pneumococcal infections

2.2.2.1 General background

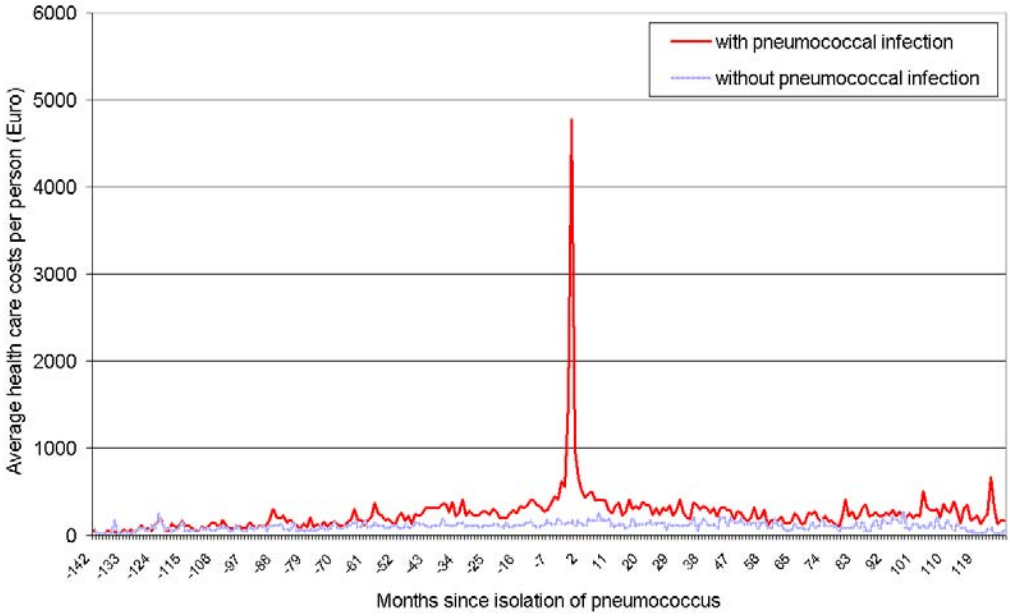
As described above, the link between the CM database of resource use with the National Reference Laboratory database of positive pneumococcal isolates, resulted in a database of 1664 people who have had a pneumococcal infection at a known point in time between 1994 and 2004. Of these, 915 surviving members were matched in terms of municipality, age, gender and social category (based on categories and regulations for reimbursement of large risks) to CM members unrelated in other aspects. Their health care resource use (from any cause) was compared as a function of time to and since isolation. These data are given in figures 10 and 11, for patients <60 months and patients ≥ 60 months of age at the time of isolation, respectively.

Figure 10: Average health care costs per person (< 60 months) with and without pneumococcal infection



Figures 10 and 11 show that there is an average cost difference during the month of isolation (month 0) of €1926 and € 4615 per person under and over 60 months of age at the time of isolation, respectively.

Figure 11: Average health care costs per person (≥ 60 months of age at time of isolation) with and without pneumococcal infection



Let Y(t) be the average costs per patient with pneumococcal infection, an Z(t) the average costs per patient without pneumococcal infection. Assuming that

$$\begin{aligned} Y(t) &= g_I(t) + \varepsilon_I(t) \\ Z(t) &= g_{NI}(t) + \varepsilon_{NJ}(t) \end{aligned} \quad (1)$$

with g(t) the true average cost and ε(t) a random error with expected value

$$\begin{aligned} E(\varepsilon_I(t)) &= 0 \\ E(\varepsilon_{NJ}(t)) &= 0 \end{aligned} \quad (2)$$

We wish to test the null hypothesis that the average cost in the two groups (infected and non infected) is equal at each time point t

$$H_0 : g_I(t) = g_{NI}(t) \quad (3)$$

Let X(t) be the difference in average cost, i.e.,

$$X(t) = Y(t) - Z(t) \quad (4)$$

Equivalently, we can define X(t) as

$$X(t) = g(t) + \varepsilon(t) \quad (5)$$

with

$$\begin{aligned} g(t) &= g_I(t) - g_{NI}(t) \\ \varepsilon(t) &= \varepsilon_I(t) - \varepsilon_{NI}(t) \end{aligned} \quad (6)$$

Under the null hypothesis

$$H_0 : g(t) \equiv 0 \quad (7)$$

Under the alternative g(t) is not equal to zero, i.e.,

$$H_1 : g(t) \neq 0 \quad (8)$$

The test statistic can be expressed as

$$F = \frac{RSS_0 - RSS_1}{RSS_1} \quad (9)$$

RSS_0 is the sum of squares under the null,

$$RSS_0 = \sum X^2(t) \quad (10)$$

and RSS_1 is the sum of squares under the alternative

$$RSS_1 = \sum \left(X(t) - \hat{g}(t)\right)^2 \quad (11)$$

Given the large cost differences during the month of isolation, it is not surprising that the overall difference in costs between persons with and without positive pneumococcal isolates, was found to be highly significant (p=0), by age. The difference in costs over time, with point wise 95% confidence intervals, is plotted in figures 12 and 13. Note that in figures 12 and 13, the first month of observation (57 months prior to isolation date for children under 60 month old at isolation date, and 141 months prior to isolation date for persons over 60 month old at isolation date) has been redefined as month 0. There are 183 and 271 months of observations for persons < 60m and persons ≥60 months of age, respectively. In figures 12 and 13 , the modeled average difference between the two groups over time (X(t)) is determined by the point at time t, as well as the surrounding points (selected based on optimal bandwidth), and not only by the difference at the time of isolation. This implies that the modeled average difference in figures 12 and 13 is

conceptually not comparable with the observed difference estimates during the month of isolation, month 0 (€1926 and € 4615 per person under and over 60 months, respectively).

It is remarkable that for both age groups, the difference in costs is significantly greater than zero, for a long period before the pneumococcal infection occurs. In children the difference is significantly greater than zero on average from about 3.5 years before infection. Indeed, the children who end up with a positive pneumoccocal isolate, on average consume € 62 more per month in health care resources than their uninfected counterparts. Furthermore, these patients remain more costly for a long time after their pneumococcal episode. Eventually, the average cost difference decreases to the same level for infected and non-infected people alike (on average from about six years after infection).

Figure 12: Loess model for the difference in average costs per patient <60 months of age and 95% point wise confidence interval based on nonparametric bootstrapping

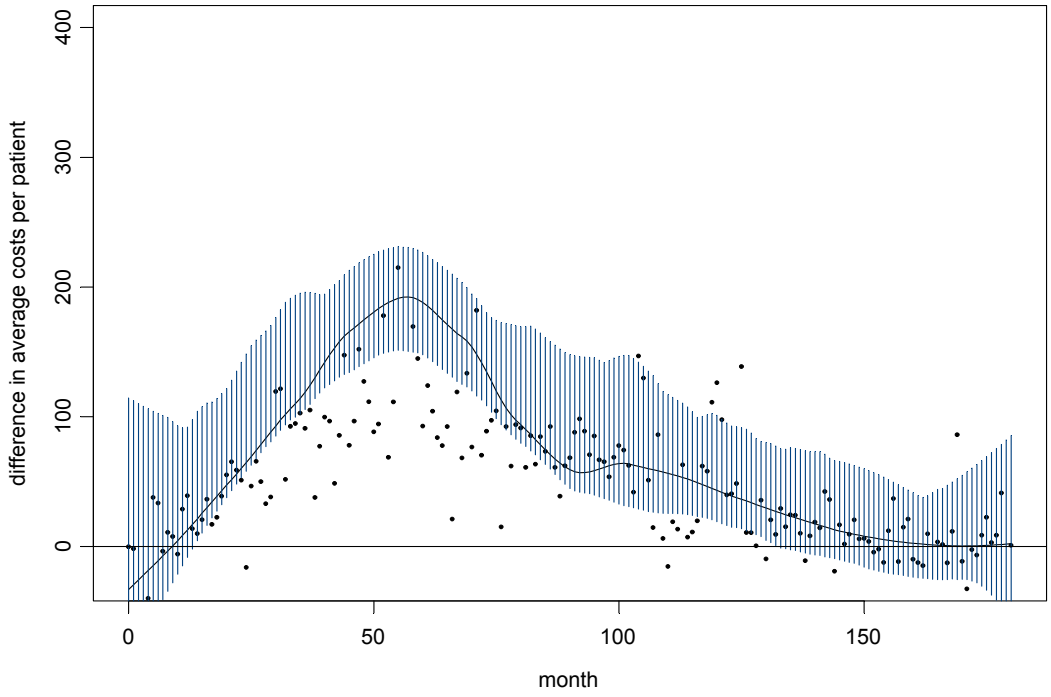
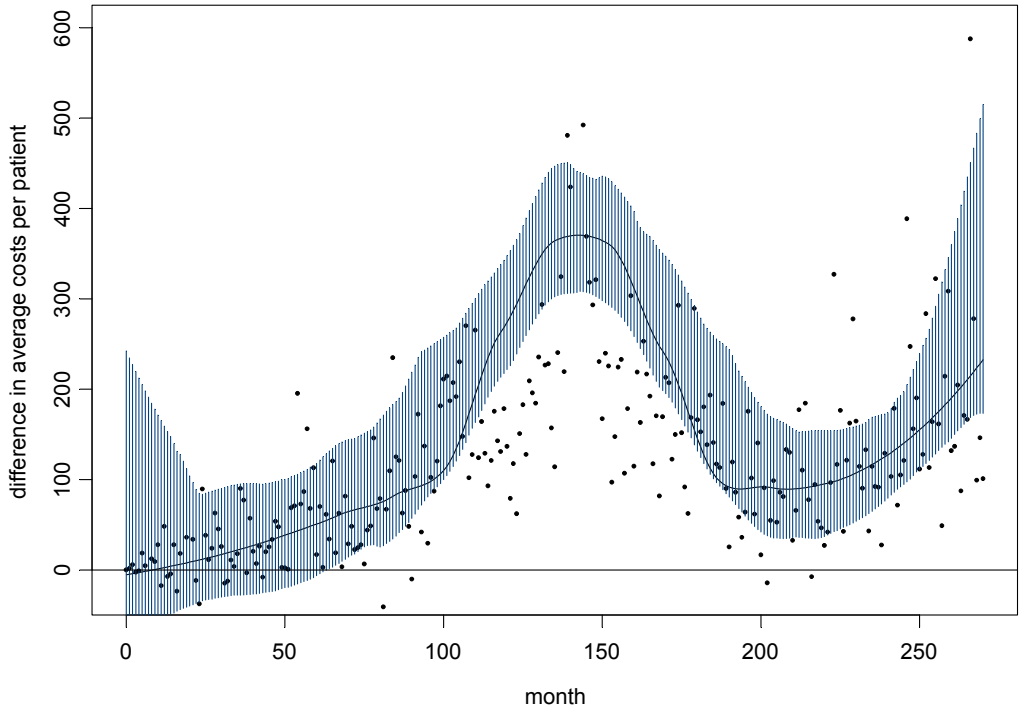


Figure 13 shows the cost difference over time for the older patients. Here too, it can be observed that the difference in costs is significant for a long period before the infected group were infected with pneumococcus (on average about 6.5 years). In contrast to the age group under 60 months of age, the older age group incurs significantly more health care costs for the entire time span of observations (up to 12 years after the isolation date).

These data suggest that people who incur an IPD episode, are on average more costly to the health care system (and presumably sicker) than similar people who do not incur an IPD episode, long before and after the IPD episode occurs. While children who have cleared an IPD episode, eventually return to the same level of "background" health care costs (and presumably associated background morbidity) as their same-age counterparts without IPD, this is not the case for persons over 5 years of age at the time of isolation. On average, these remain more costly for at least 12 years after their IPD episode.

Figure 13: Loess model for the difference in average costs per patient ≥60 months of age and 95% point wise confidence interval based on nonparametric bootstrapping



Note that a fundamental problem of these data remains that health care costs that are attributable to pneumococcal infections cannot be discerned from other health care costs, despite the knowledge of the time at which pneumococcal disease was diagnosed. However, obvious concerns over a very small group of patients causing most of these costs could be excluded based on the individual variation in the cost data at the time of diagnosis.

Therefore we can only tentatively infer in general terms the following from this general data set of 915 surviving patients:

- People who acquire serious pneumococcal infections, warranting at least diagnosis by positive isolate (these are not necessarily, but nonetheless predominantly, cases of invasive pneumococcal disease), on average are in poorer health than people who do not. Their health status is poorer than average both long before and long after their episode of pneumococcal infection. However, they generally overcome their inferior overall health status after clearing the pneumococcal infection, if they are aged less than 5 years at the time of infection. The implicit assumption that has been made in all cost-effectiveness analyses hitherto (see appendix B), namely, children with IPD have identical life-expectancy as same-age children in general, can therefore be sustained in our cost-effectiveness analysis, based on these data.
- It is likely that an IPD infection further weakens children who already have an overall weaker health status, and delays the time to recovery to the same background morbidity level as their same-age counterparts, who did not get IPD. In this respect, the approach to costing cases of IPD that is based on the pneumococcal infection costs only, may be conservative vis-a-vis the average total costs of infection.
- Older adults who acquire pneumococcal infection (usually IPD in this dataset) are not only in worse health than average before acquiring infection, but also have worse health expectations than same-age adults after their episode. While it is clear that these pneumococcus survivors will continue to consume more health care resources after their episode, it cannot be inferred from these data whether this consumption is a consequence of the IPD episode itself (which could be indirectly prevented by vaccination of children) or their overall inferior health state, which already existed before their episode (and cannot be prevented by vaccination). At the same time, their age-specific quality-adjusted life-expectancy can be expected to be lower than average. We will therefore test in sensitivity analysis the influence of a reduced quality-adjusted life-expectancy in IPD infected elderly versus non-IPD infected elderly on the overall cost-effectiveness of the program. In the baseline we will assume, like every other previous economic analysis on this subject, that life-expectancy for this group too is equal to average. This will make the comparison with decisions over other health care interventions, for which such more complex aspects are typically ignored, fairer. Furthermore, in doing so, a counterbalance is provided versus the increased costs of non-IPD health care, of which we cannot determine whether or not these arose out of a causal relation with the IPD episode.

In sum, though the basic analysis of the overall health care costs for pneumococcal versus non-pneumococcal patients reveals interesting background information, due to a lack of specific information on costs attributable to pneumococcal infections for all these patients, this information will not be used in what follows, i.e. the baseline cost-effectiveness analysis.

2.2.2.2 Costs specifically attributable to pneumococcal infections

To gain insights in costs that are attributable to pneumococcal infections, an intensive national face-to-face survey was carried out. As outlined above, surviving CM members with known pneumococcus isolation date (a total of 915) were contacted by telephone on a regional basis. Priority was given to the more specific likely clinical diagnoses (i.e. based on isolation source, in sequence: cerebrospinal fluid, blood, middle ear & pleural fluid, and others). Each regional surveyor was asked to respect this sequence at selection, and strive for balance in clinical diagnosis (eg, avoiding collecting uniquely information from those with "blood" as isolation source). The survey questionnaires used are in appendix C.

The 146 face-to-face interviews related to 55 children with an average age of 1.4 years at the time of diagnosis, and 91 adults with an average age of 54 years at the time of diagnosis. With an average duration of about 50 minutes (range 20 minutes to well over an hour) these interviews

were very labour intensive. The health care costs were based on actual expenditures of the CM sickness funds, which were identified as related to the patients' episode during the interview. The average direct costs are summarised in table 9 per disease category (see also table 3), distinguishing between health care and non-health care costs by age and payer. Additionally, for direct health care costs of conditions requiring an hospitalisation, the proportion of hospitalisation costs are given along with the rounded average length of stay in days (ALOS) in brackets.

Table 9: Average direct costs for disease caused by pneumococcus among 146 patients

	Direct health care costs (EURO)				Direct non-health care costs (EURO)			
	National Health System (a)		Personal (b)		National Health System (c)		Personal (d)	
	≤ 5 y	> 5 y	≤ 5 y	> 5 y	≤ 5 y	> 5 y	≤ 5 y	> 5 y
Meningitis	8085 (78%, 15)	7980 (89%, 20)	1267 (54%, 15)	680 (78%, 20)	6177	0	725	429
Bacteremia/ septicaemia	2383 (96%, 9)	6903 (91%, 20)	352 (90%, 9)	685 (75%, 20)	0	0	80	175
Hospitalised pneumonia	3712 (86%, 9)	5365 (89%, 16)	879 (56%, 9)	899 (75%, 16)	0	97	183	262
Non-hospitalised pneumonia	713	713	304	304	0	0	15	15
Non hospitalised OM without complications	58	58	22	22	0	0	0	0
Non hospitalised OM with complications	501	79	353	51	0	0	34	0
OM hospitalised	3072 (78%, 3)	3426 (86%, 9)	625 (50%, 3)	383 (65%, 9)	0	0	321	185
Other	3204 (97%, 7)	2299 (88%, 8)	256 (84%, 7)	355 (79%, 8)	0	0	64	64

For hospitalised cases the proportion of direct health care cost incurred in hospital is given in brackets along with the rounded average length of stay

(a) Direct health care costs for RIZIV/INAMI. These costs arose for the following categories: GP consultations, specialist consultations (paediatrics, internal medicine, neurology, Ortolaringo, other), physiotherapy, logopedist, other health care professions), Technical procedures (blood tests, X-rays), Medication (mainly antibiotics and painkillers), Care products (ointments, disinfectants), Technical physical aids (prothese, hearing aid, wheel chair), nursing (home care)

(b) Direct health care costs paid by patients and their family. The same categories as under (a) gave rise to these costs.

(c) Direct non-health care costs for RIZIV/INAMI. These costs arose for the category of revalidation only

(d) Direct non- health care costs paid by patients and their family. In this survey these costs were non-zero for the following categories: transport, revalidation, special nutrition, professional household help, additional aids to increase the comforts of living at home (elevator, walking bridge, refurbishment of bathroom)

In the baseline analysis direct health care costs arising to both the health care system and individuals are considered under the health care payer's perspective. These direct costs were directly quantifiable from the CM records. Direct non-health care costs are ignored in the baseline analysis. It could be argued that part of these direct costs are implicitly included in the QALY loss estimates (see below), and these costs are relatively rare and therefore likely less representative in this survey. The impact of including these non-health care costs is explored in sensitivity analysis. Similar problems arise when trying to estimate the future costs of long term care, on the basis of the survey. Therefore, in addition to the short term direct health care costs (based on records and interview), direct costs of long term sequelae are considered, based on estimated average costs of € 1000 for hearing aids (and replacement every 7 years), as well as costs of long term care for severe sequelae (due to meningitis), estimated at € 35,000 per year.[47] The database provided by Vergison et al.[42] denoted 25% sequelae, and 27.3% complications (see table 5). However, complications and sequelae were not unambiguously recorded (for some conditions, complications were not easily distinguishable from sequelae). In the baseline, long term sequelae were therefore estimated based on Melegaro et al (i.e., of meningitis cases, 16% would develop severe hearing deficits, and 14% neurological sequelae). These assumptions are tested in sensitivity analyses.

To reflect variability in the data, distributions were fitted to the individual cost data, of which table 9 only shows the average. Goodness of fit and subsequent selection of cost distributions was based on both the Anderson-Darling and Kolmogorov-Smirnov Statistics. As could be expected, all these cost distributions are skewed (long-tailed).

Additionally, table 9 shows, unsurprisingly, that for hospitalised cases, the majority of direct health care costs are hospital costs. Table 10 lists the most recent national data on ALOS for many of these conditions. In view of the importance of the age-specific contribution of hospitalisation costs in the direct health care costs, the distributions fitted to the costs for hospitalised conditions in table 9 were adjusted based on the average length of stay of these conditions in table 10. That is, the costs in table 9 were weighed according to proportionate hospital costs and the ratio of length of stay between tables 9 and 10 to reflect more accurately age-specific length of stay and cost differences for the age groups in table 10.

Table 10: Average Length of Stay (days) for hospital admissions (2004)

Age (years)	Pneumococcal meningitis	Pneumococcal septicemia	Pneumococca pneumonia	Other (a) pneumonia	acute otitis media
<1	14.6	7.7	5.8	5.6	2.7
1-4	11.5	6.3	5.5	5.2	1.5
5-9	10.0	7.8	6.3	5.4	0.6
10-14	11.0	9.3	7.5	6.0	0.9
15-19	11.5	7.3	6.9	7.1	0.4
20-24	11.5	18.0	6.1	5.9	1.3
25-44	21.0	10.3	9.4	7.1	1.0
45-64	15.4	11.5	13.1	10.3	2.5
65-74	15.1	16.2	15.5	13.3	4.9
75+	22.7	22.5	17.5	16.0	9.5

Source: MKG
(a): non-pneumococcal pneumonia

2.2.2.3 Health-related Quality of Life impact

Due to time constraints there was no opportunity to survey the health-related quality of life impact of pneumococcal disease states in Belgium. Estimates from the literature are used in this analysis. In the baseline, the same estimates as those used by Melegaro et al.[24] in the UK are applied in our analysis. Additionally in sensitivity analysis, the estimates by Salo et al.[28] from Finland (some of which overlap with those of Melegaro et al[24]) are applied. The estimated QALY losses are given in table 11. Note that a study for pneumococcal disease in children in the USA,[48]

found values which were orders of magnitude greater than reported in the studies in table 11, but was criticised for methodological shortcomings.[12]

Table 11: Losses in Health-related Quality-Adjusted Life-Years (QALYs) for health states related to pneumococcal disease

	Melegaro et al	Salo et al
Bacteremia:	0.0079 per case	0.006 per case
meningitis:	14% severe bilateral hearing loss at 0.460 QALY loss per case in the first year + 0.2 QALY loss for every later year	31% any deafness at 0.216 QALY loss per case in the first year + 0.054 QALY loss for every later year
Pneumonia outpatient: pneumonia inpatient:	0.004 per case 0.006 per case	0.004 per case 0.006 per case
AOM	0.005 per episode	0.005 per episode

As an additional form of structural uncertainty analysis, the results are also shown in sensitivity analysis in the form of costs per DALYs averted, based on Australian estimates of DALY weights (see Butler et al.[23]).

In multivariate sensitivity analyses, these estimated QALY losses are given simple triangular distributions.

2.3 INTERVENTION COSTS AND VACCINE UPTAKE

The marginal intervention costs consist of the purchasing costs as well as the marginal administration costs of the vaccine. The current ex-factory price per dose of the only PCV7 vaccine on the Belgian market (Prevenar®) is € 52.79. For this public program we can assume bulk purchase, and use a baseline price of € 45 per dose, which is similar to what we know of the negotiated prices in countries, which already have a publicly funded PCV7 program.

Depending on the vaccination schedule and the opportunity of adding a new injection at an existing visit, marginal administration costs will vary. Since the current infant immunization schedule has the possibility of adding another injection at months 2,3,4 and 15 it can be argued that there is no additional financial payment required to include this new vaccine. However, in order to value the additional time vaccinators will need to take to explain and make the injection, it is assumed in the baseline that the marginal costs of administration are € 5 per dose. In addition to these variable costs per dose, the model allows for inclusion of fixed administration costs (eg, for training or promotion campaigns), but assumes in all the analyses (baseline and sensitivity) that this cost is 0.

As this vaccine was found to be very safe in the review in appendix A, no costs are assigned to adverse events from vaccination.

The baseline overall costs of vaccination can also be seen as incorporating all the items discussed in this section. That is, € 50 per dose can be interpreted as covering purchase, administration and adverse events per dose administered. Changes to the assumed baseline vaccination costs are discussed in sensitivity and threshold analyses.

Vaccine uptake (or coverage) estimates are based on current uptake figures in Belgium and is estimated at 98%, 98%, 97.5% and 92.5% for injections at 2,3,4 and 15 months of age.[49] and Swennen, Vaxinfo 2005.

2.4 VACCINE EFFECTIVENESS

An extensive overview of the published literature related to the immunogenicity, safety, protective efficacy and effectiveness of PCV vaccines is given in appendix A.

Table 12 summarises the assumed vaccine efficacy estimates, based on Intention to Treat Analyses in Randomised Controlled Trials that are used in the baseline and sensitivity analyses of

this report. As explained above, vaccine efficacy was chosen for these definitions of outcomes, because these are most closely related to the available Belgian surveillance data.

Table 12: Protective vaccine efficacy estimates from Randomised Clinical Trials, used for the economic analysis

	Vaccine efficacy (95% CI)		
	VT IPD (a)	CAP (b)	AOM (c)
Cochrane reviews	88% (73%-94%)	NA	8.2% (1.2%-14.6%)
NCKP trial	93.9% (79.6%-98.5%)	6% (-1.5%-11.0%)	6% (-4%-16%)

a) Invasive Pneumococcal Disease (IPD) caused by Vaccine serotypes (VT)
b) Community Acquired Pneumonia (CAP)
c) Acute Otitis Media (AOM)

A meta-analysis conducted by Lucero et al, analysed data from the NCKP trial, the study in American Indians by O'Brien et al., as well as two large RCTs, one in Finnish (FinOm study) and the other in South African children. Lucero et al excluded data from HIV-positive children. The pooled VE against IPD caused by VT was 88% [ITT; 95%CI=73-94][50] in the meta analysis, versus 93.9% and 86.4% in Californian[51] and American Indian children,[52] respectively (see appendix A). The efficacy of PCV against any IPD type differed greatly between the latter two studies (89.1% and 54.1%, respectively). Note that the incidence of IPD in American Indian children is at least ten times higher than in non-native American children in the US.[53],[52] Because it could be argued that the inclusion of the results from specific American ethnic groups (with specific underlying diseases) renders the pooled Cochrane results unrepresentative for the Belgian population, we have chosen to use the VT IPD vaccine efficacy estimates from the NCKP trial in the baseline. We also use the efficacy estimate from the NCKP trial against CAP, because it is the only study that investigated this impact. Straetemans et al. performed another Cochrane meta-analysis for the effect of PCV on the prevention of acute otitis media. The pooled analyses only contained information from developed countries, and will therefore be used in the baseline.[54]

Comparing the two sources of effectiveness data, we are taking a non-conservative approach to estimating vaccine effectiveness. Note however, that these choices are most influential if herd immunity is ignored (because RCT results are unlikely to be influenced by herd immunity).

The model incorporates the possibility of having protective vaccine efficacy wane for each of these three outcomes, and for each dose separately, based on an exponentially declining function. In the baseline waning is set at 100% after 1 dose only from age 12m to 72m (or a 20% efficacy decline per year), at 100% for two doses only from age 36m to 96m (or a 20% efficacy decline per year), at 100% from age 60m to 10 years for those receiving 3 doses (as part of a 2+1, at 15 months; or a 3+1 schedule at 4 months, again a 20% decline per year), and at 100% from age 20 years to 50 years for those receiving 4 doses in the 3+1 schedule (on average a 3.3% decline per year). These estimates are made to illustrate the potential additional impact of a 3+1 versus a 2+1 schedule. In addition to these trial data, vaccine effectiveness estimates related to alternative schedules than those investigated in trials, as well as aspects related to herd immunity and serotype replacement can be derived from five years of widespread PCV7 use in the USA.

Important vaccine shortages occurred very early in the universal infant PCV7 program in the US, which was implemented shortly after licensure (February 2000). These vaccine shortages were not resolved until mid-2004, and as a consequence the majority of the first few vaccinated cohorts did not receive the full four-dose schedule (i.e., the three dose primary schedule, supplemented by a booster dose (noted 3+1 schedule, hereafter). In fact, in order to cope with these shortages, the US Centres for Disease Control and Prevention (CDC) actively encouraged three (2+1) and two dose (1+1) schedules in young children. Amongst children aged 19 to 35 months in 2003, the US National Immunization Survey estimates that 14% did not receive PCV7 at all, while 6.6% received a single dose, 13.0% received only 2 doses, 31.5% received only 3 doses, and only 34.9% received the full course (3+1).(CDC, http://www.cdc.gov/nip/coverage/NIS/03/toc-03.htm and unpublished data, CDC, as quoted in [55]).

The long period of vaccine shortage gave the CDC the opportunity to estimate the effectiveness of reduced schedules on VT IPD through a case-control study in US regions of the Active Bacterial Core Surveillance program (which covers 16 million people).(personal communication

CDC 2006, Whitney) No statistically significant differences were found in effectiveness between the full 3+1 and reduced schedules. Indeed, effectiveness against IPD versus no vaccination of

a. 3 doses ≤ 6 months + 1 dose 12-18 months was 100%
b. 3 doses ≤ 6 months was 92%
c. 2 doses ≤ 6 months + 1 dose 12-18 months was 95%
d. 2 doses ≤ 6 months was 96%
e. 1 dose ≤ 6 months was 67%

During the final editing process of the report, additional information from the USA was made available to us, in strictly confidential format, which confirms the above data estimates. In fact, the estimate for the 2+1 schedule was revised upwards to 98%.[98] Note that in our analysis, we use these point estimates (to weigh the estimates from the RCTs given in table 12, for each dose, and each finalised schedule separately .

Table 13: Changes in projected numbers of invasive pneumococcal disease (IPD) cases, by age group and serotype category – Active Bacterial Core surveillance (ABCs), United States, 1998-1999 and 2003 (Source: CDC)

Age group (yrs)	Serotype category*	1998-1999 average projected no. of cases	2003 projected no. of cases	change in annual projected no. of cases	Percentage change
<5	Vaccine	14293	876	-13417	94%
	Nonvaccine	2947	3578	631	-21%
	Total	17240	4454	-12786	74%
5-17	Vaccine	1195	569	-626	52%
	Nonvaccine	880	824	-56	6%
	Total	2075	1393	-682	33%
18-39	Vaccine	5023	1610	-3413	68%
	Nonvaccine	3419	3407	-12	0%
	Total	8442	5017	-3425	41%
40-64	Vaccine	8945	4167	-4778	53%
	Nonvaccine	7545	10237	2692	-36%
	Total	16490	14404	-2086	13%
>65	Vaccine	11595	4230	-7365	64%
	Nonvaccine	9169	10635	1466	-16%
	Total	20764	14865	-5899	28%
all ages	Vaccine	41051	11452	-29599	72%
	Nonvaccine	23960	28681	4721	-20%
	Total	65011	40133	-24878	38%

* Serotypes included in the 7-valent pneumococcal conjugate vaccine are defined as vaccine serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F). All other serotypes are considered nonvaccine serotypes.
Annual national projections of IPD cases were calculated by applying age- and race-specific disease rates for the aggregate ABCs surveillance area to the age and racial distribution of the US population on the basis of 2000 US Census date.
Table reproduced from CDC website

The indirect effects of PCV7 are likely caused by decreased nasopharyngeal carriage of VT strains among vaccinated children (and thence reduced likelihood of exposure in non-vaccinated children and adults (yielding so-called herd immunity)).[29] As can be seen in table 13, the reduction in VT IPD was partially offset by an increase in non-VT IPD. Nonetheless the net effect was beneficial. For persons aged ≥5 years, VT disease decreased 62% (CI = 59%-66%) from 1998-1999 to 2003,

with the largest absolute rate reduction occurring among those aged ≥65 years (rate difference: 21.7 cases per 100,000 [rate 33.6 during 1998-1999 and 11.9 during 2003]). Total IPD incidence declined 29% (CI = 25%-33%), again with the majority of the absolute rate reduction occurring among those aged ≥65 years (rate difference: 18.4 cases per 100,000 [rate 60.1 during 1998--1999 and 41.7 during 2003]). Note that, in view of the uptake figures cited above, the US herd effects observed at least until 2003 (i.e. those cited in table 13), were based on 66% of 1.5 to 3 year-olds having received either a 2+1 or a 3+1 schedule, and an average total number of doses per person in that age bracket of 2.7 (including 14% who did not receive any dose).

The data in table 13 should be interpreted with care in order to apply them to the Belgian situation.

- Secular trends cannot be excluded as a factor in the changing pattern of IPD in the United States. However, these trends would be expected to affect disease caused by all serotypes; the reductions in IPD after introduction of PCV7 have been VT specific, suggesting a vaccine effect. The decline in adult IPD is unlikely attributable to PPV23, because no decline occurred in the incidence of IPD caused by serotypes, which are included in PPV23 but not PCV7 (CDC). Indeed, the incidence of IPD caused by the 16 serotypes included in PPV23 and not in PCV7 among persons aged ≥5 years increased 11% (CI = 3%-21%) from 1998-1999 to 2003 (CDC website information). Furthermore the increase in PPV23 uptake is reported to be have been low since 1998.
- The USA introduced universal PCV7 vaccination immediately, while giving priority to risk groups, but the data used to compare the herd immunity impact with, are reflecting a situation of non-vaccination. Belgium now has a history of risk group vaccination, and of expanding private vaccination of healthy children. While in the economic analysis we compare universal vaccination to non-vaccination, it is expected that the additional effectiveness versus private vaccination is more limited. An incremental analysis versus the current situation is difficult because vaccine uptake is rapidly changing, and is likely to be geographically dispersed. It is likely however, that current uptake is not high enough to evoke large herd immunity effects.

An article published in June 2006 presents a new cost-effectiveness analysis for the USA, using vaccine effectiveness data versus all IPD over time and by age, in vaccinees and non-vaccinees. It also uses previously unpublished data on progressive herd immunity impact by year after the introduction of PCV7.

Table 14: Efficacy of PCV7 against invasive pneumococcal disease (of vaccine and non-vaccine type) among non-vaccinated persons in the USA (% reduction from baseline (1997-1999))

	Age (years)				
Year	<5y	5-15y	15-45y	45-65y	>65y
2000	5	12	20	4	4
2001	38	15	27	12	16
2002	65	28	37	20	29
2003	65	34	39	21	30
2004	68	38	47	20	36

Source: Ray et al.[32]

In our baseline economic analysis, these progressively increasing effectiveness data are used to inform the confidence intervals around the estimated vaccine effectiveness on VT and NVT IPD in non-vaccinated people. That is, the information from table 14 (all types) is used in conjunction with the information from table 13 (vaccine - non-vaccine types) to apply distributions to the estimated herd and serotype replacement effects in multivariate uncertainty analyses. More specifically in the multivariate analyses in which we assume that 3+1 infers more herd immunity than 2+1, the distribution of indirect vaccine effectiveness for the 2+1 schedule is determined by

the estimates from table 14 (weighed by VT and NVT in table 13) using the observations from 2000-2002 only. At the same time for the 3+1 schedule the entire range between 2000 and 2004 is used to inform the herd immunity effect distribution. This obviously makes, on average, the herd immunity effect assigned to the 3+1 schedule greater.

3 COST-UTILITY ANALYSIS: RESULTS

3.1 DISEASE BURDEN

The disease burden of pneumococcal infections in Belgian children is generally described in the chapter on data and methods. Since the model for children under age 5 years is based on these data, the model replicates the disease burden as reported in Vergison et al[42] (in the absence of vaccination) for this age group.

Table 15: Estimated annual disease burden of pneumococcal infections in Belgium, all ages pre-vaccination

IPD infections	1403
Meningitis	96
Bacteremia	500
Other	807
Deaths	At least 233 due to pneumococcus
Meningitis	12
other IPD	41
Multiple cause pneumonia	608
Life-years lost*	
Meningitis	347
other IPD	663
Multiple cause pneumonia	6,631
Quality-Adjusted Life-Years lost*	
IPD	1122
Multiple cause pneumonia	6869
All-cause AOM	1182

*future life-years discounted at 1.5% per year

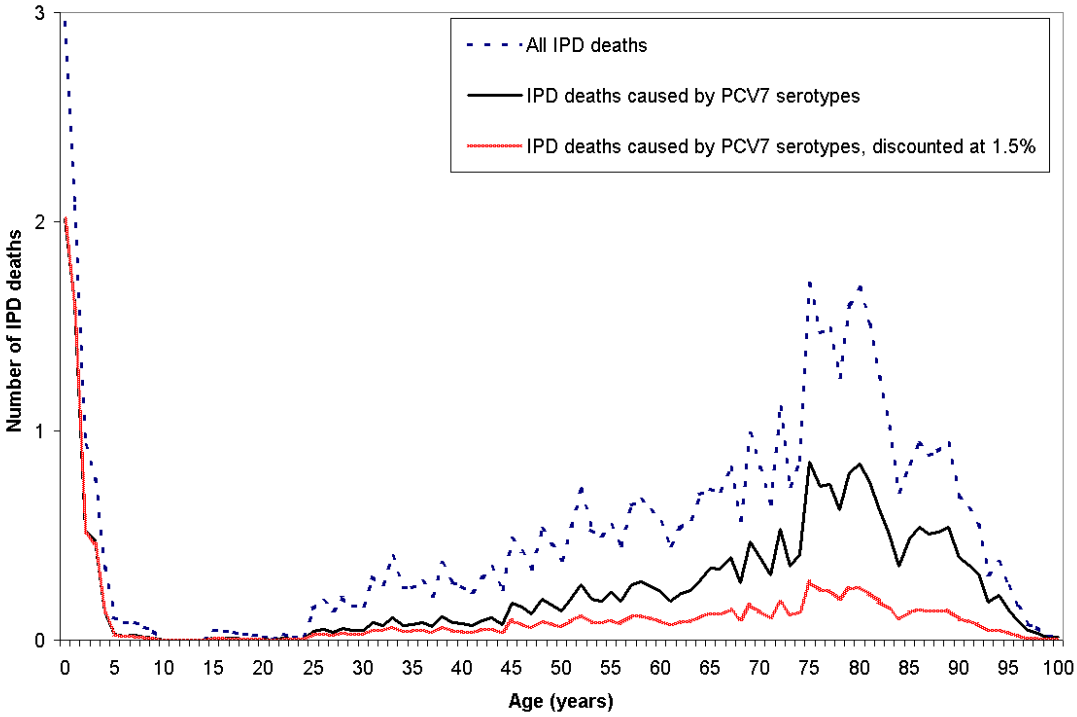
Note that in table 15 the disease burden of pneumonia and acute otitis media (AOM) is not limited to that which is definitely related to pneumococcus. We were unable to obtain reliable Belgian estimates of the proportion of these cases that are caused by pneumococcus. However, based on the hospitalisation records, we know that 2,557 hospitalisations per year had a primary diagnosis code of pneumococcal pneumonia between 2001 and 2004. Furthermore, over the same period there were 25,573 hospitalisations per year that were coded in a field from which pneumococcus cannot be excluded ("unspecified bacterial pneumonia", "unspecified pneumonia", "unspecified bronchopneumonia"). It is the combination of all these codes that we use to estimate the proportion of hospitalisations at each age. Note though, that our estimates of costs for pneumonia illness are derived from the survey in CM members (and age-adjusted based on ALOS in the codes listed above).

We also know from these records that over the same period 180 deaths at separation were given a primary diagnostic code of pneumococcal pneumonia, whereas another 2445 deaths were in these other potentially related codes.

When comparing the disease burden of AOM and pneumonia, based on table 15, one should also keep in mind that (1) table 15 accumulates the annual disease burden over all ages, and that, although AOM is much more frequent than pneumonia at a young age, it is far less frequent than pneumonia in ages over 65 years of age (cfr table 8), and generally gives much less rise to hospitalisations; (2) QALYs are a combined measure of morbidity and mortality, i.e. they express both the temporary loss in quality of life of those who survive an episode, and the permanent loss in remaining life expectancy for those who do not survive an episode (and AOM was not assumed to be lethal).

In order to estimate the direct impact of vaccination on pneumonia and AOM, by using data from Randomised Controlled Trials (RCTs), the implicit assumption in our analysis is that the proportion caused by pneumococcus is the same as in the clinical trial populations. In Australia, the proportion of CAP caused by pneumoccus was recently estimated at 25% (Wong M, personal communication, 2005), whereas in the UK it was recently estimated to be 48%.[24] In the baseline analysis we assume it is 25% for pneumonia when results are reported with the inclusion of herd immunity effects. For AOM such an additional assumption was not necessary to derive estimates of vaccine impact and cost-effectiveness, because we assume in the baseline that there are no herd immunity impacts on AOM. While it is estimated that about 6 Belgian children under 5 years of age die annually from IPD, most of the disease mortality is caused by pneumococcal infections at older ages, particularly in the age groups of the elderly (see figure 14).

Figure 14: Estimated annual number of Invasive Pneumococcal Disease (IPD) deaths by age in years in Belgium



As explained in chapter 2, figure 14 shows that most IPD deaths (and infections) <5 years are caused by PCV7 serotypes, but that considerably less of IPD at older ages is caused by the serotypes that are included in the PCV7.

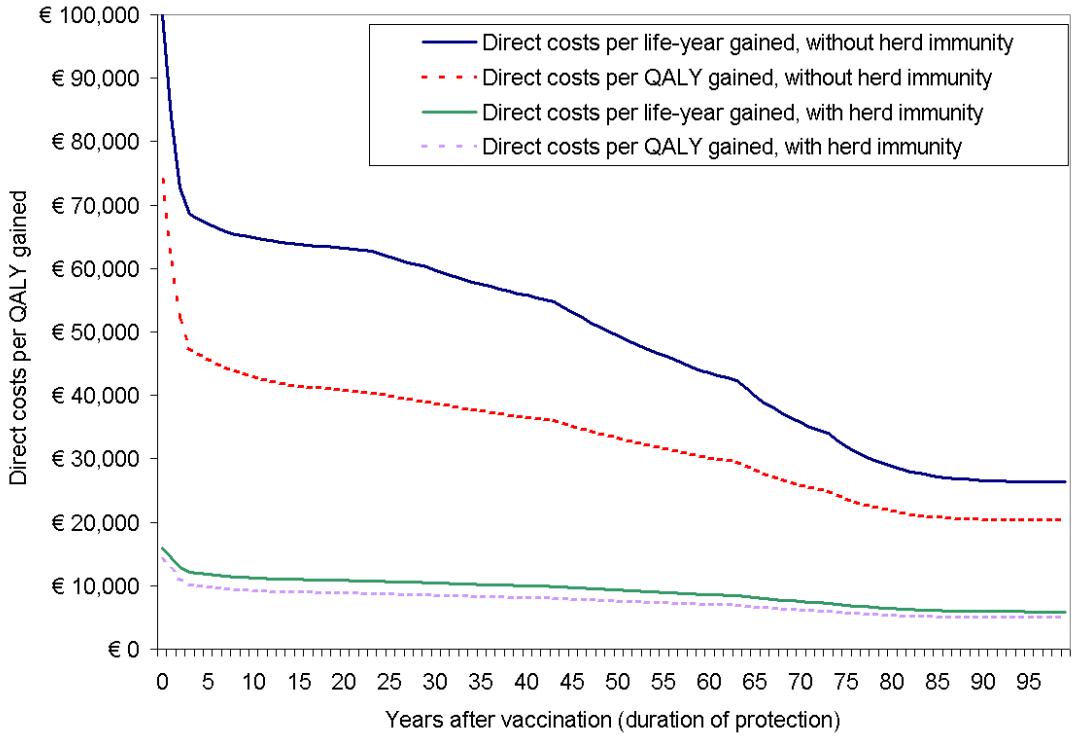
In an economic evaluation, consideration is given to societal time preference by discounting future costs and effects. Figure 14 also shows the impact of discounting at 1.5%, which is the recommended rate for effects in Belgian health economic evaluations.[56] For the estimated direct effects in the analysis, i.e. the effects that can be prevented ***within*** a vaccinated cohort, all the direct outcomes over time are discounted (costs at 3% and effects at 1.5%) as illustrated in figure 14 for deaths. Additionally expected future life-expectancy at each age of death is also discounted at a rate of 1.5% (i.e. future life-years to be gained from preventing a death are scaled down to the moment in time at which this death would occur without prevention). This implies that the future effects of the vaccine within those who have been vaccinated as a child are scaled down as an intrinsic part of the analysis, in order to be consistent for policy making at the present time. However, herd immunity effects are expected to occur from the first year of the vaccination program on, in varying degrees ***across all ages***, and therefore are not discounted when they are attributable to the first year of the simulation. That is, the indirect effects of the vaccine (infections and deaths prevented in non-vaccinated people) are expected to start occurring immediately during the first year of the program. The degree by which they occur has recently

been demonstrated to increase with progressively more and more cohorts being vaccinated, and this variability in herd immunity effects is accounted for as part of this analysis. In sum, in this analysis, the potential for direct vaccine effects in vaccinated people becomes considerably smaller with time (i.e. the dotted red line in figure 14), whereas the indirect herd effects in non-vaccinated people are accounted for immediately and are relatively stable through time (i.e. the solid black line in figure 14). It is imperative, if this analysis is to be used in a policy making process, that policy makers are aware of these adjustments, and do not add their own time preferences to the results of the analysis. Results shown in the following sections are always with costs and effects discounted, unless explicitly mentioned otherwise.

3.2 BASELINE INCREMENTAL COST-EFFECTIVENESS ESTIMATES

First we explore the incremental cost-effectiveness ratios (ICERs) over time for both options, in order to establish how long our baseline time horizon should be. All results are discounted for costs and effects unless specifically indicated otherwise. Figures 15-16 show the ICERs assuming that direct vaccine protection does not wane over time. The ICERs stabilise very rapidly up to 30 years after vaccination, indicating that the vaccine's cost-effectiveness is not highly dependent on the duration of protection within a typical decision horizon of about 30 years. As illustrated by these figures, the period of observations from the RCTs and the five-year use of PCV7 in the USA clearly indicate that a five year protection horizon is not a major source of uncertainty to establish the cost-effectiveness of this vaccine. However, they also show that the influence of extending the time horizon beyond 30 years could be large, if the vaccine's protective efficacy could be assumed to last that long. This question is currently unresolved.

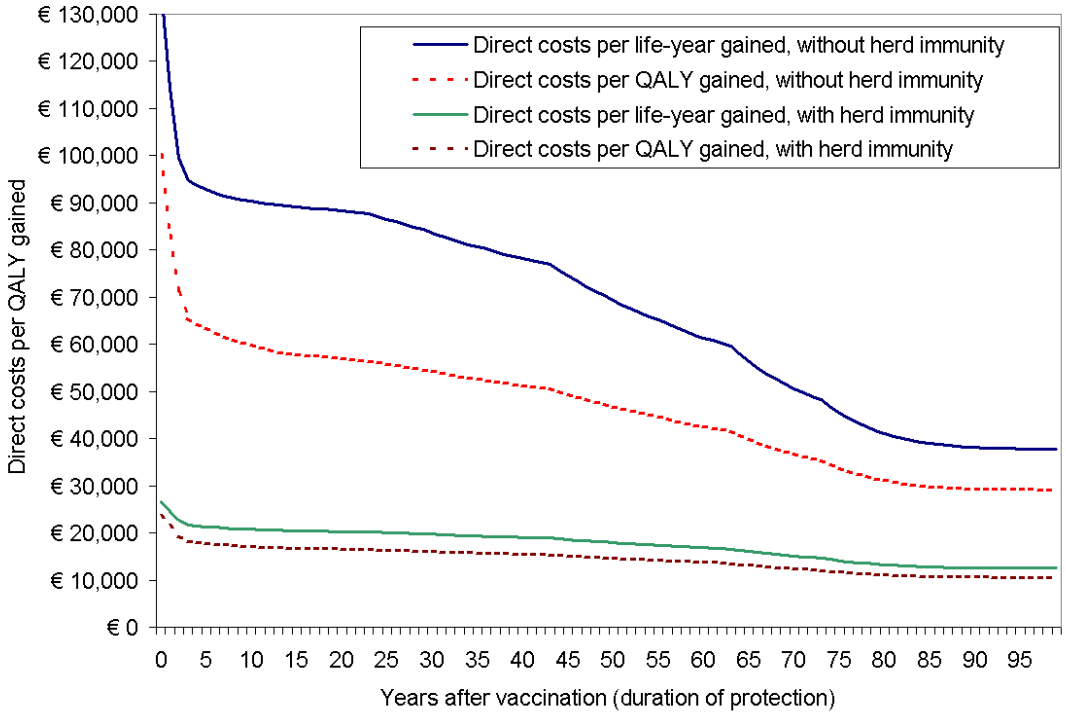
Figure 15: Incremental cost-effectiveness over time for option 1 (2+1 schedule) in the absence of waning vaccine protection



These figures can be used as follows. Determine for each option the period of full protection in successfully vaccinated children you want to consider. Read the corresponding cost-utility ratio at that point, and compare both options for the schedule shown here. It seems clear that it is virtually impossible to have the reduced schedule (2+1) yield worse cost-effective than the full schedule (3+1), based on the argument of a reduced duration of protection, if direct protection under both vaccine schedules is assumed to wane to the same degree. Unless, of course, the impact of herd immunity can be assumed to be smaller for the 2+1 versus the 3+1 schedule. We

will return to the issue of waning immunity under the different schedules in the sensitivity analysis (below).

Figure 16: Baseline incremental cost-effectiveness over time for option 2 (3+1 schedule), in the absence of waning vaccine protection



Furthermore, it also shows that the impact of health-related quality of life is most influential if herd immunity is ignored. That is, the enormous immediate life-saving potential dwarfs the additional gains in quality of life to be had from herd immunity effects.

In the baseline analysis below, waning is set at 100% after 1 dose only (at 2 months), from age 12m to 72m (or a 20% efficacy decline per year), at 100% for two doses only (at 3 months) from age 36m to 96m (or a 20% efficacy decline per year), at 100% from age 60m to 10 years for those receiving 3 doses (as part of a 2+1, at 15 months; or a 3+1 schedule at 4 months, again a 20% decline per year), and at 100% from age 20 years to 50 years for those receiving 4 doses in the 3+1 schedule (on average a 3.3% decline per year). These estimates are made to illustrate the potential additional impact of a 3+1 versus a 2+1 schedule. It is important to remember, however, that these estimates about waning are not based on observations. Therefore, in the baseline, waning can be seen as quite conservative for both schedules, given that immunity is assumed to wane very rapidly, starting quite early after each dose, particularly under the 2+1 schedule, including its booster dose (and much less so for the booster dose in the 3+1 schedule). Furthermore, in the baseline analysis herd immunity effects are included, based on observations in the USA. Since at the time these observations were made, about 65% children aged 19 to 35 months in the USA had not received the full 3+1 schedule, the baseline analysis reflects this by considering the herd immunity effects to be equal under both options for the schedule.

Table 16: Estimated baseline costs* and effects prevented by vaccination versus no vaccination using a 2+1 schedule (option 1) or a 3+1 schedule (option 2)

Outcomes prevented	Directly in vaccinees (accumulated after 30 years (effects undiscounted))		Indirectly in non-vaccinees
	Option 1	Option 2	Option 1 & 2
IPD infections	200	219	154
Meningitis	22	24	6
Bacteremia	120	126	45
Other IPD	55	66	102
All pneumonia	545	814	1,235
AOM episodes	10,721	14,420	-
Deaths	4.1	4.5	33
IPD	4.1	4.4	7
Pneumonia	0.04	0.1	26
Life-years lost	320	346	391
IPD	318	337	108
Pneumonia	3	9	282
Quality-adjusted life-years lost	436	485	406
IPD infections	377	400	117
Pneumonia	6	13	289
AOM	54	72	0
Direct treatment costs	4,124,942	4,619,955	6,247,498
IPD	2,049,795	2,156,178	1,113,464
Pneumonia	1,058,841	1,240,364	5,134,035
AOM	1,016,305	1,223,414	-
Direct vaccination costs	-16,498,745	-21,763,167	-
Variable admin costs	- 1,649,874	-2,176,317	-
Vaccine purchase	-14,848,870	-19,586,850	-
Total direct health care costs	- 12,373,803	-17,143,211	6,247,498

Estimates per vaccinated one-year cohort
Costs in Euro, negative prevented costs signify additional costs versus the comparator

Table 16 shows the extent to which both options impact on the disease burden, distinguishing between prevented effects and costs within vaccinated cohorts, and in the non-vaccinated population (which includes non-vaccinated members of vaccinated and non-vaccinated cohorts across all ages). The difference between options 1 (2+1 schedule) and option 2 (3+1 schedule) are related to greater assumed protective efficacy after the booster dose under option 2, and more rapid waning of vaccine efficacy after the booster dose under option 1 versus 2.

Table 17 shows the baseline results of options 1 and 2 versus no vaccination, as well as the incremental cost-effectiveness of option 2 versus option 1. It shows, for instance, that the 2+1 schedule would cost about Eur 10,000 per QALY gained with and Eur 45,000 per QALY gained without herd immunity versus no vaccination. The ICER of adding the extra interspersed dose at age 4 months under option 2, would be much higher at over Eur 150,000 per QALY gained.

Table 17: Incremental Cost-effectiveness ratios (ICERs) for both options, with baseline waning assumptions (results for a 30 year time span)

ICERs (EUR)	option 1 (2+1 schedule) vs no vaccination		option 2 (3+1 schedule) vs no vaccination		option 2 vs 1
	excl herd effects	Incl herd effects	excl herd effects	incl herd effects	
Direct costs per IPD infection prevented	63,921	17,969	81,011	29,800	309,065
Direct costs per death averted	3,090,708	169,898	3,917,801	291,669	14,982,342
Direct costs per life-year gained	66,635	11,785	85,265	19,926	370,726
Direct costs per QALY gained	44,984	9,869	55,405	16,304	155,619

3.3 SENSITIVITY ANALYSES

Sensitivity analyses in this report focus on parameter uncertainty as well as structural uncertainty (by adapting the model). First we will show simple univariate sensitivities to parameter changes. Second, multivariate uncertainty in the cost-effectiveness plane, and associated cost-effectiveness acceptability curves (CEAC) are shown (all input parameters were given distributions based on the underlying primary data (if available)). The focus of the explorations in sensitivity analysis is on waning vaccine efficacy in vaccinees, indirect herd immunity effects in non-vaccinees and vaccination costs.

3.3.1 Univariate sensitivity analysis

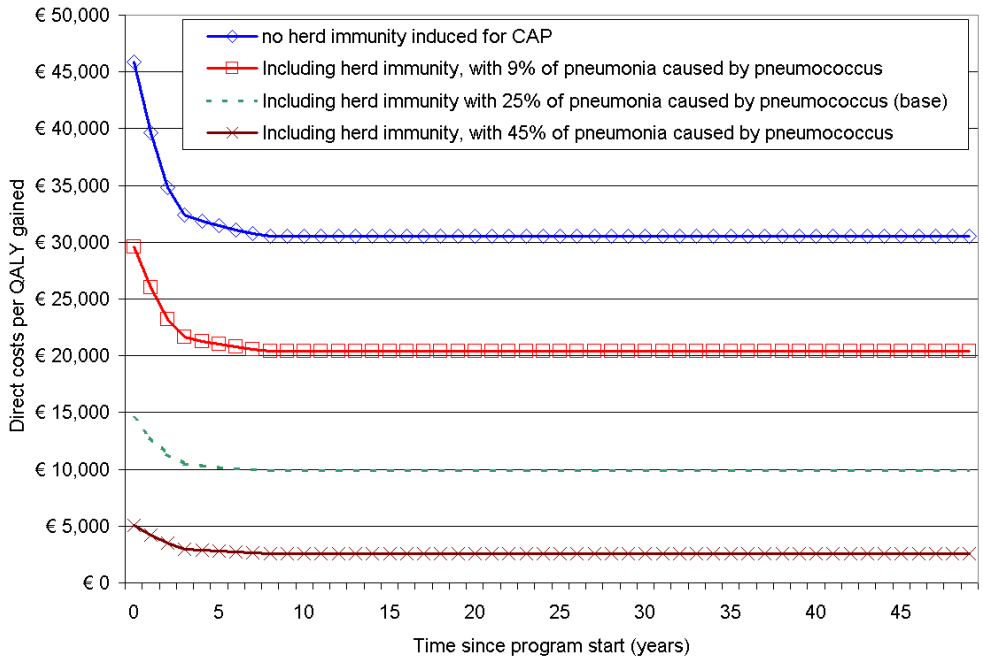
Table 18 shows that none of the listed individual parameter changes had a major impact on the base case results.

Table 18: Univariate sensitivity analysis of direct costs per QALY gained for a range of potentially influential parameters

	Option 1		Option 2		
	Excluding herd effects	Including herd effects	Excluding herd effects	Including herd effects	2 vs 1
Base	44,984	9,869	55,405	16,304	155,619
Discount rate					
5% costs, 5% effects	89,252	15,998	109,777	25,763	334,545
3% costs,3% effects	62,564	12,003	77,282	19,968	222,977
3% costs, 0% effects	28,737	7,471	35,378	12,235	98,938
5% costs, 0% effects	30,141	8,276	36,703	13,031	101,680
Salo et al's approach to QALYs	47,163	10,103	57,930	16,688	158,776
Direct costs per DALY averted (instead of QALY gained)	45,067	9,608	57,148	16,101	219,606
Time span 100 years	47,163	10,103	50,855	15,475	83,773
Doubling the costs of long term sequelae from IPD	39,797	7,183	50,529	13,648	156,691
Vaccine efficacy versus IPD based on Cochrane meta analysis (instead of NCKP trial in base)	47,850	10,297	58,636	16,879	303,763
Inclusion of direct non-health care costs	43,979	8,815	54,986	15,506	155,161
Exclusion of personal direct health care costs	49,238	10,155	60,853	17,122	158,234
Reduction of age-specific life-expectancy of infected people					
all ages > 50y, by 20%	44,984	10,834	55,405	17,804	155,619
all ages > 50y, by 50%	44,984	12,790	55,405	20,802	155,619
all ages > 50y, by 80%	44,984	15,778	55,405	25,278	155,619
all ages < 5y, by 20%	49,900	10,838	60,853	17,122	158,234

Based on the general background analysis of cost data in section 2.2.2. we inferred in general terms that those who are seriously ill from pneumococcus (and may consequently die from it), may have lower than average life-expectancy as their same-age counterparts. It is noteworthy in table 18 that such adjustments to life-expectancy, do not have a large impact on the results.

Figure 17: Impact of assumed proportion of community acquired pneumonia (CAP) caused by pneumococcus on herd immunity impact for option 1 (2+1 schedule) versus doing nothing



Note also that figures 17 and 18 show the effects of differences in baseline waning up to year 50 of the time span (i.e. showing that the 2+1 schedule remains more cost-effective than the 3+1 schedule)

Figure 18: Impact of assumed proportion of community acquired pneumonia (CAP) caused by pneumococcus on herd immunity impact for option 2 (3+1 schedule) versus doing nothing

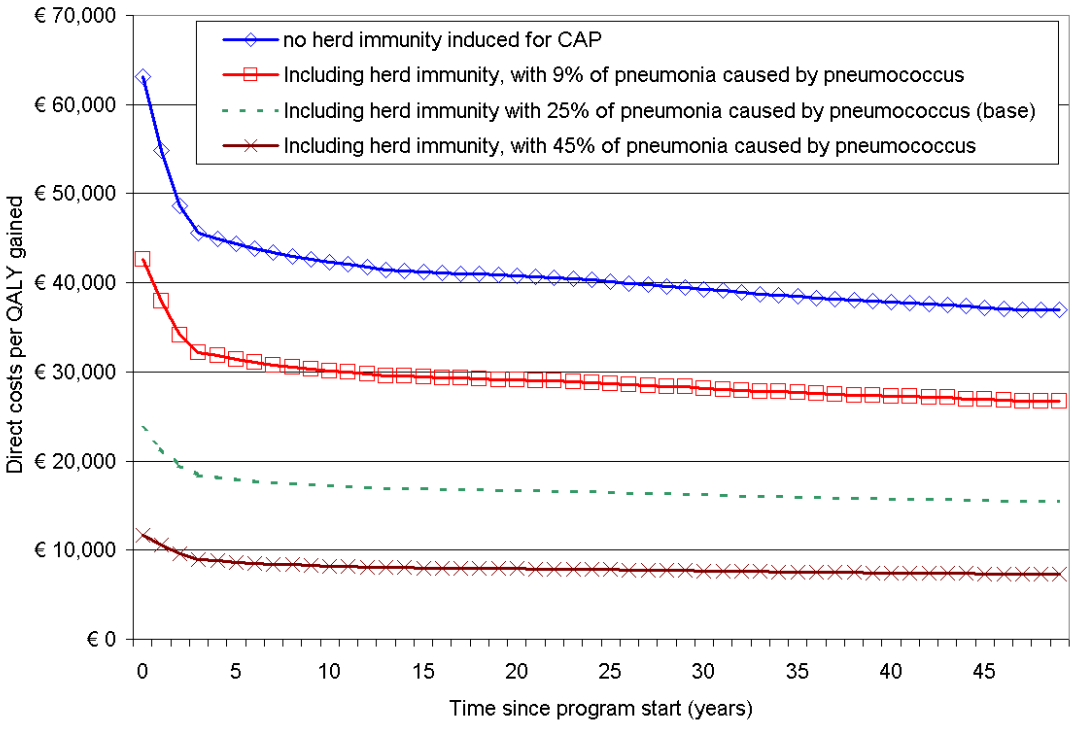


Figure 19 shows that between 30 and 50 years' hence for the 3+1 schedule to be cost-effective versus the 2+1 schedule, not only a substantial greater degree of waning has to be assumed for 2+1, but also that the 3+1 schedule induces greater herd immunity effects, with certainty. There is currently no evidence for either of these differences in effectiveness (see also section 1 and appendix A).

Figure 19: Impact of assumed differences in herd immunity impact on incremental cost-effectiveness of a 3+1 schedule versus a 2+1 schedule

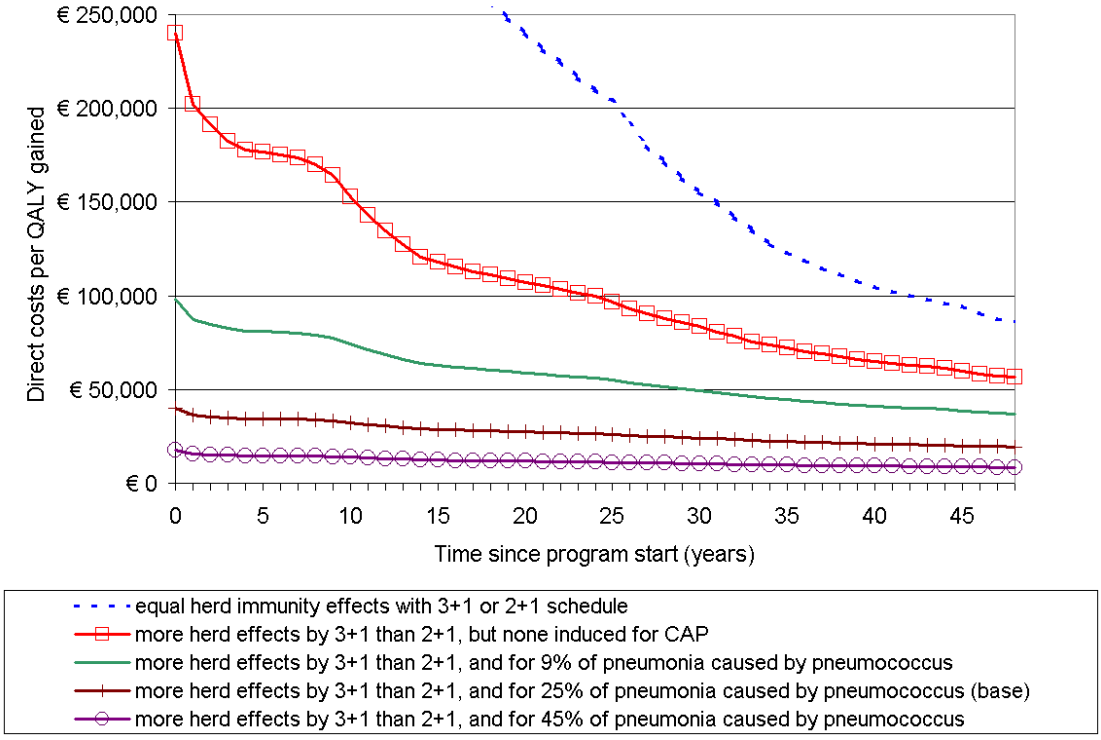


Table 19: Incremental Cost-effectiveness ratios (ICERs) for both options, with pessimistic (=baseline) waning assumptions for option 1 and optimistic waning assumptions for option 2 (results for a 30 year time span)

ICERs	option 1 (2+1 schedule) vs no vaccination		option 2 (3+1 schedule) vs no vaccination		option 2 vs 1
	excl herd effects	Incl herd effects	excl herd effects	incl herd effects	
Direct costs per IPD infection prevented	63,921	17,969	80,588	29,664	292,583
Direct costs per death averted	3,090,708	169,898	3,895,053	290,805	14,072,967
Direct costs per life-year gained	66,635	11,785	84,833	19,851	349,423
Direct costs per QALY gained	44,984	9,869	55,015	16,222	146,594

It is noteworthy that in table 19 the assumptions regarding waning of immunity for the 2+1 schedule seem very pessimistic (as they are in the baseline), and those for the 3+1 schedule overly optimistic. It was assumed that the 3+1 schedule gives dose-specific immunity from each dose until the end of the time span, while any direct protection for those following the 2+1 schedule is assumed to decline rapidly after each dose, and to have completely disappeared by age 10 years (see above). Still the incremental cost-effectiveness of the 3+1 versus 2+1 schedule is unfavourable after 30 years.

Since the main difference between the 2+1 schedule and the 3+1 schedule lies in the extra dose at month 4 under the 3+1 schedule, one could argue that the period between month 4 and month 15 (when the booster dose is administered) is the most crucial for assessing the differences between both schedules. Note that there is currently no evidence that there would be significant differences in immunogenicity levels between both schedules, during the period between the second dose and the booster dose. Indeed such a head-to-head comparison was made by Goldblatt et a.l[6] for PCV9 and no significant differences were found for any of the serotypes contained in PCV7 (see also appendix A). Nonetheless, in table 20, the results are shown assuming that

after dose 1 at month 2, waning immunity starts immediately in month 2, with complete (100%) waning by month 12

after dose 2 at month 3, waning immunity starts immediately in month 3, with with partial (20%, 50%) to complete (100%) waning by month 15

after dose 3 at month 4 (i.e. only option 2, 3+1 schedule) , waning immunity starts only in month 60, with complete (100%) waning by month 120

after the booster dose at month 15, under option 1 waning immunity starts in month 60, with complete (100%) waning by month 120, and under option 2 there is no waning at all.

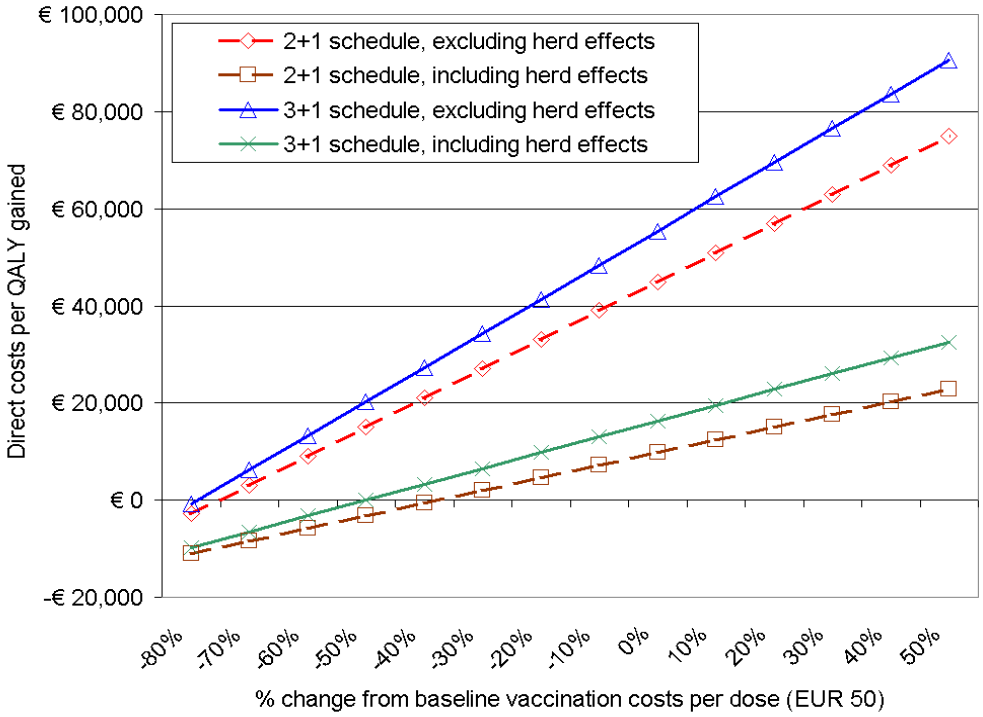
These are clearly very unrealistic assumptions, given the state of current evidence, i.e. that there is no significant difference in waning between both schedules. We show these results in table 20 to provide counterfactual proof. That is, even making these highly unrealistic assumptions that bias the analysis against the 2+1 schedule, the incremental cost-effectiveness of 3+1 versus 2+1 remains high.

Table 20: Incremental cost-effectiveness of 3+1 schedule versus 2+1 schedule, assuming exaggerated large and rapid waning after each dose, by degree of waning of second dose protection between month 3 and 15.

	Degree of waning from second dose between month 3 and 15			
CERs	25%	50%	75%	100%
Direct costs per IPD infection prevented	228,572	197,935	176,816	159,070
Direct costs per death averted	10,956,626	9,468,857	8,443,687	7,567,157
Direct costs per life-year gained	261,672	222,915	196,846	175,087
Direct costs per QALY gained	124,970	113,249	104,544	94,021

Note that in tables 20 and 21 both schedules are assumed to have an equal impact on herd immunity (which seems also a realistic assumption, given today's state of the evidence).

Figure 20: Sensitivity of options for vaccination to changes in vaccination costs per dose in the baseline, using a 30 year time span of expected costs and effects



Baseline cost is € 50 (€ 45 for vaccine purchase and € 5 for administration).

Figures 20-22 show the impact of changing vaccination costs per dose (which can be interpreted as comprising both purchasing and administration costs) for various scenarios and options.

Figure 21: Sensitivity of options for vaccination to changes in vaccination costs per dose in the baseline, using a 100 year time span of expected costs and effects

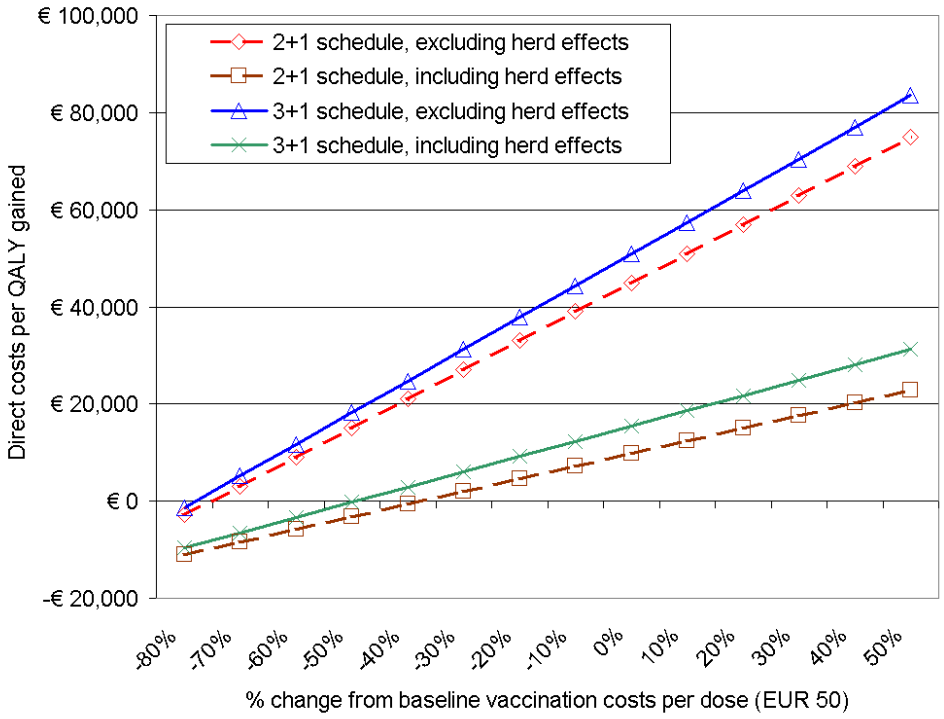
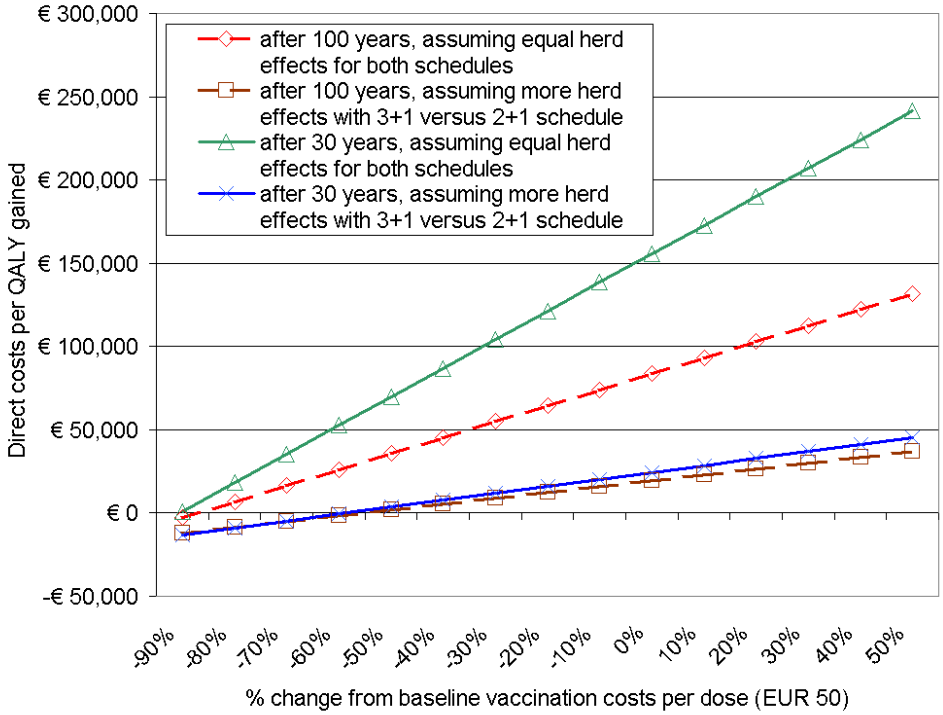


Figure 22: Sensitivity of options for vaccination to changes in vaccination costs per dose in the baseline, using a 100 year time span of expected costs and effects of option 2 versus 1



3.3.2 Structural sensitivity analysis

With regards to herd immunity, the models are used in two broad approaches. A first approach attributes the average expected herd immunity effects to a single vaccinated cohort, by using the average herd effects reported in the USA (CDC, based on tables in the section on methods and data). A second approach uses a multicohort framework, and calculates direct costs and effects expected from vaccinating 5 subsequent cohorts of infants, in each of these cohorts, as well as the progressively increasing herd immunity effects observed across all ages during the first five years of the US PCV7 program. This last approach is used by Ray et al, 2006. From the same paper, we use the estimates on increases in herd immunity effects over time as well (see table 14, data and methods section). Note that all the previous economic evaluations on PCV7 that have attempted to include herd immunity effects, were based, by lack of data on progression, on the first approach.

Table 21: Baseline cost-effectiveness ratios obtained by using a multi-cohort approach (Euro)

ICERs	Option 1 (2+1 schedule)	Option 2 (3+1 schedule)	Option 2 versus option 1
Direct costs per IPD infection prevented	17,033	28,365	289,846
Direct costs per death averted	164,355	283,114	14,050,680
Direct costs per life-year gained	11,265	19,116	347,673
Direct costs per QALY gained	9,425	15,631	145,942

As can be seen in table 21, the use of the multicohort approach produces baseline estimates which are very similar to those produced by the alternative (baseline) approach (see table 17) in this report. Note also that if we apply the same discount rates in our basecase as Ray et al.[32] (3% for both costs and effects), using the first approach, we estimate for the 3+1 schedule versus doing nothing, € 131,359 per life-year gained ignoring herd immunity, and € 24,629 when including herd immunity. In the US, Ray et al.[32] who assumed a vaccinated child received on average 3.7 doses, found $US 112,000 (~€ 89,000) per life-year gained), and $US 7,500 (~€ 6000), respectively.

3.3.3 Multivariate sensitivity analysis

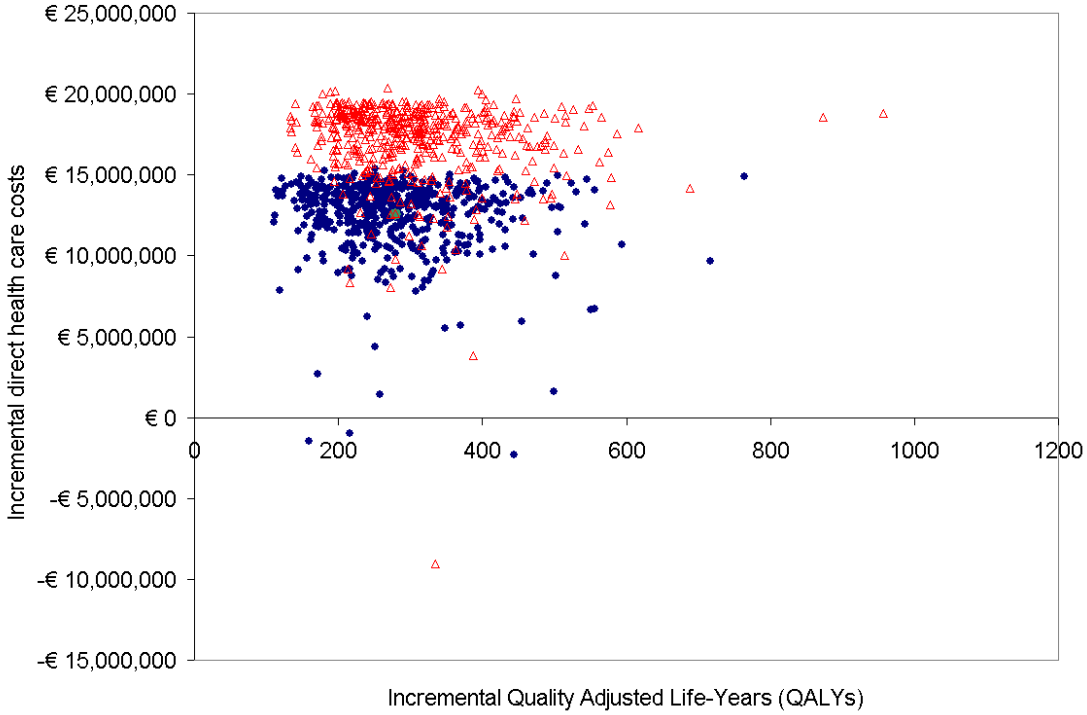
In multivariate probabilistic sensitivity analysis, all parameters in the model are varied according to a specified distribution. In this analysis, the distributions were almost always specified by data (usually beta distributions for incidence rates and proportions, and gamma distributions for costs). For those parameters for which no data driven distribution could be specified, a triangular distribution was defined, based on a plausible range (and plausibility based on the literature). Furthermore all such non-data driven parameters were explored in the univariate sensitivity analyses above.

The only parameters that were not varied in this multivariate sensitivity analysis were vaccination costs per dose and discount rates, as these are known to be highly influential (see above), but not a source of the type of uncertainty we wish to explore here.

The multivariate sensitivity analysis is based on 10,000 simulations, using Latin Hypercube sampling. For clarity, the cost-effectiveness planes depicted below show results for a random sample of 500 points.

All these analyses assume that the 3+1 schedule (option 2) induces longer lasting protection in vaccinees, and has a greater probability of providing larger herd immunity effects in non-vaccinees than the 2+1 schedule (option 1), unless specified otherwise.

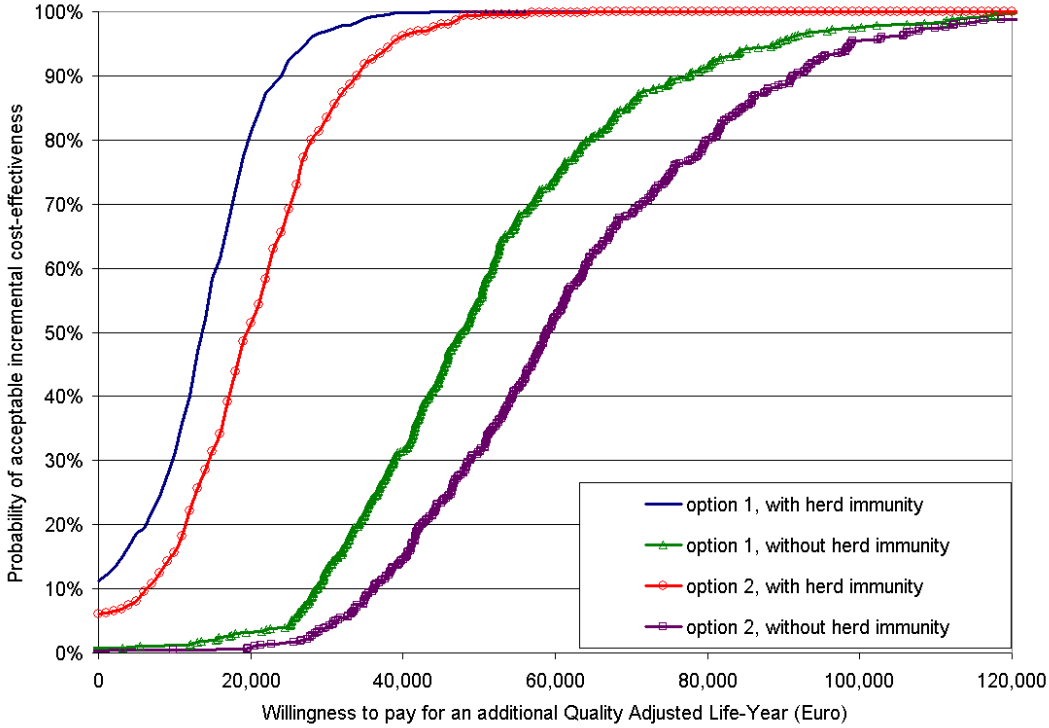
Figure 23: Cost-effectiveness plane for incremental costs and effects of option 2 and option 1 versus doing nothing, assuming both options induce equal herd immunity effects



red triangles: option 2
blue dots: option 1

The cost-effectiveness planes show the dispersion of the estimates produced by the multivariate sensitivity analysis.

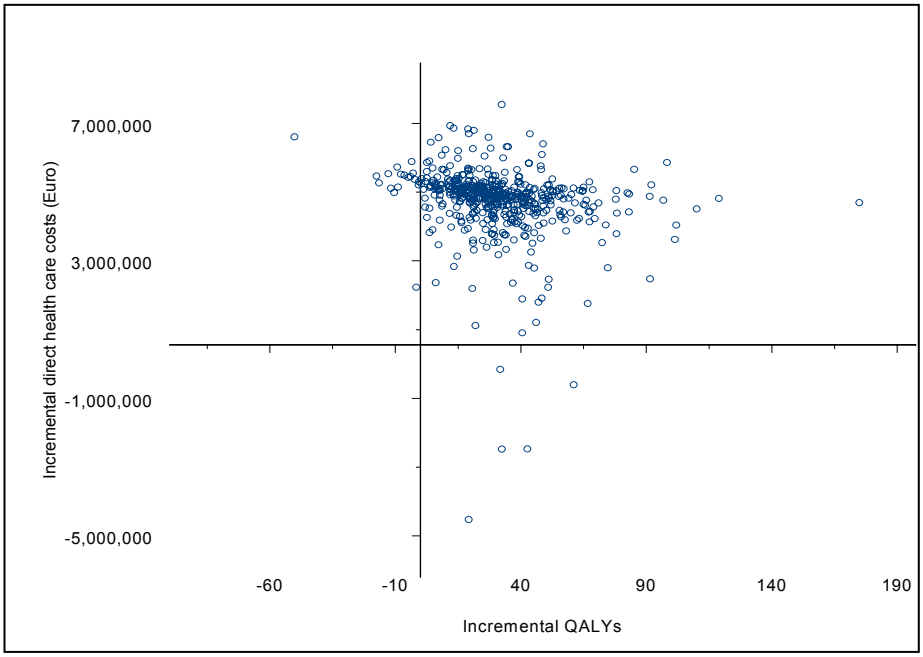
Figure 24: Cost-effectiveness acceptability curves for option 2 and option 1 versus doing nothing.



The information from the cost-effectiveness planes is "translated" into cost-effectiveness acceptability curves, by relating the probability of ending up in one of the quadrants of the cost-effectiveness plane to willingness to pay for an increase in health. A point in the south-east quadrant (less costly, more effective) shows dominance to be accepted (i.e. cost-saving at any level of willingness to pay) over the comparator (plotted in the origin of the cost-effectiveness plane). A point in the north-west quadrant shows dominance to be rejected by the comparator, whereas the acceptability of points in the north-east and south-west quadrants depends on the willingness to pay of the decision maker.

Figure 24 shows, for instance, that, including herd immunity effects, the probability of option 1 being cost-effective versus doing nothing is about 90% at a willingness to pay of € 20,000 per QALY gained, and virtually 100% at a willingness to pay of € 40,000.

Figure 25: Cost-effectiveness plane for incremental costs and effects of option 2 versus option 1, assuming both options induce equal herd immunity effects



Figures 25 and 26 are illustrations of the incremental cost-effectiveness analyses of option 2 versus option 1, showing that the impact of greater herd immunity assumptions for option 2 versus option 1 is to increase the negative correlation between costs and effects in the planes. The difference in herd assumptions used to produce the analysis shown in figure 26, are explained under data and methods, in the section of table 14.

Figure 26: Cost-effectiveness plane for incremental costs and effects of option 2 versus option 1, assuming option 2 induces greater herd immunity

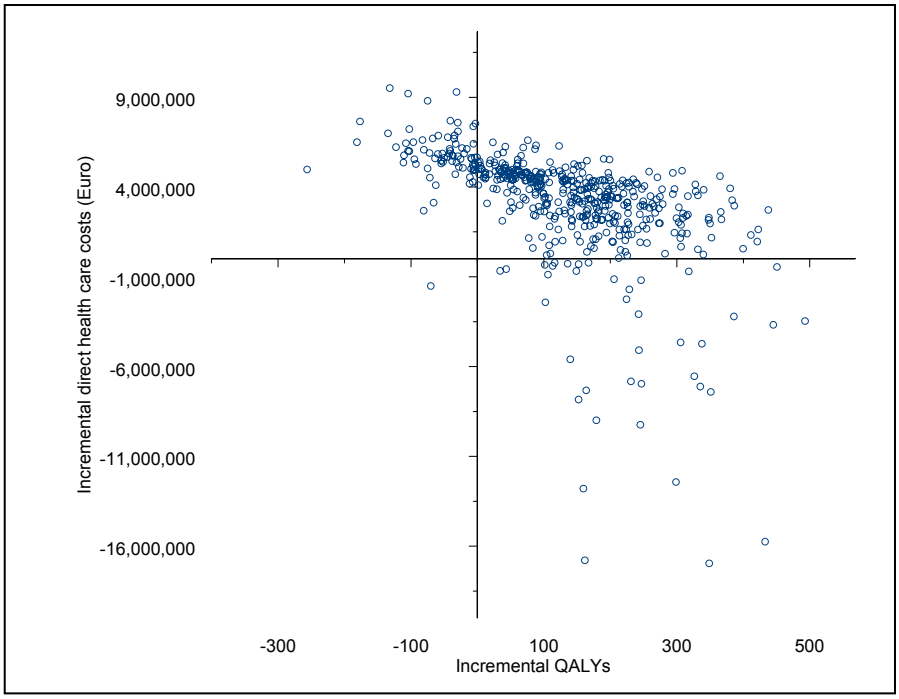


Figure 27: Cost-effectiveness acceptability curves for option 2 versus option 1, for two extreme scenarios of differences in herd immunity and waning of vaccine efficacy

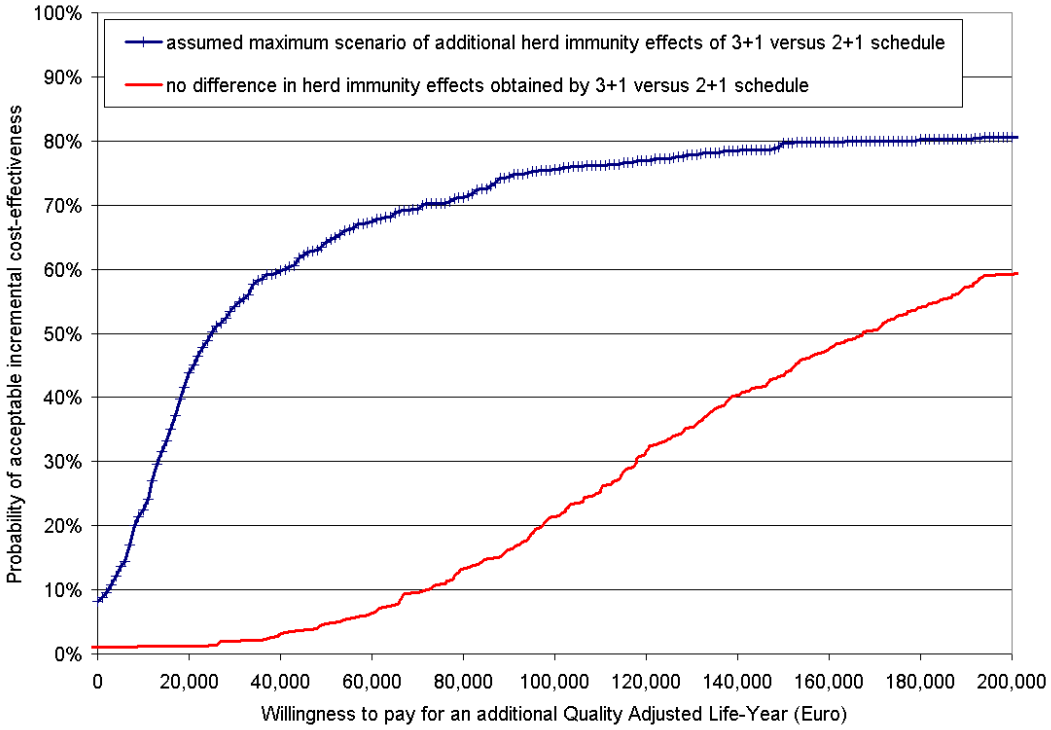


Figure 27 illustrates that the willingness to pay for a QALY must be high, in order to prefer a 3+1 schedule over a 2+1 schedule. Indeed where it falls within what is usually regarded as acceptable, uncertainty is great, even when the assumed herd impact is more favourable for the 3+1 schedule than for the 2+1 schedule.

4 POLICY IMPLICATIONS: SCHEDULE AND BUDGET

4.1 UNIVERSAL PNEUMOCOCCAL CONJUGATE VACCINATION IN OTHER COUNTRIES

Table 22 shows a non-exhaustive list of other countries, which have started, or are about to start in the near future with a publicly funded universal pneumococcal conjugate vaccination program for children. We list these particular countries, because we had reliable information to report that was directly communicated to us, or is publicly available. Pneumococcal conjugate vaccines are currently considered around the globe for inclusion in developed and developing world countries (The Lancet, online edition, 18th May, 2006, and http://preventpneumo.org/pdfs/lancet_may_06.pdf). Since the main impediment to a more rapid implementation of PCV vaccination programs, has been, and still appears to be, its cost, one can expect that more countries are pondering over the cost-effectiveness of this vaccine, and/or are on the verge of deciding on how to use it in a public program.

Table 22: Other countries with or with advanced plans for public PCV7 vaccination of shildren

Country	Start date	PCV7 schedule	Catch-up	Price per dose (public vaccination)
USA (a)	2000	2, 4, 6 + 12-15 m	Yes	US$ 56.8 (~€ 44.5)
Australia (b)	January 2005	2,4,6 m	Yes =<2y	A$ 81 (€ 46.3); A$ 71.3 (€ 40.1) in the catch-up program
Canada (c) Quebec Other provinces	 January 2005 January 2005	 2,4,12 m 2,4,6 + 12 m	 NA	~$CAN 70 (~€ 50)
The Netherlands (d)	June 2006	2,3,4 + 11 m	No	Undisclosed
Norway (e)	July 2006	3,5,12 m	No	NA
UK (f)	Summer 2006 (pending timely vaccine supply)	2,4,13 m	Yes=<2y	Undisclosed
Switzerland (g)	2006 , date unknown	2+1 schedule	NA	~ 80 Swiss Fr (~ € 51)
Germany (h)	Summer 2006 (pending approval of the German states)	3+1 schedule	NA	NA
France (i)	pending	3+1 schedule	NA	~ € 65 (de facto private price, see (i)

a) Based on personal communication CDC, Dr Cynthia Whitney, May 2006, and http://www.cdc.gov/nip/vfc/cdc_vac_price_list.htm ; http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4909a1.htm

b) Based on "Media release, Minister of Health and Ageing Australia", 11th June 2004

c) Based on personal communication Dr Philippe De Wals, May 2006, and Quebec Immunization Committee, 2005: http://www.inspq.qc.ca/pdf/publications/391-ImmunizationConjugateVaccine.pdf

d) Based on personal communication Dr Loek Van Alphen, May 2006, and Ministerial Advice of the Health Council of The Netherlands, 25th October 2005.

e) Based on Bergsaker and Feiring, 2006: http://www.eurosurveillance.org/ew/2006/060302.asp#4

f) Based on personal communication Dr John Edmunds, May 2006, and http://www.immunisation.nhs.uk/newsitem.php?id=56 ;

g) Based on personal communication Dr. Claire-Anne Siegrist, May 2006

h) Based on personal communication Dr. Joe Schmitt, May 2006 and STIKO

i) Based on personal communication Dr Daniel Levy-Bruhl, May 2006. France has currently a "targeted" PCV7 vaccination program, whereby the risk groups have been defined very widely, covering probably as much as 80% of French infants. The expansion to a universal program will require relatively little additional spending, and is therefore likely to be based on 4 doses. Reimbursement is obtained through social security (for 65%), and through sickness funds for the remaining 35% for those who have a membership (about 80% of the French population).

Note that the exact negotiated vaccine price is not public information in many countries. For countries for which we know this with certainty, the term "undisclosed" is listed in table 22. For countries for which we were unable to obtain certified information the phrase "not applicable (NA)" is used. Prices which were reported as being "about" a certain level are marked "~".

The baseline price in the cost-effectiveness analysis for Belgium of € 45 was chosen to correspond with the public prices that were available from the USA and Australia.

As an additional source of information of pricing, table 23 lists the current market prices from a selection of European countries.

A second important observation in table 22 is that at least 5 countries have chosen to adopt a reduced 2+1 schedule, rather than the 3+1 schedule. Finally, as there seem to be at least 5 other European countries about to embark on a universal program, the capacity of the manufacturer to meet production targets on time is an important issue. This has been a problem in the past, with severe vaccine supply shortages in the US program, on and off from 2000 until 2004. However, since the US program was implemented almost immediately upon completion of the NCKP trial and production capacity needed to be created, structural production shortages seem unlikely to reoccur to the extent that they did in the US.

Table 23: comparison of prices for Prevenar® by country (€)

Country	Producer	Pharmacy sales price (incl VAT)	Pharmacy sales price (excl VAT)	Pharmacy purchase price	Ex-factory price
Austria	Wyeth	117.85	98.21	61.43	55.59
Belgium (a)	Wyeth	66.15	62.41	54.97	52.79
Finland	Wyeth	84.64	78.37	55.63	52.96
France	Wyeth Lederle	63.34	62.04	52.92	49.00
Germany	Wyeth	72.22	62.26	52.58	49.60
Germany	Wyeth Pharma	62.42	53.81	51.45	48.54
Greece	Wyeth Lederle Vaccines	76.40	70.74	52.40	48.33
Hungary	Wyeth	57.01	54.30	50.90	48.47
Ireland	Wyeth Lederle SpA	88.40	80.36	60.27	53.84
Luxembourg	Wyeth	68.47	66.48	57.40	54.74
Portugal	Wyeth Lederle Vaccines	71.88	68.46	54.77	49.29
Portugal	Wyeth Lederle Vaccines	53.91	51.34	41.07	36.97
Spain	Wyeth Pharma	78.19	75.18	54.21	49.00
Sweden	Wyeth Lederle Nordiska	62.62	62.62	55.65	53.54
Switzerland	Wyeth	72.02	70.51	nv	45.59
The Netherlands	Wyeth	nv	nv	51.94	45.19
United Kingdom	Wyeth Pharma	nv	nv	56.77	49.67

Table 23 adapted from Antony et al.[57]
(a) Personal communication, Kristel Van Beirendonck, Wyeth, 2006

4.2 CURRENT PRACTICE IN BELGIUM (MAY 2006)

Current practice in Belgium can be summarized as follows.

The 7-valent pneumococcal conjugated vaccine is recommended by the Superior Health Council, for all infants, starting at the age of 2 months, in a 4 doses schedule and offered according to the current infant immunization programme in Belgium: i.e. at the age of 2, 3, 4 and 13-18 months. If the pneumococcal vaccination is started between 2 and 6 month of age, a 4-doses schedule will be offered with 4-8 weeks between the 3 first doses, and the fourth dose at age 13-18 months. If started between 7 and 11 months of age, a 3-doses schedule will be offered with 6-8 weeks between the 2 first doses, and the third dose at age 13-18 months.

If pneumococcal immunization is started between 12 and 23 months a 2-dose schedule will be offered, with 6-8 weeks timing between the 2 doses.

Starting above the age of 24 months is only recommended for those children and infants at increased risk of IPD (see introduction).

Based on scientific evidence, the PCV7 vaccine currently marketed in Belgium, Prevenar®, can be concomitantly administered with Infanrix-Hexa, in use in the universal infant immunization programme since 2004.

As the PCV7 vaccine is recommended by the Superior Health Council, at all consultations of the well baby clinics (Kind en Gezin; ONE) parents are systematically informed about the disease, the vaccine and the possibility of having their infant vaccinated, be it at their own cost. Those parents who consult a GP or a paediatrician will be informed by these respective doctors.

Thus, at the well baby clinics as well as at the consultation of the GP or paediatrician the vaccine can be prescribed, and is then available at the pharmacies in Belgium, at €66.15 per dose.

4.3 REQUIRED BUDGET

If no catch-up program is carried out , the investment costs of the introduction of the program should be as follows, at € 50 per dose (€ 45+5):

For a 2,3,4,15m schedule € 21.7 million per vaccinated annual age cohort

For a 2,3,15m schedule € 16.7 million per vaccinated annual age cohort

Depending on the phasing of the introduction (with or without catch-up) there may be fluctuations on this amount.

5 CONCLUSIONS

A mathematical simulation model, by definition, is not reality. It is a tool, which helps to understand complex issues, and project a range of scenarios that cannot be tested in the real world, because of time, ethical and practical constraints. In this case, it may help understand the implications of deciding on how to use the currently available seven-valent pneumococcal conjugate vaccine (PCV7) to our greatest advantage. In health economic evaluation, as applied in this report, what is to our society's greatest advantage is defined as the combination of interventions leading to the greatest possible health gains, for as many people as possible (i.e. maximization of health gains (expressed here mainly as life-years and Quality-Adjusted Life-Years (QALYs) gained)), under a given budget constraint.

We have reviewed the international published and unpublished literature, and collected and analyzed a wide range of Belgian epidemiological and cost data. A simulation model was developed, parameterised and fitted by using scientifically validated data, as much as possible from Belgian sources. Simulations were performed to estimate how effective and cost-effective universal PCV7 vaccination of Belgian children would be.

We conclude the following from our baseline calculations:

- At € 9869 per QALY gained in the baseline, PCV7 vaccination using a 2+1 schedule with injections at 2,3 and 15 months of age is cost-effective compared to other widely accepted interventions in Belgian health care.
- At € 155,619 per QALY gained in the baseline (using already more pessimistic assumptions for the 2+1 than the 3+1 schedule), the incremental cost-effectiveness of a 3+1 schedule (2,3,4, 15 months) versus a 2+1 schedule (2,3 and 15 months) compares unfavourably to other widely accepted interventions in Belgian health care.

Sensitivity analyses showed the first conclusion to be very robust to various plausible changes in input parameters, as well as in multivariate probabilistic sensitivity analysis, in which all parameters were varied simultaneously according to (as much as possible) data driven distributions. It was also shown to be consistently robust to more implausible scenarios, such as ignoring the occurrence of herd immunity effects altogether (when the incremental cost-effectiveness increases to € 44,984 per QALY gained). Overall, it is important to remember that the baseline calculations were as realistic as possible, yet generally conservative where information is currently lacking. The model ignores any positive impact PCV7 vaccination may have on the long-term incidence of antibiotic resistant pneumococcal strains. Furthermore, herd immunity effects observed in the US were used only net of negative changes in non-vaccine type incidence in invasive pneumococcal disease. That is, herd immunity effects taken into account in this analysis, were always reduced to allow for (what are likely) serotype replacement effects observed over the first 5 years in the US program (and the shape of the incremental cost-effectiveness ratios over time in our analysis showed that most of the discounted benefits are realised within 5 years). Furthermore, since this first conclusion remained valid if herd immunity is completely ignored, it is bound to remain valid under scenarios of large serotype replacement effects over much longer time periods (whereby non-vaccine types take over from vaccine types). Of note is also that there are several multivalent pneumococcal conjugate vaccines (9 and 11-valent) likely to be marketed within 5 years from now, which would provide at least partial solutions to such serotype replacement effects. Additionally, the use of the 23-valent polysaccharide vaccine (which is currently not licensed in Belgium for children under 2 years of age), as a potential booster vaccine at age 15 months (instead of PCV) needs also to be further investigated, as it may provide an effective remedy for serotype replacement effects in children.

It is nonetheless important to remain vigilant with regards to potential serotype replacement impacts over time, as well as direct vaccine associated adverse events that might occur (our safety review indicated that particularly the potential association with asthma needs to be monitored closely), and careful surveillance (preferably based on serotyping) is necessary.

The second conclusion is more uncertain. Its validity depends on the ***difference*** in effect the extra interspersed dose (at 4 months) may have on long term (beyond 30 years hence) direct protection against clinical disease in vaccinees, as well as the extent of herd immunity

immediately inferred to non-vaccinated people. In the USA, where due to serious vaccine shortages over the first 3 years of the program, eligible children received only an average of 2.7 doses (and only 35% received a full 3+1 schedule), no significant differences in effectiveness between both schedules could be detected. During the final editing process of this report, additional information from the USA was made available to us, in confidential format, which revises the effectiveness estimates for the 2+1 schedule slightly upwards. These estimates were not included in our analysis, but would only makes the case for the 2+1 schedule as a more cost-effective option than the 3+1 schedule, stronger.

Furthermore in clinical trials, immunogenicity induced for the seven serotypes did not differ significantly between the two schedules. In the analyses presented in this report we pessimistically assumed there would always be at least a difference in direct vaccine protection. Yet only when this difference is assumed to be large and long lasting would the additional effectiveness of the extra dose at 4 months warrant the extra costs that it would take. There is currently no evidence that a 3+1 schedule evokes greater herd immunity than a 2+1 schedule. Yet, we have assumed this to be the case in multivariate sensitivity analyses (reasonably bounded by data from the US), and still could not demonstrate a clear-cut case for the 3+1 schedule.

Indeed, given a willingness to pay of € 40,000 per QALY gained, we find in multivariate sensitivity analysis, that infant immunisation with PCV7 is always cost-effective. Using the same criterion for cost-effectiveness, the incremental cost-effectiveness of the 3+1 versus the 2+1 schedule was only in 5% of the simulations acceptable, when herd immunity is the same under both schedules (which seems the most likely assumption, given current evidence), and was acceptable in about 60% of simulations when we take an optimistic view of the difference in herd immunity between both schedules. Given a willingness to pay of € 200,000 per QALY gained, these percentages increased to about 60% and 80%, respectively.

Additional elements that plead for the use of a 2+1 schedule are related to overcrowding of the schedule, and the knowledge that more new vaccines are expected to become available for introduction soon. The introduction of these new vaccines may be deterred by a lack of existing vaccination opportunities on the schedule, and additional high introduction costs if new vaccination opportunities need to be created.

It is important to remember that in this analysis, the introduction of PCV7 was assumed not to affect the uptake of other vaccines in the program. Clearly, since many of the existing vaccinations are for severe, and highly prevalent diseases (in the absence of vaccination), any negative interference with vaccine uptake of other vaccines could be detrimental to the attractiveness of PCV7 introduction. Therefore, in practice it is important that other due vaccinations are not postponed for the benefit of receiving a PCV7 injection.

The current situation in Belgium, whereby parents and their insurers pay private market prices for a four-dose schedule is likely to be very cost-ineffective from a societal perspective. Indeed, current uptake seems too low to yield large herd immunity effects, whereas private vaccination costs are about 45% higher than they could reasonably be expected to be with a public program. From a societal perspective, i.e. when all costs and benefits are accounted for no matter whom incurs or receives them, the present situation is much more costly and less effective than what could be achieved by a public program. Furthermore, an overall increase in PCV7 uptake will reduce inequities in health expectations (for those who are currently unable to receive the vaccine for medical reasons (eg, those aged under 2 months), and those who cannot afford it), an aspect which was also observed in the USA.

Appendices

6 APPENDIX A: IMMUNOGENICITY, EFFICACY, SAFETY AND EFFECTIVENESS OF PNEUMOCOCCAL CONJUGATE VACCINES

6.1 INTRODUCTION

Unlike the 23-valent pneumococcal polysaccharide vaccine (PPV), Pneumococcal Conjugate Vaccines (PCV), are immunogenic in children younger than two years of age. They are formulated in the same way as the *H. influenzae type b* and meningococcal type C vaccines. Polysaccharides that form part of the capsule of the most commonly occurring serotypes of *Streptococcus pneumoniae* are conjugated to a carrier protein. This causes the immune response of what are normally weakly immunogenic polysaccharides in children to be strongly increased.[7]

Pneumococci in humans can cause, amongst other things, invasive illness (mainly bacteraemia and meningitis), pneumonia, otitis media or sinusitis.[7] Worldwide they are the primary cause of bacteraemia, bacterial meningitis, and acute otitis media. The incedence of invasive pneumococcal disease (IPD) in children younger than 2 years is higher compared to older children: for instance, in the Netherlands and Germany the incidence in this age group is approximately 14/100.000 and in Spain it is more than 90/100.000. [58]

In February 2000 the first 7-valent PCV (PCV7) went on the market in the United States (US) (Prevnar©, Wyeth), after it had been shown to be highly effective against IPD in the Northern California Kaiser Permanente (NCKP) study. This vaccine contains serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. In the NCKP trial PCV7 was administered in a 4-dose schedule to babies at the age of 2, 4, 6 and 12-15 months. After the introduction of PCV7 into the US infant vaccination programme, a reduction in the incidence of IPD of 69% in children younger than one year, 68% in children between one and two years and 44% in children between two and three years was observed (data from 2001 compared to 1998 and 1999). No reduction was seen in children from three to four years.[8] Moreover, PCV7 was shown to be effective against pneumococcal pneumonia and otitis media.

This 7-valent PCV came onto the market in Europe in 2002. At the present time the development of PCVs against more than seven serotypes is continuing undiminished. Merck also developed a PCV7, but with another carrier protein. Wyeth is also testing a 9-valent vaccine (PCV9) and Glaxo SmithKline Biologicals an 11-valent vaccine (PCV11).

In this review, the methods and results of clinical trials are compared with regard to immunogenicity, efficacy and safety, based on the international scientific literature. Only studies on PCVs containing at least seven serotypes, and which went further in development than phase 2 were included.

6.2 METHODS

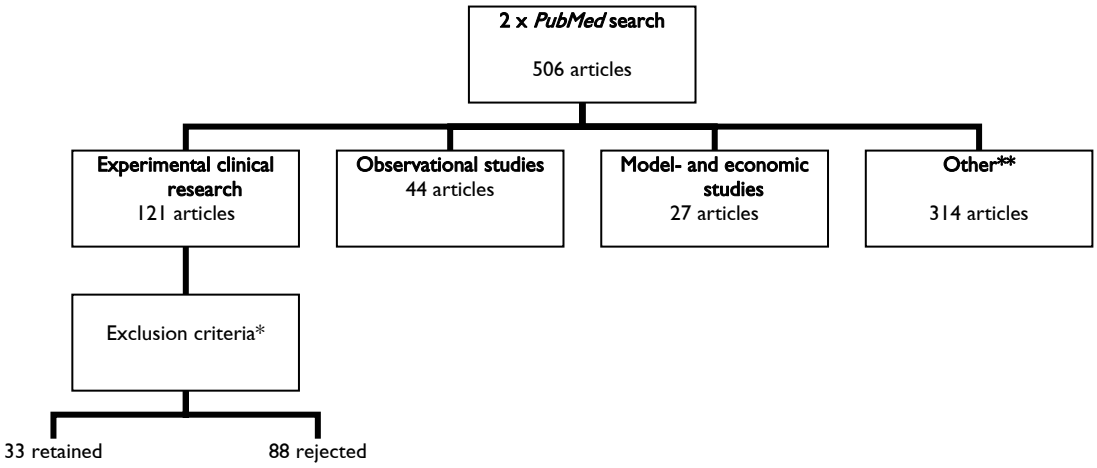
Two broad PubMed searches were performed using the Entrez search system. Each search started from 1998 because only then did the first relevant publications appear on PCVs with more than seven serotypes.

The first time, on 19-01-2006, the search term "pneumococcal conjugate vaccin* NOT review [ptyp]" was used, limited to the search field "Title/Abstract", resulting in 354 hits. Because it seemed that a number of important publications were missed using this method, another PubMed search was performed (on 13-02-2006) using the broader search term "pneumococcal AND conjugate AND vaccin* NOT review [ptyp]" with the exclusion of the articles found earlier, and limiting to "Title/Abstract", age: "All Child 0-18y" and "Humans". Another 152 publications were thus identified.

We initially categorised the studies based on abstracts (and full content if needed), as shown in Figure A1. The experimental clinical research category includes studies in which the investigators decided which participants would receive which vaccine. The only observational study included in this category is by Kayhty et al. This study differs from the other observational studies in that participants underwent immunological tests at well-defined time points before and after the administration of PCV7 doses.[2] Not every article describing clinical research states the phase of

the trial, requiring inference from the methods section. In case of doubt between phase 2 and 3, we assumed that phase 3 research applies if at least 100 trial subjects take part. Nonetheless, one trial (Sigurdardottir et al.) on 160 subjects was not retained, as the information seemed to be outdated. Eight polysaccharides were conjugated to diphtheria toxoid in one vaccine and to tetanus toxoid in the other. Immunogenicity data showed a mixed carrier vaccine to be more ideal. Further testing of the original two vaccines was abandoned, and has now shifted to the mixed carrier vaccine.[3]

Figure A1: Categorisation and selection of search results



* Non PCV-studies, < phase 3, publication < 1998, duplicate publications (and follow-up studies only included if presenting additional material), adults, developing countries, risk groups (HIV-infection, sickle cell anaemia, …), outcome = antoibodies in saliva or urine, avidity of antibodies/ opsonophagocitic activity.
** biological, animal, case report, vaccine uptake, diagnostics, methodological, technical, epidemiological, theoretical impact of PCV, antimicrobial resistance, nasopharyngeal carriage, Prevnar programmatic issues, reviews, conference minutes, commentaries.

A final update of the PubMed search was made end of April 2006, repeating the last search strategy. This produced one more article, published by Prymula et al.[4] In addition, we included two very recent articles we became incidentally aware of, by Scheifele et al.[5] and Goldblatt et al.[6] The clinical trials review was finally written on the basis of 36 publications.

6.3 PNEUMOCOCCAL VACCINES

In Wyeth's PCV7 and PCV9, the different polysaccharides are bound to cross reacting material (CRM) 197. This is a non-toxic mutant of the diphtheria toxin. Merck selected the outer membrane protein complex (OMPC) of *Neisseria meningitidis* serogroup B as carrier protein for its 7-valent vaccine (PncOMPC). For its 11-valent PCV, Glaxo SmithKline Biologicals used the D protein of *Haemophilus influenzae* to bind the polysaccharides. The tables below describe the composition of the different pneumococcal vaccines in more detail.

Publications on clinical research into PCV7 (including PncOMPC) are described in Tables A1-A4. Tables A1 and A2 comprise randomised controlled trials (RCTs and follow-up trials), and Table A3 clinical trials. Table A4 details studies in which PCV7 or PncOMPC were administered in combination with PPV. The published articles about PCV9 and 11 trials are summarised in Table A5, and in Table A6 there are some more clinical trials that take only nasopharyngeal carriage as clinical endpoint.

In the tables the type of research conducted is given per study. As a general rule, the following hierarchical order is applied to the different kinds of studies: 1 RCT, 2 controlled clinical trial without randomisation, 3 cohort- or case-control study, 4 comparative time-series analyses and 5 guidelines from a number of authorities.[59]

Table A1: Randomized Controlled trials on 7-valent PCV

Trial	Country	composition	design	Comment
Scheifele DW, 2006 [5]	Canada	CRM-197 = PS 4, 6B, 9V, 14, 18C, 19F, 23F	RCT, evaluator blinded, multicentre, phase 4	Random assignment (block randomization) to receive intervention or control regimen, but randomisation method not described in detail. Table with comparison of baseline characteristics of the intervention and control groups present.
Tichmann-Schumann I, 2005 [60]	Germany	CRM-197 = PS 4, 6B, 9V, 14, 18C, 19F, 23F	RCT, multicentre, phase 3 or 4	Random assignment to receive intervention or control regimen, but randomisation method not described. Table with comparison of baseline characteristics of the intervention and control groups also not present.
Reinert P, 2003 [61]	France	CRM-197 = PS 4, 6B, 9V, 14, 18C, 19F, 23F	RCT, multicentre, phase 3 or 4	Random assignment to receive intervention or control regimen, randomisation via central office. Table with comparison of baseline characteristics of the intervention and control groups not present.
Schmitt HJ, 2003 [62]	Germany	CRM-197 = PS 4, 6B, 9V, 14, 18C, 19F, 23F	RCT, multicentre, phase 3 or 4	Random assignment to receive intervention or control regimen, randomisation with computer generated list. Table with comparison of baseline characteristics of the intervention and control groups not present.
O´Brien KL, 2003 [52]	US	CRM-197 = PS 4, 6B, 9V, 14, 18C, 19F, 23F	RCT, double blind, multicentre, phase 3	Random assignment to receive intervention or control regimen, group-randomization with clusters of existing communities, computerized randomisation (block randomization). Table with comparison of baseline characteristics of the intervention and control groups present. Staff and subjects blinded. (Moulton LH, 2001) [63]
Choo S, 2000 [64]	UK	CRM-197 = PS 4, 6B, 9V, 14, 18C, 19F, 23F	RCT, multicentre, phase 3	Random assignment to receive either of the intervention regimens or control regimen, randomisation with computer generated list. Table with comparison of baseline characteristics of the intervention and control groups not present.
Shinefield HR, 1999 [65]	US	CRM-197 = PS 4, 6B, 9V, 14, 18C, 19F, 23F	RCT, multicentre, phase 3	At the start of the study random assignment to receive intervention or control regimen and before receiving the booster another randomisation within each group. Randomisation method not described. Table with comparison of baseline characteristics of the intervention and control groups not present. Which people were blinded and with help of which method not reported.

TABLE A1 PART 1

ref.	subjects				intervention		control		co-administration		evaluation points	results	
	number (drop-outs)	description	age	recruitment	vaccine	regimen	vaccine	regimen	vaccine	regimen	blood sample	immunology	efficacy [95%CI]
[5]	376 (8)	Healthy	2m		DTaP-IPV-Hib (SP) + HepB (Merck) + PCV7 simultaneously	2, 4 and 6 m	DTaP-IPV-Hib (SP) + HepB (Merck) (+ PCV7 op 3, 5 and 7 m)	2, 4 and 6 m			before and 1-2 m after last vaccination	95%CI present. Cut-off GMC 0.15 and 0.50µg/ml. After 3rd dose above cut-off of 0.50µg/ml for all serotypes regarding 93.5-100% of hte subjects, except 6B (84.6%) and 23F (87.8%).	NA
[60]	345 (79)	healthy, a term (36-42 w)	8-16 w		Infanrix Hexa (GSK) + PCV7 simultaneously	2, 3, 4 en 11-14 m	Infanrix Hexa (GSK) (+ PCV7 between 7 and 11 m)	2, 3, 4 and 11-14 m			2 and 5 m ,before and 1 m after booster.	95%CI present. (PP 80.9% of the subjects) Cut-off GMC 0.05 µg/ml. After 3rd dose above cut-off for all serotypes regarding 97.2-100% of the subjects.	NA
[61]	157 (6)	healthy, a term (37 w)	7-11 w	Via 12 private pediatric practices.	PCV7 + DTP-Polio-Hib	2, 3 and 4 m	DTP-Polio-Hib	2, 3 and 4 m			2 and 5 m	95%CI present. (PP 70.1% of the subjects) Cut-off GMC 0.15 and 0.5 µg/ml. After 3rd dose above cut-off of 0.5 µg/ml for all serotypes regarding 84.9-96.3% of the subjects.	NA
[62]	231 (8)	Healthy	57-112 d		PCV7 + DTaP-IPV-Hib-HepB simultaneously	2, 3, 4 and 11-15 m	DTaP-IPV-Hib-HepB, afterwards PCV7	DTaP-IPV-Hib-HepB: 2, 3, 4 and 11-15 m. PCV7: 6, 7, 8 and 11-15 m.			2, 3, 4 and 5 m, 1 m after booster	(PP 68.4% of the subjects) Cut-off GMC 0.15 and 0.50µg/ml. After 4th dose above cut-off of 0.50µg/ml for all serotypes regarding 96.9-98.4% of the subjects.	NA
[52]	8292	100% native Indians	6 w - 24 m	By Indian field workers or via pediatric hospitals.	PCV7	Children < 7 m: 3 doses with interval of 2 m and children > 7 m: 2 doses with interval of 2 m. Booster at 12-15 m .	MenC (Wyeth)	simultaneously	DTaP, Hib, OPV, MMR, Varicella	simultaneously	In case of sepsis, meningitis, suspicion of IPD or unexplained fever > 39.4 C.	NA	VE of PCV7 against IPD caused by VT in children < 2y: 81.7% [16.3 to 96.0] (PP 78.9% of the subjects) or 86.4% [40.3 to 96.6] (ITT 97.6% of the subjects). VE against all IPD in children < 2y: 54.1 [-13.6 to 81.5] (PP) or 46.3 [-16.5 to 75.3] (ITT).

ref.	subjects				intervention		control		co-administration		evaluation points	results	
	number (drop-outs)	description	age	recruitment	vaccine	regimen	vaccine	regimen	vaccine	regimen	blood sample	immunology	efficacy [95%CI]
[64]	368 (42)	Healthy	6-10 w	Contact parents of neonates on maternity ward or routine Child Health Care visits.	PCV7. 1st intervention: co-administration separate injection site. 2nd intervention: combined in 1 injection with co-administration. PPV as booster.	PCV 7: 2, 3 and 4 m. PPV: 13-16 m.	PCV7 + PPV	PCV7: 5, 6 and 7 m. PPV: 13-16 m.	DTwP, Hib, OPV, MMR	DTwP + Hib + OPV: 2, 3 and 4 m. MMR: 13-16 m.	2 and 5 m, before and 1 m after booster	(PP 96.5% of the subjects) Cut-off GMC 0.15 and 1.0 µg/ml. Results 1st intervention arm: after 4th dose above cut-off of 1.0 µg/ml for all serotypes regarding 93-100% of the subjects. Results 2nd intervention arm: after 4th dose cut-off above of 1.0 µg/ml for all serotypes regarding 92-99% of the subjects.	NA
[65]	302 (38)	Healthy	2 m	Via North California Kaiser Permanente Health Plan.	PCV7. Booster: After 2nd randomisation PCV7 or DTaP + Hib or combination.	2, 4 6 and 12-15 m	MenC	2, 4 and 6 m	DTwP-Hib, OPV, HepB	2, 4 and 6 m (for HepB half of subjects concomitant, the rest two weeks before or after studyvaccine)	2 and 7 m, before and 1 m after booster	(PP) Cut-off GMC 0.15 and 1.0 µg/ml. After 4th dose above cut-off of 0.15 and 1.0 µg/ml for all serotypes.	NA

TABLE A1 PART 2

Footnote 1: PCV was provided by Wyeth in all the studies.

Footnote 2: exclusion criteria of the subjects are described in all the studies, except the study of Shinefield HR, 1999.

Footnote 3: in all the studies in which immunologic results were presented, the follow-up period was 1 month after the last vaccination.

Tabel A2: Follow-up trials on 7-valent PCV

Trial	country	firm	composition	design	comment
Finnish Otitis Media study: Eskola J, 2001[66] Kilpi T, 2003 [67] Straetemans M, 2003 [68] Palmu AA, 2004 [69]	Finland	1st intervention: Wyeth. 2nd intervention: Merck.	1st intervention: CRM-197 = PS 4, 6B, 9V, 14, 18C, 19F, 23F. 2nd intervention: OMPC = PS 4, 6B, 9V, 14, 18C, 19F, 23F.	RCT, double blind, multicentric, phase 3	Random assingment to recieve either of the intervention or the control regimen, block randomisation with use of sealed envelopes. Table with comparison of baseline characteristics of the intervention and control groups present. Blinding of vaccinators and subjects.
Zangwill KM, 2003 [70]Yeh SH, 2003 [71]	US	Merck	OMPC = PS 4, 6B, 9V, 14, 18C, 19F, 23F. Lot 1	RCT, fase 3. Controlled Clinical Trial, fase 3	Random assignment to receive either of the intervention regimens, but randomisation method not described. Table with comparison of baseline characteristics of the intervention groups not present.
North California Kaiser Permanente study: Black S, 2000 [51] Shinefield H, 2002 [72] Black S, 2002 [73] Fireman B, 2003 [74]	US	Wyeth	CRM-197 = PS 4, 6B, 9V, 14, 18C, 19F, 23F	RCT, double blind, multicentric, phase 3	Random assignment to receive either of the intervention or the control regimen, randomisation method not described. Table with comparison of baseline characteristics of the intervention and control groups present. Which people were blinded and by which method not reported.

TABLE A2 PART 1

ref.	Subjects		intervention		control		co-administration		evaluation points		follow-up	results	
	number (drop-outs)	recruitment	vaccine	regimen	vaccine	regimen	vaccine	regimen	blood sample	other		immunology	efficacy [95%CI]
66 67 68 69	2497 (1% PCV7-group, 4% HepB-group)	Via prenatal health clinics and child health centres.	1st intervention: PCV7. 2nd intervention: PCV7 (booster = PPV for 187 subjects).	2, 4, 6 and 12 m	Hep B	2, 4, 6 and 12 m	DTwP-Hib, IPV, MMR	DTP-Hib: 2, 4 and 6 m. IPV: 7 and 12 m. MMR: 18 m.	2, 4, 6, 7, 12, 13 and 24 m	Tympanometry en pneumatic otoscopy: 7 and 24 m	For immunology 12 m after last vaccination. For AOM 12 m after last vaccination. For AOM 3-4 y after last vaccination.	Cut-off GMC 0.3, 0.5 and 1.0µg/ml. Results 1st intervention arm: after 4th dose above cut-off of 1.0 µg/ml for all serotypes regarding 90.9-100% of the subjects. Results 2nd intervention arm: after 4th dose all serotypes above cut-off of 1.0µg/ml regarding 83.0-99.1% of the subjects.	(PP 95% of the subjects) VE of PCV7 against episodes of AOM cause by VT: 57% [44 to 67]. VE against all episodes of AOM: 6% [-4 to 16]. (PP) VE of PncOMPC against episodes of AOM caused by VT: 56% [44 to 66]. (ITT) OR of AOM/ OME/tympanostomy tube placement in PCV7-group compared to HepB-group 0.94. In case of older siblings 1.04 [0.79 to 1.39] and in case of no older siblings 0.81 [0.55 to 1.20]. (ITT) VE of PCV7 against all episodes of AOM from 12 m up to 3-4y after last vaccination: 8% [-2 to 16].
70 71	240. 81 (14)	Via pediatric hospital.	1st intervention: PCV7 + DTwP or Hib. 2nd intervention: PCV7 + Hib-HepB or Hib. PCV7	PCV7 and DTwP or Hib-HepB at 2, 4 and 6 m. PCV7 and Hib at 12 m. 2, 4, 6	PCV7 + DTwP or PPV. None.	PCV7 and DTwP at 2, 4, and 6. PCV7 or PPV at 12 m.	other routine pediatric vaccines		2, 4, 6, 7, 12 and 13 m	NP-swab: 2, 6, 7, 12 en 13 m.	For immunology 1 m after last vaccination.	Cut-off GMC 0.15 and 1.0µg/ml. After 4th dose all serotypes above cut-off of 1.0 µg/ml.	NP-carriage: only serotype 23F significant less prevalent in intervention arm.

ref.	Subjects		intervention		control		co-administration		evaluation points		follow-up	results	
	number (drop-outs)	recruitment	vaccine	regimen	vaccine	regimen	vaccine	regimen	blood sample	other		immunology	efficacy [95%CI]
				and 12 m.									
51 72 73 74	37868	Via North California Kaiser Permanente Health Plan. With use of hospitalisation discharge codes.	PCV7	2, 4, 6 and 12-15 m	MenC	2, 4, 6 and 12-15 m	DTwP-Hib and OPV, later DTaP and IPV. Also HepB, MMR, varicella.	Concomitant or two w before or after study vaccine.	2 and 7 m, before and 1 m after booster	NA	For immunology 1 m after last vaccination.	(PP) Cut-off GMC 0.15, 0.50 and 1.0 µg/ml. After 3rd dose above cut-off of 0.50 µg/ml regarding 82-97% of the subjects.	VE of PCV7 against IPD caused by VT: 97.4% [82.7 to 99.9] (PP) or 93.9% [79.6 to 98.5] (ITT). VE against all IPD: 89.1% [73.7 to 95.8] (ITT). VE of PCV7 against IPD in preterm or low-birth-weight children: 100% (p=0.01-0.03). (ITT) VE of PCV7 against VT pneumonia: 87.5% (p=0.04). VE of PCV7 against prescription of AB: 5.7% [4.2 to 7.2] (PP) or 5.4% [4.0 to 6.7] (ITT).

TABLE A2 PART 2
Footnote 1: in FinOM study also data on PncOMPC, in study of Zangwill and Yeh only data on PncOMPC.
Footnote 2: exclusion criteria of the subjects described in all the studies, except for the study of Zangwill KM, 2003 and Yeh SH, 2003.
Footnote 3: in all studies the subjects are healthy and 2 months old at the study start.

Table A3: Clinical Trials on 7-valent PCV

trial	country	composition	design	subjects			intervention		co-administration		evalutation points	results
				number (drop-outs)	description	age	vaccine	regimen	vaccine	regimen	blood sample	immunology
de Aristegui Fernandez J, 2005 [75]	Spain	CRM-197 = PS 4, 6B, 9V, 14, 18C, 19F, 23F	Clinical Trial, multicentre, phase 3 or 4	115	no specifications	24-36 m	PCV7	1 dose at 24-36 m	none		before and 1 m after vaccination	95%CI present. (PP 82.6% of the subjects) Cut-off GMC 0.15 and 0.50 µg/ml. Above cut-off of 0.50 µg/ml for all serotypes regarding 95-99% of the subjects.
Esposito S, 2005 [76]	Italy	CRM-197 = PS 4, 6B, 9V, 14, 18C, 19F, 23F	Clinical Trial, phase 3 or 4	92	healthy, 46 preterm (32-36 weeks) and 46 a term	75-105 d	PCV7	3, 5 and 11 m	IPV, DTaP, HepB, Hib	according to guidelines	3, 6, 11 and 12 m	Cut-off GMC 0.15, 0.35 and 1.0 µg/ml. Results a terme children: after 3rd dose above cut-off of 1.0 µg/ml for all serotypes regarding 93.5-100 % of the subjects.
Kayhty H, 2005 [2]	Sweden	CRM-197 = PS 4, 6B, 9V, 14, 18C, 19F, 23F	Clinical Trial, descriptive study, multicentre, phase 4	101 (2)	healthy, 46 preterm (32-36 weeks) and 46 a term	3 m	PCV7	3, 5 and 12 m	DTaP-IPV-Hib	3, 5 and 12 m	3, 6, 12 and 13 m	Cut-off GMC 0.20 and 0.35µg/ml. After 3rd dose above cut-off of 0.35 µg/ml for all serotypes regarding 86-100% of the subjects.

Footnote 1: in all the studies PCV was provided by Wyeth.
Footnote 2: only in the study of Kayhty H, 2005 the method of recruitment is described. A letter was sent to the parents of neonates.
Footnote 3: in all the studies the exclusion criteria of the subjects are described, except for in the study of Kayhty H, 2005.
Footnote 4: the follow-up period for the immunology results was 1 month after the last vaccination in all the studies.

Table A4: Trials on 7- and 9-valent PCV + PPV

Trial	country	composition	design	comment
Goldblatt D, 2006 [6]	UK	CRM197 = PS 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F	RCT, phase 3 or 4	Random assignment to receive the intervention or control regimen, but randomisation method not described. Table with comparison of baseline characteristics of the intervention and control groups not present.
Van Kempen MJ, 2006 [77]	Belgium	CRM197 = PS 4, 6B, 9V, 14, 18C, 19F, 23F	RCT, double blind, phase 3 or 4	Random assignment to receive the intervention or control regimen, randomisation list sent from central office. Table with comparison of baseline characteristics of the intervention and control groups present. Blinding of staff and subjects by means of two independent study nurses who administered all the vaccines.
Veenhoven R, 2003 [54] Veenhoven R, 2004 [78] Bogaert D, 2005 [79] Brouwer CN, 2005 [80]	The Nederlands	CRM197 = PS 4, 6B, 9V, 14, 18C, 19F, 23F	RCT, double blind, multicentric, phase 3	Random assignment to recieve the intervention or control regimen, assignment of vaccines through randomisationlist. Tabel with comparison of baseline charasteristics of the intervention and control groups present. Dokters and subjects remained blinded, because vaccines were administered by study nurse.
Blum MD, 2000 [81]	Israel	OMPC = PS 4, 6B, 9V, 14, 18C, 19F, 23F	RCT, multicentre, phase 3	Random assignment to receive either of the intervention or control regimen, in intervention groups another randomisation before administration of the booster. randomisation method not described. Table with comparison of baseline characteristics of the intervention and control groups not present.

TABLE A4 PART 1

ref.	Subjects				intervention (start of study = 0 m)		control		co-administration	evalution points		follow-up	results	
	number (drop-outs)	description	age	recruitment	vaccine	regimen	vaccine	regimen	vaccine	blood sample	other		immunology	efficacy
6	92 (10)	No specifications	12 m	Via practices of general practitioners.	PCV9 + PPV	PCV9: 0 m. PPV: 6 m.	PCV9 + PPV	PCV9: 0 and 2 m. PPV: 6 m.	MMR	0, 1-3, 6 and 7 m		For immunology 1 m after last vaccination.	Cut-off GMC 0.2, 0.35 and 1.0 µg/ml. Results intervention group: after 1st dose above cut-off of 1.0µg/ml for all serotypes regarding 80-100% of the subjects, except 6B (49%). Results control group: after 2nd dose above cut-off of 1.0µg/ml for all serotypes regarding 92-100%of the subjects. After booster with PPV above cut-off of 1.0µg/ml for all serotypes regarding 92-100% of the subjects.	NA
77	74 (6)	At least 2 clinical episodes of AOM in the past y.	1-7 y	Via department of otorhinolaryngology of University of Ghent.	PCV7 + PPV	PCV7: children 12-24 m at 0 and 1 m, children ≥ 25 m at 0 m. PPV: 7 m.	HepA (GSK)	simultaneously		0, 1, 2 and 8 m	NP swab: 0, 7, 14, 20 and 26 m	For immunology 19 m after last vaccination. For efficacy 18 m after last vaccination.	no cut-off GMC	(PP) Total number of episodes of AOM in intervention arm: 32, in control arm 26.

ref.	Subjects				intervention (start of study = 0 m)		control		co-administration	evalution points		follow-up	results	
	number (drop-outs)	description	age	recruitment	vaccine	regimen	vaccine	regimen	vaccine	blood sample	other		immunology	efficacy
54 78 79 80	383 (20)	At least 2 clinical episodes of AOM in the past y.	1-7 y	Via GP, pediatrician or otorhinolaryngologist referred to or direct enrollment at pediatric outpatient clinic of general hospital and university pediatric hospital.	PCV7 + PPV	PCV7: Children > 2 j: 0 m, children < 2 j 0 en 1 m. PPV: 7 m.	HepA (children > 2j) or HepB (children < 2j)	HepA: 0 and 7 m. HepB: 0, 1 and 7 m.		0 and 8 m	NP swab: 0, 7, 14, 20 en 26 m. Questionairs: 0, 14 and 26 m.	For episodes of AOM 18 m after last vaccination. For immunology 1 m after last vaccination. For NP carriage 19 m after vaccination. For quality of life 19 m after last vaccination.	Cut-off GMC 1.0µg/ml. After PPV-booster above cut-off of 1.0µg/ml for all serotypes regarding 100% of the subjects, except 6B in children < 2 y.	Percentage of AOM caused by VT in PCV7 + PPV-group: 4%, in control group: 9%. Percentage of all AOM in PCV7 + PPV-group: 58%, in control group: 56% (PP 95.8% of the subjects). VE vs VT AOM: 51% NP carriage of VT pneumococcus in PCV7 + PPV-group for vaccination: 46%, after vaccination: 26%.
81	123	healthy	Intervention arm: 12-18 m, control arm: 24-30 m.		1st intervention: PCV7 + booster (PCV7 or PPV). 2nd intervention: PPV + booster (PCV7 or PPV)	PCV7 or PPV: 0 m. Booster: 12 m.	PCV7 or PPV	0 m	DTP, Hib, OPV, MMR	before and 1 m after vaccination	NA	1 m after last vaccination	no cut-off GMC	NA

TABLE A4 PART 2

Footnote 1: For all the studies PCV was provided by Wyeth, except for the study of Blum, 2000 where it was provided by Merck.

Footnote 2: In the study of Goldblatt D, 2006 there is no clarity which of the two intervention groups is the control group. Therefore the group with the two administrations of PCV9 has been named the control group.

Footnote 3: Age of subjects=age at study start. In vaccination regimen month 0=start of study.

Footnote 4: in the study of Blum MD, 2000 the co-administered vaccines are given according to guidelines.

Footnote 5: Exclusion criteria of the subjects are described in all the studies, except for in the study of Goldblatt D, 2006.

Table A5: Trials on 9- and 11-valent PCV

trial	country	composition	design	comment
Goldblatt D, 2006 [6]	UK	CRM197 = PS 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F	Controlled Clinical Trial, multicentric, phase 3 or 4	There is a random assignment to recieve PCV or PPV as a booster, but this randomisation is not applicable for the groups that are compared in the analysis of the results.
Dagan R, 2001 [82] Dagan R, 2002 [83] Gion-Lavi N, 2003 [84] Dagan R, 2003 [85] Dagan R, 2005 [86]	Israel	CRM197 = PS 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F	RCT, double blind, multicentric, phase 3	Random assignment to recieve the intervention or control regimen, but randomisation methode not described. Tabel with comparison of baseline charasteristics of the intervention and control groups present. The dokters and subjects remained blinded because a study nurse administered the vaccines.
Prymula R, 2006 [4]	Tzech Republic and Slovakia	Proteine D = PS 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F	RCT, double blind, multicentric, phase 3	Random assignment to recieve the intervention or control regimen, but randomisation via cetral internet system. Tabel with comparison of baseline charasteristics of the intervention and control groups present. Which people were blinded and with help of which method not reported.

TABLE A5 PART 1

ref.	subjects				intervention		control		co-administration		evaluation points		follow-up	results	
	number (drop-outs)	Description	age	recruitment	vaccine	regimen	vaccine	regimen	vaccine	regimen	blood sample	other		immunology	efficacy [95%CI]
6	172 (11)	no specifications	2 m	Via practices of general practitoners.	PCV9 + booster (=PPV for 85 subjects, for the rest PCV)	PCV9: 2 and 4 m. Booster: 12 m.	PCV9 + booster (=PPV for 85 dsubjects, for the rest PCV)	PCV9: 2, 3 and 4 m. Booster: 12 m.	DTaP-Hib, MenC, OPV	2, 3 and 4 m	2, 5, 12 en 13 m	NA	For immunology 1 m after last vaccination.	Cut-off GMC 0.2, 0.35 and 1.0 µg/ml. Results with 2 priming doses: after 2nd dose above cut-off of 1.0µg/ml for all serotypes regarding 72-93% of the subjects, except 6B (56%) en 23F (54%). Results with 3 priming doses: after 3rd dose above cut-off of 1.0µg/ml for all serotypes regarding 74-94% of the subjects, except 6B (52%) and 23F (64%).	NA
82 83 84 85 86	264. In FU-study 23 siblings of subjects from the intervention group were compared with 23 siblings of subjects of the control group.	Healthy children in day-care centers. Siblings not in day care.	12-35 m. Siblings 18 m.	Via day-care centers.	PCV9. Siblings did not recieve a vaccine.	Children up to 17 m: 2 doses with interval pf 2-3 m. Children from 18 m and up: 1 dose.	MenC. Siblings did not recieve a vaccine.	simultaneously			1 m after last vaccination	Rapporting of infections by parents: each m in 1st y after last vaccination, every 2 m in 2nd y. NP swab: each m in 1st y after last vaccination, every 2 m in 2nd y.	For respiratory tract infections and NP carriage 25 m after last vaccination. For immunology 1 m after last vaccination.	no cut-off GMC	VE of PCV9 against URTInfecties, LRT-problems and otitis media: 15, 16 and 17% resp. Number of NP VT carriers in PCV9-group before and after vaccination: 39 and 13%, in control group before and after vaccination: 41 and 21%. Number of NP VT carriers in siblings of PCV9-group after vaccination: 21%, in siblings of control groep after vaccination: 34%.

ref.	subjects				intervention		control		co-administration		evaluation points		follow-up	results	
	number (drop-outs)	Description	age	recruitment	vaccine	regimen	vaccine	regimen	vaccine	regimen	blood sample	other		immunology	efficacy [95%CI]
[4]	4968	no acute illnes	6 w – 5 m	Via pediatricians where subjects visited with parents in hospitals.	PCV11	3, 4, 5 and 12-18 m	Hep A	3, 4, 5 and 12-18 m	DTaP-Hib-HepB	? and 15-18 m	3 and 6 m, before and 1 m after booster (in 257 subjects)	NP swab: 15-18 m (in 352 subjects)	For immunology 1 m after last vaccination. For efficacy 12 m after last vaccination. For NP carriage 3 m after last vaccination.	95%CI present. (PP 98,7% of the subjects) Cut-off GMC 0.2µg/ml. After 3rd dose above cut-off for all serotypes regarding 96% of the subjects, except 6B (80.5%) and 23F (91.4%).	VE of PCV11 against episodes of VT AOM: 57.6% [41.4 to 69.3] (PP). VE against all episodes of AOM: 33.6% [20.8 to 44.3] (PP). NP carriage of VT after last vaccination in PCV11-group: 6% and control group: 11%.

TABLE A5 PART 2

Footnote 1: PCV was provided by Wyeth in all the studies, except for in the study of Prymula R, 2006 where it was provided by GlaxoSmithKline.

Footnote 2: In the study of Goldblatt D, 2006 there is no clarity which of the two intervention groups is the control group. Therefore the group with the 3 administrations of PCV9 in the priming series has been named the control group.

Footnote 3: exclusion criteria of the subjects are described in all the studies, except the study of Goldblatt D, 2006.

Table A6: Nasopharyngeal carriage studies concerning 7-valent PCV

trial	country	composition	design	subjects					intervention		control	evaluation points	follow-up	results [95%CI]
				number (drop-outs)	description	age	recruitment	exclusion	vaccine	regimen	vaccine	NP swab		
Frazao, 2005 [87]	Portugal	CRM-197 = PS 4, 6B, 9V, 14, 18C, 19F, 23F	Controlled Clinical Trial, phase 3 or 4	695 (5)	healthy children in daycare	6 m – 6 j			PCV7	0, 1 and 6 m. (m 0 = start of study). Children of < 1j 3 doses, of 1-2 j 2 doses and of > 2 j 1 dose.	none	NP swab: 0, 1, 6, 9, 18 and 21 m. Reporting by parents: 0, 1, 6, 9, 18 and 21 m.	15 m after last vaccination	NP carriage of drug resistant VT pneumococci in de PCV7-groep: after 0 doses 81% [p<0.05] and after 3 doses 5% [p<0.05]. In control group: after 0 doses 59% and after 3 doses 76%.
Ghaffar F, 2004 [88]	US	CRM-197 = PS 4, 6B, 9V, 14, 18C, 19F, 23F	Clinial Trial, multicentre, phase 3 or 4	278 (23)	no specifications	2 m	Via private practice and via Continuity Care Clinics integrated in Children's Medical Centre.	description of criteria	PCV7	2, 4, 6 and 12-15 m	NA	2, 4, 6, 9, 12-15 and 15-18 m		NP carriage of VT: 6 [3 to 9], 18 [13 to 23] and 9% [5 to 13] at resp. 2, 12-15 and 15-18 m.
Lakshman R, 2003 [89]	UK	CRM-197 = PS 4, 6B, 9V, 14, 18C, 19F, 23F	Controlled Clinical Trial, multicentre, phase 3 or 4	267	healthy	2-5 y	Intervention group: children known for study in past. Control group: parents contacted via day-care and GP.	description of criteria	PCV7 + PPV	PCV7: 2, 3 and 4 m. PPV: 13 m.	none	At least 11 m after vaccination, 1 in the summer and 1 in the winter.	11-47 m after last vaccination.	NP carriage of pneumococcus in PCV7 + PPV-group: 24.7% (p=0.7) in the summer and 43.4% (p=0.8) in the winter. In control group: 27.0% (p=0.7) in the summer and 41.0% (p=0.8) in the winter.

Footnote: the PCV-study vaccine in all the studies was delivered by Wyeth.

6.4 IMMUNOGENICITY AND VACCINATION SCHEDULES

6.4.1 Protection and cut-off value

To demonstrate the immunogenicity of PCV, most researchers describe the percentage of participants whose serum contains a geometric mean concentration (GMC) of IgG antibodies above a certain cut-off value, per polysaccharide. How high the cut-off value is set is fairly arbitrary. In various studies the values of 0.05, 0.2, 0.3, 0.15, 0.35, 0.5 and 1.0 µg/ml were used.

Cut-off values of 0.15 and 1.0 µg/ml are used in *H. influenzae* type b vaccine studies as correlates for short- and long-term protection. The World Health Organisation determined a cut-off value that correlates to protection against IPD in several stages. Jodar et al. published the provisional results in 2003. Based on an analysis of data from the NCKP study a protective cut-off value of 0.2µg/ml was arrived at after a third dose of PCV7 within the priming series. The authors stated that it would be better to use a cut-off value per polysaccharide, but could only determine a cut-off value for serotype 19F, which was 0.4µg/ml, with the available data.[90] Later, using the same model based on the results from the NCKP study and two more large RCTs with PCV7 and PCV9, a final protective cut-off value of 0.35 µg/ml was established.[2]

6.4.2 Immunogenicity

The studies under review have very similar immunogenicity results after the administration of a third dose of PCV7. The percentage of participants who were above the cut-off GMC level of (at least) 0.35µg/ml after the third dose of the priming series was analysed, (measured one month after the third priming dose). Various randomised studies reported that 82-100% of participants achieved a GMC above the selected cut-off value for all serotypes.[51, 66, 61, 62, 60, 5]

A number of authors studied the immunogenicity of a priming series of PCV7 at 2, 3 and 4 months as opposed to the classical series at 2, 4 and 6 months. Both schedules result in comparable antibody concentrations, an observation which was confirmed in the studies by Tichmann-Schumann et al., Reinert et al., Schmitt et al and Choo et al. [64, 61, 62, 60]

Two clinical trials investigated the immunogenicity after a priming series of two doses of PCV7 instead of three. Bearing in mind the peak incidence of invasive pneumococcal infections in young children (6-11 m),[7] it is important to look at the percentage of infants who achieved a GMC above the minimum cut-off value of 0.35µg/ml after the second vaccination. The results show a slightly wider spread, i.e., 76-100% for all serotypes, except 6B and 23F which reach lower percentages.[76, 2]

PncOMPC is somewhat less immunogenic than PCV7, with 82.4-88.8% of participants achieving a GMC above the chosen cut-off value after three priming doses (measured one month after the third priming dose).[67] The immunogenicity of PCV9 was compared after administration in a 2, 4 and 12 month schedule and a 2, 3, 4 and 12 month schedule. In the group who received two priming doses, 89-100% of the infants had a GMC above the cut-off level of 0.35µg/ml after the third dose. In the group who received three priming doses, this percentage was 84-100% after the second dose.[6] There are not enough published data to make a similar comparison for PCV11.

Several studies showed that PCV7 can be given concomitantly with the Sanofi Pasteur-MSD DTwP-IPV-Hib combination vaccine,[61] DTaP-IPV-Hib from Sanofi Pasteur[5] and from Glaxo SmithKline Biologicals,[2] the Glaxo SmithKline Biologicals DTaP-IPV-Hib-HepB vaccine,[62, 60] the Lederle DTaP and OPV vaccines, the Wyeth Hib vaccine,[65] and the Merck hepatitis B vaccine.[5] Each of these studies looked at whether it was possible to administer PCV7 simultaneously with the vaccines listed above, on the basis of immunogenicity and safety data. In addition, it appeared from the NCKP study that the efficacy of PCV7 against acute otitis media is not diminished when it is administered at the same time as DTwP or DTaP vaccines.[74]

Only a few studies have been done in which infants were given PPV as a booster (4th dose) in a 4-dose pneumococcal vaccine schedule. PCV7 or PncOMPC were then given as priming dose at 2, 4 and 6 or 2, 3 and 4 months. PPV as booster gave higher antibody concentrations than PCV7 and PncOMPC, but not necessarily a higher efficacy (only studied for VT otitis media).[64, 67, 70] More research has been done in older children to look at the use of PPV after priming with PCV, but little data has been published on the resulting immunogenicity, in which levels of cut-off were used.[81, 54, 6, 77]

A number of the polysaccharides used in pneumococcal vaccines repeatedly appear to be less immunogenic after the priming series. These are the polysaccharides that should offer protection against serotypes 6B, 23F and 9V.[65, 64, 3, 54, 76, 2, 4, 5] However, for serotypes 6B and 23F, it has been reported that despite a low immunogenicity after the priming series, the antibody concentrations after the administration of a booster dose are high or very high. It also appears, therefore, that a low immunogenic serotype does not always offer less protection against AOM.[67, 4]

6.5 PROTECTIVE EFFICACY AGAINST CLINICAL DISEASE

6.5.1 IPD and pneumonia

The efficacy of PCV in preventing IPD, pneumonia, otitis media and nasopharyngeal (NP) carriage of pneumococci has been investigated. Out of this list of illnesses, PCV offers most protection against IPD and pneumonia. In the NCKP trial, a PCV7 vaccine efficacy (VE) of 97.4% [95%CI=82.7 to 99.9] against IPD caused by vaccine serotypes (VT) was found in the per protocol (PP) analysis and 93.9% [95%CI=79.6 to 98.5] in the intention to treat (ITT) analysis. The VE against IPD in general was 89.1 [95%CI=73.7 to 95.8] in the ITT analysis. In one group of more than 6000 preterm children and children with a low birth weight, the investigators recorded a level of protection of 100% (p=0.01 to 0.03).[51, 72]

In a study population of American Indian children younger than two years, O´Brien et al. recorded a lower VE against IPD of 81.7% [95%CI=16.3 to 96.0] in the PP analysis and 86.4% [95%CI=40.3 to 96.9] in the ITT analysis. In these children, the annual incidence of pneumococcal bacteraemia is 1820/100.000 versus 130-140/100.000 in non-Native American children in the US.[53] The VE against IPD caused by VT and non-VT serotypes was 54.1% [95%CI=-13.6 to 81.5] in the PP analysis and 46.3% [95%CI=-16.5 to 75.3] in the ITT analysis.[52]

Only one publication on the efficacy of PCV7 against clinically diagnosed pneumonia was retained, i.e., the NCKP vaccine study.[73] The VE of PCV7 against pneumococci and VT pneumonia with bacteraemia were comparable at 90.0% (p=0.01) and 87.5% (p=0.04), respectively, according to the ITT analysis. Against a first episode of any all-cause pneumonia VE was 4.3 [95%CI=-3.5 to 11.5] (PP) and 6.0 [95%CI=-1.5 to 11.0] (ITT). The protective efficacy against radiologically confirmed all-cause pneumonia was 17.7% [95%CI=4.8 to 28.9] according to the ITT analysis. It is noteworthy that this aspect of VE seemed to decline with increasing age: in < 1 year-olds: 24.3% [95%CI=4.1 to 40.2], in 1-2 year-olds 22.7% [95%CI=8.7 to 34.5] and in > 2 years -6.1% [95%CI=-43.7 to 21.7], also according to the ITT analysis.

Only five cases were reported in which a child partially or fully vaccinated with PCV7 still developed VT pneumococcal pneumonia. In the NCKP study there was one participant who had pneumococcal pneumonia with bacteraemia and another, a leukaemia patient (leukaemia diagnosed during the study) treated with radiotherapy, developed pneumococcal bacteraemia. Both of these patients had had a full course of PCV7, and both were infected by serotype 19F. A third child in the NCKP trial developed a pneumococcal infection caused by serotype 6B, approximately 11 months after the administration of the first dose of vaccine.[51]

In the study described by O´Brien et al., two participants developed pneumococcal bacteraemia after three doses of PCV7.[52]

6.5.2 Otitis media

PCV offers moderate protection against acute otitis media (AOM). The Finish Otitis Media (FinOM) study was designed to study this in more depth. Both PCV7 en PncOMPC vaccines were given to infants in a 2, 4, 6 and month schedule. The PP efficacy of PCV7 for clinically diagnosed AOM caused by VT was 57% [95%CI=44 to 67] and for all-cause AOM 6% [95%CI=-4 to 16]. VE in avoiding placement of tympanostomy tubes was 4% [95%CI=-19 to 23] in the original study period. For a number of study participants it was possible to trace the number of episodes of AOM they had experienced in the 3 to 4 years since the last vaccination. This group appeared to be more susceptible to AOM than the original participants who could not be included in the follow-up study, possibly because the group with more pathology was easier to follow-up. The ITT efficacy of PCV7 against AOM during this period was 8% [95%CI=-2 to 16]. In the same period the ITT efficacy for tympanostomy tubes placement was 39% [95%CI=4 to 61].[66, 69]

Despite the fact that PncOMPC appeared to be somewhat less immunogenic, its PP efficacy against AOM caused by VT was almost the same as that of PCV7, i.e., 56% [95%CI=44 to 66]. Whilst AOM caused by vaccine-related types (6A, 9N, 18B, 19A en 23A) was reduced with PCV7 by 51% [95%CI=27 to 67] in PP analysis, PncOMPC apparently showed no preventive activity for these types.

The administration of PCV as a 4th dose instead of PncOMPC produces higher antibody titres, but in the FinOM study this did not lead to increased protection against AOM. For both PncOMPC and PCV7 vaccines the lowest level of protective activity was against serotype 19F.[67]

These results from the FinOM study confirm those of the NCKP study. The publication by Black et al. (2000) showed that the efficacy of PCV7 against clinically diagnosed episodes of AOM as a result of VT was 66.7% (p=0.035) PP, and 64.7% (p=0.077) in the ITT analysis. The VE against episodes of AOM caused by all pathogens was 7.0% [95%CI=4.1 to 9.7] in the PP analysis and 6.4% [95%CI=3.9 to 8.7] in the ITT analysis. Protection against the placement of tympanostomy tubes was notably higher in the NCKP study than in the FinOM study in the original study period, i.e., 20.1% [95%CI=1.5 to 35.2] in the PP analysis and 20.3% [95%CI=3.6 to 34.1] in the ITT analysis.[51]

In two studies the efficacy of 1 to 2 doses of PCV7 with a booster of PPV on AOM was examined. These vaccines were administered to children aged 1-7 who had experienced two clinically diagnosed episodes of AOM in the year preceding the study. Neither of the two studies recorded a beneficial effect of this vaccination schedule on the occurrence of AOM caused by all pathogens, but they did for the occurrence of AOM caused by VT pneumococci, where the VE was 51%.[54, 77]

Additionally, VE of PCV9 against all-cause acute otitis media in Israeli children aged 1-3 yearswas 17% (as reported by the parents).[82]

A recent article on PCV11, using a 3, 4, 5 and 12-18 month schedule, found the PP efficacy against AOM to be 57.6% [95%CI=41.4 to 69.3], when caused by VT, and 33.6% [95%CI=20.8 to 44.3] when caused by all pathogens. The PP efficacy against episodes of AOM resulting from vaccine-related serotypes (6A, 9N, 18A, 18B, 18F, 19A en 23A) was 65.5% [95%CI=22.4 to 84.7]. Serotypes 3 and 4 individually appear to offer no, or hardly any, protection against AOM. The efficacy for the remaining serotypes was lowest against 18C and 19F. According to the PP analysis, the choice of carrier protein means that PCV11 offers 35.3% [95%CI=1.8 to 57.4] protection against AOM caused by nontypable *H. influenzae*.[4]

At the time of the NCKP publication (2000), six fully or partially vaccinated children in the follow-up phase of the trial had an episode of AOM caused by VT pneumococcal serotypes. It apparently involved the same serotype each time: 19F.[51]

After vaccination with PCV an increase in non-vaccine type (NVT) pneumococcal AOM can occur, which can be disease inducing. After vaccination with PCV7 en PncOMPC in the FinOM study, AOM caused by NVT occurred more frequently in the vaccinated group than in the control group. (10,14). In the NCKP study and in research done by Prymula et al., a similar replacement of VT by NVT was not recorded for PCV7 and PCV11.[51, 4]

In addition to these studies in infants, a clinical trial in children aged 1-7 years with a medical history of AOM found no substitution of VT pneumococci by other pathogens in middle ear fluid (collected during the first episode of AOM after vaccination with PCV7 and PPV).[54] It has not as yet been demonstrated that possible replacement can lead to IPD.

6.6 NASOPHARYNGEAL CARRIAGE

It is not yet clear how relevant the reduction in NP-carriage of pneumococci is in the prevention of pneumococcal disease. In one small study, without a control group, infants received four doses of PCV7. NP cultures were taken from the children at different time points. The results of this study showed that the percentage of VT-positive cultures before vaccination was almost the same as after the fourth dose.[88] In another small trial in infants (with control group), after four doses of PncOMPC only serotype 23F was significantly less present in the nasopharynx of the vaccinees versus the controls.[71]

We also report on two larger studies with control groups and with NP-carriage as clinical endpoint. In the first, infants ≥ 6 months were given a maximum of three doses (<1y: 3 doses; 1-

2y: 2doses; >2y: 1 dose) a maximum of two doses. A significant reduction only in carriage of VT antibiotic-resistant pneumococci was found in vaccinees versus non-vaccinees. This effect was nullified by the replacement of these VT pneumococci by NVT and nontypable AB-resistant pneumococci in the nasopharynx.[87]

In the second study, no significant difference in NP-carriage of VT was seen in vaccinated children 2-5 years of age who had received three doses of PCV7 as infants, with a dose of PPV as booster, versus controls.[89]

In another population of children, aged 1-7 and with a medical history of AOM, a combination of PCV7 and PPV was also administered. Compared to the previous studies, this is the first randomised study with PCV7 conducted with a control group and with NP-carriage as endpoint. In the intervention group NP-carriage was 46% before vaccination and 26% afterwards. In the control group the percentages were 58% and 54%, respectively.[79] A later smaller study with a very similar design found 26% carriage of VT pneumococci before vaccination and 10% thereafter.[77]

Carriage was also studied with PCV9 in a randomised study amongst children in day-care. They received one or two doses, depending on their age. Two years after the last vaccination, NP cultures were taken from the participants. The vaccination(s) resulted in a significant reduction in NP-carriage of VT 6B, 9V, 14 and 23F, but not 19F. There was, however, a reduction in carriage of the vaccine-related serotype 6A. These effects were mainly seen in children younger than 3 years.[83] Brothers and sisters of children vaccinated with PCV9 are less frequent carriers of VT.[84]

A large RCT was performed to study carriage of *S. pneumoniae* and *H influenzae* after vaccination with PCV11. In a subgroup of infants, NP cultures were taken three months after administration of the booster (4th dose). The protective effect against carriage of VT pneumococci was 42.8% [95%CI=-16 to 71.9] and against nontypable *H. influenzae*, 41.4% [95%CI=-4.9 to 67.3]. The latter was not statistically significant.[4]

A whole series of studies describe how the administration of PCV7 (also in combination with PPV) leads to VT replacement in the nasopharynx.[76-78,80] In one study with PCV9 this replacement was also found in unvaccinated siblings of vaccinees.[84]

6.7 SAFETY

The data on safety are presented in table A7.

The administration of PCV has been shown to be safe for children younger than 7 years, and also for newborns who are premature or dysmature.[72] in full term infants PCV7 causes pain at the injection site in 1.0 to 39.1%, pain that limits movement in 6.8 to 15.7%, erythema in 10.0 to 58.1%, erythema greater than 2 cm in 0.6 to 18.2%, induration in 5 to 69.4% and induration greater than 2 cm in 1.2 to 21.2% of cases. Administration of PncOMPC to infants showed a similar pattern of side effects.[67, 70]

Blum et al.[81] looked at local reactions to the administration of PncOMPC, with either the same vaccine or PPV as booster in children from 12 to 30 months. The results of this study are shown in Table A7.

After administration of PCV9 in children from 12-35 months, 25.2 to 37.5% also experienced pain at the injection site, 5.3 to 6.3% had erythema and 7.0 to 12.5% induration.[82]

In the majority of studies there were no reports of related serious adverse events. In the studies by O´Brien et al. and Kayhty et al., however, a number of these events were seen after administration of PCV7. Also Prymula et al. observed feverish reaction with viral infection, immunization reaction with viral infection, vomiting, depressed rate of conciousness, purpura and breath holding spells for PCV11. Often in these cases other vaccines were administered concomitantly with PCV. It is therefore difficult to establish which vaccine gave rise to the serious reaction.[52,2,4]

Table A7: Safety of PCV

study	local < 10%	local > 10%	systemic	total SAE	related SAE
Scheifele DW, 2006 [5]	E > 2cm (1.2-1.6%), I > 2cm (1.2-4.8%).	P (24.4-29.8%), E (19.4-36.7%), I (25.6-27.7%).	T ≥ 39 C 0-1.2%.	4	0
Tichmann-Schumann I, 2005 [60]	(PP) P gr 3 (0.6-2.2%), E > 20mm (0.6-11.6%), I > 20mm (2.4-7.2%).	P (15.9-37.7%), E (37.1-51.4%), I (22.5-37.0%).	T ≥ 38.0 C (33.5-49.4%), T > 39.5 C (0-2.9%), somnolence (32.4-44.9%), somnolence gr 3 (1.2-2.3%), irritability (31.8-42.0%), irritability gr 3 (1.4-2.9%), anorexia (14.7-34.8%), anorexia gr 3 (0-2.2%).	8	0
Reinert P, 2003 [61]	P that limits movement (6.8-9.5%), E > 2.4cm (5.4-7.0%).	P (28.8-37.0%), E (37.2-58.1%), I (50.0-69.4%), I > 2.4cm (10.1-13.3%).	T ≥ 38 C (51.0-56.0%), T > 39 C (4.1-5.7%), irritability (42-71%), somnolence (34-49%).	10	0
Schmitt HJ, 2003 [62]	(ITT) Results intervention arm: P (7.5-20.2%).	E (14.2-31.9%), I (10.5-20.9%).	T ≥ 38 C (29.0-48.2%), T ≥ 39.1 C (2.9-8.3%), anorexia (14.4-19.8%), somnolence (22.7-45.7%), irritability (20.2-28.3%).		
O´Brien KL, 2003 [52]					10 (6 after PCV7)
Choo S, 2000 [64]	Results 1st intervention arm: none.	P (19-24%), E (22-25%), I (17-21%).	Irritability/somnolence/excessive crying (44-58%).	12	0
Shinefield HR, 1999 [65]	(ITT) I (9-11%).	P (21-24%), E (16-18%).	T≥ 38 C (21.5-33.5%), irritability (58.1-68.9%).	13	0
Finnish Otitis Media study: Eskola J, 2001[66] Kilpi T, 2003 [67] Straetemans M, 2003 [68] Palmu AA, 2004 [69]	Results 1st intervention arm: P (3-8%), E > 2.5cm (0-0.9%), I (5-6%), I > 2.5cm (0.5-1.3%). Results 2nd intervention arm: (ITT) P (5.9-12.3%), E > 2.5cm (0.1-1.6%), I (5.9-10.6%), I >2.5cm (1.0-4.1%).	E (14-20%). E (17.4-31.4%).	T > 39.0 C (0.4-2.0%), excessive crying (28-42%). T > 39.0 C (0.4-1.6%), excessive crying (30.9-47.0)%.		
Zangwill KM, 2003 [70]Yeh SH, 2003 [71]	E (0-4%), I (1-8%).	P (47-61%).	T ≥ 38.3 C (38-47%), T ≥ 38.9 C (2-10%), irritability (63-80%), somnolence (50-78%), diarrhoea (8-17%), high pitched crying (0-6%), crying ≥ 4 hours (0-1%), vomitus (4-13%).		0
North California Kaiser Permanente study: Black S, 2000 [51] Shinefield H, 2002 [72] Black S, 2002 [73] Fireman B, 2003 [74]	E > 3 cm (0-0.6%), I (9.8-12.1%), I > 3cm (0.1-0.6%).	P (14.7-23.3%), E (10.0-13.8%).	T ≥ 38 C (15.1-23.9%), T > 39 C (0.9-2.5%).		

study	local < 10%	local > 10%	systemic	total SAE	related SAE
de Aristegui Fernandez J, 2005 [75]	(ITT) I > 2.5cm (9.6%).	P(39.1%), P that limits movement (15.7%), E (40%), E > 2.5cm (17.4%), I (32.2%).	T ≥ 38 C (up to 7.0%), T ≥ 39 C (up to 0.9%), anorexia (up to 24.3%), restless sleep (up to 20%), irritability (up to 18.3%), somnolence (up to 13%), vomitus (up to 12.2%), diarrhoea (up to 10.4%).		
Esposito S, 2005 [76]	Results a terme children: E > 3cm (4.3-8.7%). I/P (0-2.2%).	none	T ≥ 39 C (0-17.4%), irritability (2.2-19.6%), somnolence (0-19.6%), restless sleep (0-4.3%), diarrhoea (0-4.3%), vomitus (0-4.3%), anorexia (0-10.9%).	1	0
Kayhty H, 2005 [2]	P (1.0-8.1%), I > 2cm (5.9-21.2%), E > 2cm (3.0-18.2%).	none	T≥ 38 C (38-62%), T ≥ 39.1 C (4-14.1%).	5	1 (after PCV7 concomitant)
Van Kempen MJ, 2006 [77]	NA	NA	NA	NA	NA
Veenhoven R, 2003 [54] Veenhoven R, 2004 [78] Bogaert D, 2005 [79] Brouwer CN, 2005 [80]				0	0
Blum MD, 2000 [81]	Results 1st intervention arm after boosting with PCV: E 1-2 inches (up to 2.8%), E > 2 inches (up to 0%), / 1-2 inches (up to 8.3%), I > 2 inches(up to 0%). Results 1st intervention arm after boosting with PPV: E 1-2 inches (up to 4.7%), E > 2 inches (up to 4.7%), I 1-2 inches (up to 84.7%), I > 2 inches(up to 4.7%).	Results 1st intervention arm after boosting with PCV: P (up to 27.8%). Results 1st intervention arm after boosting with PPV: P (up to 53.5%).	Results 1st intervention arm after boosting with PCV: T ≥ 38.3 C (up to 29.7%), irritability (up to 11.1%). Results 1st intervention arm after boosting with PPV: T ≥ 38.3 C (up to 18.2%), irritability (up to 20.9%).		
Goldblatt D, 2006 [6]					
Dagan R, 2001 [82] Dagan R, 2002 [83] Gion-Lavi N, 2003 [84] Dagan R, 2003 [85] Dagan R, 2005 [86]	E (5.3-6.3%), I (7.0-12.5%).	P (25.2-37.5%).	T ≥ 38 C (14.5-43.8%), irritability (tot 24.4%).		
Prymula R, 2006 [4]	NA	NA	NA	999	14 (1 after PCV11 and 7 after PCV11 concomitant)

6.8 DISCUSSION

A meta-analysis conducted by Lucero et al., analysed data from the NCKP trial, the study in American Indians by O'Brien et al., as well as two large RCTs, one in Finnish (FinOm study) and the other in South African children. Lucero et al excluded data from HIV-positive children. The pooled VE against IPD caused by VT was 88% [ITT; 95%CI=73-94][50] in the meta analysis, versus 93.9% and 86.4% in Californian[51] and American Indian children[52], respectively (see above). The efficacy of PCV against any IPD type differed greatly between the latter two studies (89.1% and 54.1%, respectively). Note that the incidence of IPD in American Indian children is at least ten times higher than in non-native American children in the US.[53],[52]

For radiologically confirmed pneumonia caused by all pathogens, the pooled VE in the aforementioned meta-analysis was 22% [95%CI=11 to 31], drawing on data from the ITT analyses of the NCKP study and the study in South African children by Klugman et al.[50] The ITT efficacy of PCV7 for the first radiologically confirmed case of pneumonia was found to be 17.7%.[73]

Straetemans et al. performed a meta-analysis in which the effect of PCV on the prevention of acute otitis media caused by all pathogens was calculated. Use was made of the data from the NCKP study, the FinOM study, the Israeli trial with PCV9 and a study (Veenhoven et al.[54]) amongst children with a medical history of AOM. The first two studies were in infants and the latter two in older children, aged 12-35 months and 1-7 years, respectively. The pooled rate ratio (RR) (i.e., total number of episodes AOM in intervention group / number of children in group x follow-up period in months) / total number of episodes of AOM in control group / number of children in that group x follow-up period in months) was found to be 0.921 [95%CI=0.894 to 0.950]. A pooled RR of 1.090 was achieved when only the data from the older children who were more susceptible to the development of AOM were used. When the effect of PCV on VT AOM was measured, the observable impact was much higher than for AOM in general: the pooled RR was 0.430 [95%CI=0.344 to 0.537]. Only the results from the FinOM trial and the study by Veenhoven were used here.[91]

In the studies we discuss, the effect against AOM caused by all pathogens is not large. The VE of PCV7 in the FinOM trial was 6% in the PP analysis and 7% in the NCKP study ITT analysis. The efficacy against VT AOM was clearly higher in these infant studies: 57% (PP) and 66.7% (ITT), respectively. For PncOMPC the percentage was 56 and for 11-valent PCV it was 57.6. [51, 66, 67, 4]

In research conducted in older children only a moderate effect of PCV7 (with PPV as booster) against AOM was noted when cases of illness caused by VT were taken into account. [82, 54]

Vaccine failure was only reported for PCV7. Very sporadically, children who had been fully or partially vaccinated still developed pneumonia, AOM or another pneumococcal infection caused by VT. Usually this was disease induced by serotype 19F. In only one case it was serotype 6B. [52]

The serotypes that most commonly give rise to pneumococcal disease vary between countries and between age groups.[58] An important question is whether the inclusion of more than 7 serotypes in a pneumococcal vaccine offers much added value. It is likely that research will soon be undertaken into the efficacy of PCV11 against IPD and pneumonia in various parts of the world.

It is clear that PCV7 and 9 are sufficiently immunogenic after administration of a 4-dose vaccination schedule in infants.[51, 64, 66, 61, 62, 60, 6, 5] PncOMPC gives lower concentrations of antibodies against VT pneumococci, even in a 4-dose schedule, though this may have no repercussions for the protective efficacy against clinical disease.[67] The efficacy of PCV7 against VT IPD is very high, against (clinically diagnosed) pneumonia it is high, and against VT AOM it is moderate.

From an economic and programmatic point of view it would of course be interesting if the same levels of efficacy and effectiveness can be achieved with fewer doses.

In the publications discussed here, a schedule of 3 doses of PCV7 leads to a GMC under 0.35µg/ml for serotypes 6B and 23F in 30-60% of the participants.[76, 2] The research conducted by Goldblatt et al. with PCV9 resulted in antibody titres measured one month after completion of the priming series that met the cut-off level set by WHO for both schedules (2 or 3 priming doses).[6]

The vaccination schedules that comprised 2 priming doses and 1 booster of PCV did in fact lead to lower antibody concentrations for a number of serotypes just before the administration of the booster dose compared to the corresponding concentrations from the NCKP study (3 priming doses and 1 booster).[51, 76, 2] This suggests that infants are possibly not as well protected against pneumococcal disease under such a schedule.

The Centers for Disease Control and Prevention (CDC) have made a comparison in the US between a group of children up to age 6 vaccinated with PCV7 and a control group, and the efficacy against VT IPD was measured under various infant vaccination schedules. When 3 doses were given before the age of 6 months, VE was 92% [95%CI=83 to 97]. If an additional booster was given between the ages of 12 and 18 months, VE rose to 100% [95%CI=-12 to 100]. In children who received two doses before the age of 6 months VE was 95% [95%CI=33 to 100] without a booster and 96% [95%CI=88 to 99] if they had been given a booster between the ages of 12 and 18 months. Some of the children were given only one dose, with a resulting VE of 67% [95%CI=28 to 85].[55]

Only two RCTs were able to demonstrate that PCV reduces global NP carriage of any serotype (in 1-7 year olds).[79, 77] Additionally, reductions in type-specific carriage have been reported for children < 3 years (6A, 6B, 9V, 14 and 23F) and for infants (23F only).[83, 71]

Vaccination-induced replacement of VTs by non-vaccine types has been observed in several NP carriage studies,[88, 79, 87, 77] but could only be linked to an increase in pneumococcal disease in the FinOM trial , for AOM.[66, 67]

Dagan et al. observed reductions of VT carriage in unvaccinated siblings of vaccinated Israeli children. This phenomenon may provide a basis for the substantial herd immunity effects observed in the US. One year after the introduction of PCV7 in the US national infant vaccination program, surveillance data showed a decline in IPD incidence versus previous years. Whilst these indirect effects were also noticeable in unvaccinated children < 3 years, the most remarkable decreases in incidence were in unvaccinated adults: 32% in 20-39 year olds, 8% in 40-64 year-olds, and 18% in those aged over 65 years.[8] These reductions occurred despite the fact that only a minority of the children had received the full vaccination course. Indeed due to vaccine shortages, 14% was not vaccinated, while 6.6% received a single dose, 13% received only 2 doses, 31.5% received only 3 doses, and only 34.9% received the full course (3 doses and a booster). Later observational studies from the US confirmed this first study, with ever-larger reductions in IPD incidence in adults as time went by.

In their systematic review, Lucero et al.[50] report that in both the NCKP trial and O´Brien et al, PCV7 was found to be safe. The Vaccine Trialist Group in South-Africa,[92] observed a small increase in incidence of general convulsions and asthma in those vaccinated with PCV9 versus non-vaccinated.

In the other studies we discussed, such side effects were not reported as being related to PCV.[52,2,4]. Klugman et al discuss their deviating findings regarding safety, as follows: (1) there was an apparent increase in generalised seizures and a decrease in "unspecified seizures" in the vaccinated group, while there was no significant difference in the overall rate of seizures (and this was also not found in other pre- and post marketing studies with specific follow-up for seizures after PCV7 vaccination); (2) The observed increased risk of asthma in vaccine recipients (2.96 cases per 1000 vaccinees versus 1.66 per 1000 controls) should be interpreted in the context of a reduced risk of radiologically confirmed pneumonia in vaccine recipients (17.9/1000 vaccinees versus 21.5/1000 controls), and no such association was found in the NCKP trial [REF Davis RL, Fireman B, Shinefield HR. Pneumococcal conjugate vaccine in children. N Engl J Med. 2004 Jan 1;350(1):84-5; author reply 84-5.] The interpretation of differences between these trials' observations are muddled due to a different concomitant vaccine regime for the controls: meningococcal conjugate vaccine in controls only in the NCKP trial, and Haemophilus influenzae type B vaccine in all children in the South African trial. Further follow up studies post marketing, particularly for the possible association of PCV7 and PCV9 with asthma seems therefore necessary.

There are many issues still open for discussion, not least those related to nasopharyngeal carriage, antimicrobial resistance, reduced vaccination schedules, cross reactivity and serotype replacement. However, many of these issues can only be resolved by widespread use of the vaccine, accompanied by elaborate and dedicated surveillance. In the mean time, it seems clear

that PCVs significantly reduce the disease burden from pneumococcal infections in vaccinated and unvaccinated people and are generally very well tolerated and safe.

7 APPENDIX B: ECONOMIC EVALUATIONS OF PEDIATRIC PNEUMOCOCCAL CONJUGATE VACCINATION - A REVIEW (2002-2006)

7.1 SUMMARY

We review 15 economic analyses of pneumococcal conjugate vaccines, published between 2002 and 2006, in terms of methodology, assumptions, results and conclusions. We found a great diversity in assumptions (eg, vaccine efficacy parameters, incidence rates for both invasive and non-invasive disease) mainly due to local variation in data and opinions. Accordingly, the results varied greatly, from total net savings to over €100,000 per discounted QALY gained. The cost of the vaccination program (determined by price per dose and schedule (4 or 3 doses, or less)), and likely herd immunity impacts are highly influential though rarely explored in these published studies. If the net long-term impact (determined by a mixture of effects related to herd immunity, serotype replacement, antibiotic resistance and cross reactivity) is beneficial and if a 3-dose schedule confers near-equivalent protection to a 4-dose schedule, the cost-effectiveness of PCV7 vaccination programs (at current public vaccine prices) would be comparable to or better than that of many other health care interventions in developed countries.

7.2 INTRODUCTION

Streptococcus pneumoniae is a bacterial pathogen that affects children and adults worldwide. It is a major cause of illness in children, especially those under the age of 24 months, in whom it can cause disseminated invasive infections (including meningitis and bacteraemia), lower respiratory tract infections (including pneumonia) and upper respiratory tract infections (including otitis media and sinusitis). In children, Streptococcus pneumoniae is currently one of the leading causes of meningitis and otitis media. Treatment of pneumococcal diseases is aggravated by the emergence of pneumococcal strains resistant to penicillin and other antibiotics.

The substantial disease burden and the availability of pneumococcal conjugate vaccines (with the seven-valent vaccine (PCV7) already on the market; eight and nine-valent (PCV8 and PCV9) in end-stage phase III trials and eleven-valent (PCV11) vaccines in phase II trials) give the potential introduction of a universal childhood pneumococcal conjugate vaccination program a prominent place on the health policy agenda in many countries. The PCV7 is currently licensed in Australia, North America, most parts of Europe and Central and South America. It is also part of the US, Australian and The Netherlands's universal vaccination program since 2000, 2005 and 2006, respectively.[1] Given the high investment costs associated with this program, countries considering its implementation would prefer to do so on the basis of sound assessments of its population effectiveness, budget-impact and cost-effectiveness. Given the country-specific nature of the prevalence of circulating pneumococcal serotypes, such assessments are likely to differ from one country to the next.

This paper reviews the literature on economic evaluations of pediatric PCV use, focusing on the main differences in input data, methods and results.

7.3 METHODS

Published economic evaluations of conjugate pneumococcal vaccine were identified using Medline and EconLit with the search terms "pneumonia", "pneumococcal", "vaccine", "cost" and "economic". Abstracts of journal articles were reviewed to retrieve full economic evaluations (as defined in Drummond et al). Only the articles published between August 2002 and February 2006 were selected, because a review article of economic evaluations on the same topic up to August 2002 had already been published by the current first author, and the rapidly changing insights make the more recent analyses much more relevant than older ones.[12, 13] Our search identified 15 new studies,[15-17, 93, 18-28] each of which was systematically reviewed in terms of methodology, assumptions, results and conclusions. As such, our review substantially differs from a recent overview, which interprets and presents results of studies, without such thorough review.[94] All cost data reported in our review were transformed to Euro 2002 values on the basis of local Consumer Price Indices and Purchasing Power Parities.

7.4 RESULTS

Our findings are mainly presented in comparative tables. Table B1 lists the selected studies and presents their general characteristics. Note that throughout this paper, we use the term "efficiency" in a restricted way, meaning the measures of relative efficiency used in health care delivery, expressed specifically as cost-effectiveness, cost-utility or cost-benefit ratios.

The studies' assumptions in terms of vaccine efficacy, epidemiological and economic burden are reported in tables B2, B3, and B4, respectively. Table B5 presents the studies' results.

7.4.1 Differences in set-up

Eleven published studies were performed in 7 European countries (Finland,[28] Germany,[16] Italy, [25] Spain,[22, 27] Switzerland,[93, 21] The Netherlands,[15] UK,[19, 24, 26]), three in Canada,[17, 18, 20] and one in Australia.[23]

All 15 studies analysed the efficiency of universal infant vaccination and three studies[17, 93, 22] additionally assessed the impact of catch-up programs for older children (Table B1). The universal infant program was usually defined in line with the pivotal clinical trials, as consisting of four doses of the PCV7 vaccine administered before the age of 18 months. In Melegaro et al.[24], however, 3 doses of the vaccine were assumed to suffice to invoke an equally good protective vaccine efficacy as observed in the trials, and this approach was also explored in sensitivity analysis by Marchetti et al.[25] In Ruedin et al.[21] the impact of universal vaccination programs using a hypothetical combined vaccine against nine serotypes of pneumococci and serogroup C meningococci (PCV9-MenC) was analysed. All these studies were model-based and investigated the impact of vaccination over a 5 to 10 year period after birth (over lifetime in Melegaro et al.[24]). None of these studies modelled the positive impact of herd immunity and reduced antibiotic resistance, nor the negative impact of serotype replacement in their base-case analysis. In Melegaro et al.[24] the potential impact of herd immunity and serotype replacement were estimated separately in the sensitivity analysis, and McIntosh et al.[26] extend on their earlier study[19] to explore the impact of herd immunity.

Table B1: Design and assumed vaccination costs in published economic evaluations of conjugate pneumococcal vaccines [a] (08/2002 – 01/2006)

Study	Country /Region	Publication year	Study type	Perspective	Time span (years)	Discount Rate (%)	Vaccination costs per dose (price + administration) in Euro 2002
Salo et al[28]	Finland	2005	CEA, CUA, CBA	Payer Society	5	C:3 B:3	51.55 (49.97+1.58)
McIntosh et al[26]	UK	2005	CEA	Payer	10	C: 6 B: 0;6	72.23 (57.56+14.67)
Navas et al[27]	Catalonia, Spain	2005	CEA, CUA	Payer Society	10	C:5 B:5	60.84 (53.38+7.46)
Marchetti et al[25]	Italy	2005	CEA	Payer Society	14	C:3 B: NS	44.00 (44.00+0)[b]
Butler et al[23]	Australia	2004	CEA, CUA	Payer	5	C: 5 B: 5	72.46 (68.65+3.81)
Asensi et al[22]	Spain	2004	CEA	Payer Society	10	C: 3 B: 3	63.00 [b]
Melegaro et al[24]	England & Wales	2004	CEA, CUA	Payer	Lifelong	C: 3.5 B: 1.5; 0	58.66 (44.00+14.67)
Mcintosh et al[19]	England & Wales	2003	CEA	Payer Society	10	C: 6 B: 0	72.23 (57.56+14.67)
Ess et al[93]	Switzerland	2003	CUA	Payer	5	C: 3 B: 0	53.47 (48.57+4.91)
Ruedin et al[21]	Switzerland	2003	CUA	Payer	10	C: 3 B: 3; 0	81[a]
Claes et al[16]	Germany	2003	CEA	Payer Society	10	C: 5 B: 5	67.47 (64.60+2.87)
Bos et al[15]	The Netherlands	2003	CUA	Payer Society	10	C: 4 B: 4	45.49 (40.25+5.23)
Lebel et al[18]	Canada	2003	CEA	Payer Society	10	C: 3 B: 3	54.78 (54.78+0)
De Wals et al[17]	Canada	2003	CEA, CUA	Payer Society	10	C: 3 B: 3	52.41 (47.07+5.34)
Moore et al[20]	British Columbia, Canada	2003	CEA	Payer	5	NS	54.78 (54.78+0)

CEA: cost-effectiveness analysis; CUA: cost-utility analysis; C: costs; B: benefits; NS: not stated.
a All studies assess the 7-valent pneumococcal conjugate vaccine, with the exception of Ruedin et al.[21] who assess an hypothetical vaccine combining 9 pneumococcus serotypes with meningococcus serotype C.
b not explicitly stated, deduced estimate

Eight studies used Quality-Adjusted Life Years (QALY)[15, 17, 93, 21, 24, 27, 28] or Disability-Adjusted Life Years (DALYs)[23] as a measure of health outcome (i.e. they performed a cost-utility analysis (CUA)), while 6 studies focused on life-years (LY)[16, 18-20, 22, 26] without quality adjustment (i.e. cost-effectiveness analysis (CEA)).[11] Conceptually, the latter studies therefore underestimated the effectiveness (limiting it to the consequences of mortality, rather than morbidity and mortality combined) and produced a simpler and more conservative measure of efficiency.[12] All studies adopted a health care payer's perspective, i.e. including only direct medical costs and five of these also took on a societal perspective, in which indirect productivity costs (due to morbidity alone) were included in the numerator of the ratio.[15, 17-19, 22] In another three studies,[16, 27, 28] not only were productivity costs due to morbidity monetised but also those due to averted mortality to express a societal viewpoint. By doing so as part of CEAs or CUAs, these

analysts may have double counted mortality costs, as they appear as a gain in life-years in the denominator of the ratio as well.

7.4.2 Differences in assumptions

7.4.2.1 Vaccine efficacy

Estimates for the efficacy of the vaccine against invasive and non-invasive disease varied greatly between studies (particularly for community acquired pneumonia, see Table B2), though they all relied on the same clinical trials (USA[51, 95] and Finland[66]). In those trials, based on Intention To Treat (ITT) results, PCV7 was estimated to prevent 97% of vaccine serotype invasive disease (89% of all invasive disease), 4% of clinically diagnosed pneumonia (not necessarily with X-ray taken) and 6% of all-cause otitis media in children. Five studies did not adjust vaccine efficacy by estimates of serotypes circulating in their own country.[18, 20, 21, 27, 28] Their implicit assumption was thus that the prevalence of circulating serotypes in their country is identical to that in the US trial, and some authors indicated that they made a rough comparison to verify this. The duration of protection afforded by the vaccine remains uncertain and it was usually assumed that protection lasts for the model duration. Six studies have assumed that protection wanes after vaccination.[15, 17-19, 22, 25] Another difference between the studies was the estimated vaccine uptake. Seven studies assumed unrealistically 100% vaccine uptake in the targeted population.[15, 16, 18, 22, 24, 25, 28] In the absence of herd effects, this should have no or a limited impact on the cost-effectiveness ratios, but it could produce misleading estimates of the impact of the program on the disease burden and health care budgets.[96]

Table B2: Baseline vaccine efficacy assumptions of published economic evaluations of conjugate pneumococcal vaccines (08/2002 – 01/2006)

	Vaccine uptake	Vaccine efficacy (%) against				Adjusted efficacy for	Duration	Waning of
	(%)	IPD	AOM	CAP	Other	serotypes circulating in home country	Protection (years)	Immunity Per year
Salo et al[28]	NR	89.1	6.0	17.7	Tymp: 20.3	No	5	No
McIntosh et al[26]	NR	97.4	NR	4.3		IPD	10	1-3%[c]
Navas et al[27]	95	89.1	6.4	22.7	Tymp: 23.2	No	IPD: 10 AOM, CAP: 2 Tymp: 3.5	No
Marchetti et al[25]	100[a]	89.1	6.4	17.7		No (IPD in sens an)	14	3%>5y
Butler et al[23]	100[a]	93.9	6.4	8.9		IPD	5	No
Asensi et al[22]	100	97.4	5.8	11.4	RAOM: 10.6 SP: 33 MP: 24.9	IPD	5	3% > 5y
Melegaro et al[24]	100	63-87[b]	7.0	17.7		IPD	10	No
Mcintosh et al[19]	95	97.4	7.0	6.0		IPD	1	1-3%[c]
Ess et al[93]	70	97.0	7.0	11.0		IPD AOM - CAP	5	No
Ruedin et al[21]	80	89-87[c]	6.0	11.0		No	10	No
Claes et al[16]	100	85.0	6.0	9.1-32.2[d]		IPD	10	No
Bos et al[15]	100	86-95[a]	5.8	11.4		IPD	5	3% > 5y
Lebel et al[18]	100	89.1	5.8	11.4	RAOM: 10.6 SP: 33 MP: 24.9	No	5	3% > 5y
De Wals et al[17]	80	97.0	8.2	10.7	MP: 24.9	IPD	10	1% > 3y
Moore et al[20]	90	89.0	7.0	11.0		No	5	No

IPD: invasive pneumococcal disease; AOM: acute otitis media; CAP: community acquired pneumonia; MP: myringotomy procedure; RAOM: recurrent acute otitis media; SP: severe pneumonia;
a dose distribution (% receiving only 1,2,3, or 4 doses assumed to be 9%, 9%, 24%, 58%, respectively, identical to the NCKP trial) ;
b Efficacy after adjustment for circulating serotype in England and Wales;
c Varies according to age;
d Varies according to time since vaccination

7.4.2.2 Burden of disease

The reliability of the input data clearly determines the accuracy of the projected cost-effectiveness results. Due to diagnostic divergence, however, and because clinically diagnosed otitis media and pneumonia can be caused by micro-organisms other than *Streptococcus pneumoniae*, the incidence of non-invasive pneumococcal pneumonia is difficult to define, but could nonetheless be highly influential for the cost-effectiveness of the program.

Invasive pneumococcal disease (IPD), though not the most common manifestation of *Streptococcus pneumoniae*, is responsible for most severe pneumococcal disease. An accurate assessment of the disease burden of IPD (particularly in terms of incidence and lethality) is therefore also essential, and was noted for its influence in many of the economic analyses.[15, 93, 18, 19, 22, 24, 25] The assumed incidence and case-fatality ratios of invasive pneumococcal disease are presented in Table B3. All studies used local morbidity and mortality data (with the exception of the incidence of pneumonia and non-focal bacteremia, and case-fatality ratios, reported in Navas et al [27] and case-fatality ratios reported in Bos et al[15]), originating from databases (hospital, laboratory or surveillance records)[17], observational studies [16, 93, 18, 20-22] or both [15, 21, 23, 25, 26, 28]. Four studies reported estimates of the incidence and case-fatality ratios for all invasive pneumococcal diseases in general (i.e. including pneumococcal meningitis, bacteraemia, sepsis, peritonitis…)[93, 20, 21, 23, 28] while other studies limited the burden of disease to pneumococcal meningitis and/or bacteraemia.[15, 17, 18, 22, 24] Though the different age categories hamper easy comparisons, the incidence of invasive pneumococcal disease seems to vary greatly between countries. This could reflect differences in diagnostic practices (i.e. whether blood or cerebrospinal fluid cultures are taken) between countries, as well as true divergence in incidence rate. In addition to showing similar differences in reported case-fatality ratios, Table B3 also indicates that several studies lack transparency for (some of) these vital input estimates.

Table B3: Burden of disease assumptions of published economic evaluations of conjugate pneumococcal vaccines (08/2002 – 01/2006)

Study	Incidence of IPD (per 100,000 population)			Case-fatality ratios (%)				
				IPD				Non IPD
	All IPD	Meningitis	Bacteraemia	All IPD	Meningitis	Bacteraemia	Other [g]	Pneumonia
Salo et al[28]	1-2y: 54.9	0.1y: 5.3 1-2y: 2.4	0-1y: 25.0 1-2y: 52.5	0-5y: 1.4	NA	NA	NA	0
McIntosh et al[26]	NR	NR	NR	NR	NR	NR	NA	NR
Navas et al[27]	NR	NR	NR	1.4	NA	NA	NA	0.4
Marchetti et al[25]	0-1y: 27.1[h] 1-4y: 20.9 [h] 5-14y: 5.0 [h]	0-1y: 7.6 1-4y: 2.1 5-14y: 0.5	0-1y: 12.7 1-4y: 13.6 5-14y: 3.3	NA	0-1y: 14.0 2-4y: 7.0 5-10y: 1.0	0.9	0.9	0
Butler et al[23]	0-1y: 105.6 2-4y: 35.2	0-1y: 13.7 2-4y: 2.1	0-1y: 67.6 2-4y: 22.8	NA	0-1y: 11.5 2-4y: 7.1	0-1y: 0.4 2-4y: 1.4	0-1y: 1.5 2-4y: 0.5	0 y: 0.65 1 y: 0.15 2-4 y: 0.03
Asensi et al[22]	NA	0 - 10 yrs: 3.4	0 - 10 yrs: 27.5	NA	0 - 10 yrs: 9.3	0 - 10 yrs: 1.0	NA	0
Melegaro et al[24]	NA	0-1y: 14.6 1-4y: 1.6 5-9y: 0.2 10-14y: 0.2 15-19y: 0.1 20-24y: 0.2 25-44y: 0.3 45-64y: 0.5 65-74y: 0.9 75+y: 0.6	0-1y: 27.3 1-4y: 10.6 5-9y: 1.9 10-14y: 0.7 15-19y: 1.2 20-24y: 1.8 25-44y: 3.1 45-64y: 6.5 65-74y: 18.7 75+y: 42.5	NA	0-1y: 4.0 1-4y: 4.0 5-9y: 3.0 10-14y: 0 15-19y: 11.0 20-24y: 0 25-44y: 11.0 45-64y: 18.0 65-74y: 29.0 75+y: 43.0	0-1y: 4.0 1-4y: 1.0 5-9y: 0 10-14y: 0 15-19y: 0 20-24y: 8.0 25-44y: 20.0 45-64y: 26.0 65-74y: 27.0 75+y: 40.0	NA	0-1y: 1.0 1-4y: 0 5-9y: 1.0 10-14y: 2.0 15-19y: 2.0 20-24y: 3.0 25-44y: 3.0 45-64y: 14.0 65-74y: 29.0 75+y: 46.0
Mcintosh et al[19]	NR	NR	NR	NR	NR	NR	NR	Yes - NR
Ess et al[93]	0-2y: 31[a] 0-5y: 11[a]	0-2y: 5.6 0-5y: 3.1	NA	0-5y: 9.0 [a]	0-5y: 9.0	NA	NA	0
Ruedin et al[21]	0-9y: 7.4 [b] 1-10y: 5.7 [b]	NA	NA	0-10y: 5.0 [b]	NA	NA	NA	0
Claes et al[16]	NA	1-2y: 8.0 3-4y: 1.6 5-10y: 0.04	1-2y: 12.2 3-4 y: 3.4 5-10 y: 0.8	NA	1-10y: 8.3	1-10y: 1.5	NA	1-10y: 0.08
Bos et al[15]	NA	0-10y: 113 [d] 0-10y: 114 [d]	0-10y: 226 [d]	NA	0-10y: 17.0	0-10y: 6.0	NA	0
Lebel et al[18]	NA	0-10y: 3.0	0-10y: 25.0	NA	0-10y: 6.6	0-10y: 1.26	NA	0
De Wals et al[17]	NA	0-4y: 0.47 - 19.37 [e] 5-9y: 0.46	0-4y: 12.8-94.8 5-9y: 4.6	NA	0-10y: 6.5 [f]	0-10y: 2.0 [f]	NA	0-10y: 0.1 [f]
Moore et al[20]	0-2y: 90-150 [c] 2-4y: 10-50 [c]	NA	NA	0-4y: 0.02	NA	NA	NA	0-4y: 0.0005

IPD: invasive pneumococcal disease; yr(s): year(s); NA: not applicable; NR: not reported;
a for all IPD minus meningitis;

b for the 9 serotypes included in the hypothetical PCV9-MenC vaccine;
c high and low incidence estimates;
d Number of cases per year in Dutch children aged between 0 to 10 years;
e Estimates vary according to age;
f Not stated – estimates obtained from Petit et al.[97]
g Other invasive pneumococcal infections: Sepsis, peritonitis, bone and joint infection
h not stated as such; derived from other estimates

The cost burden preventable by PCV7 is mainly influenced by the following factors:

- The probability of acquiring a disease stage and the severity of that stage. For infections with *Streptococcus pneumoniae*, the costs of meningitis are high per case of meningitis, but the population-wide risk of pneumococcal meningitis is limited (see table B3). Acute otitis media, on the other hand, is highly frequent, but generally mild and not costly to treat, whereas pneumococcal bacteremia and pneumococcal pneumonia are situated between those two extremes (the former much more like meningitis, the latter more like otitis media).
- The PCV7's protective efficacy, which is high for IPD, and relatively low for all-cause OM and all-cause pneumonia. Virtually all studies used the effectiveness of PCV7 versus pneumonia confirmed by X-ray, as more specific incidence data on OM and pneumonia, caused specifically by pneumococcus (against which PCV7 is much more efficacious) was not available. Clearly, depending on the scope of the available incidence data on non-invasive pneumococcal disease, the appropriately corresponding measure of efficacy needs to be applied (and this is in this case usually not the most specific measure of protective efficacy from the clinical trials).
- When considering herd effects, the costs of pneumonia, and the proportion of pneumonia caused by pneumococcus amongst adults > 50 years of age is influential, because at those ages pneumonia is relatively frequent and severe.

These three factors make it relevant to produce reliable estimates for each disease stage, in terms of costs per case and incidence. The estimated pneumococcal meningitis incidence varies substantially between the various countries under review (see table B3). This is also the case for the estimated treatment costs of pneumococcal meningitis, which are given in Table B4. Treating an uncomplicated case of meningitis (without sequelae) costs between €4,886 in Switzerland[93] to twice that amount (€8,344) in Canada.[17] In many studies the costs of long-term sequelae (neurological and hearing impairments) after pneumococcal meningitis were taken into account. The substantial costs of special education or residential care needs were explicitly considered in six studies.[15, 16, 93, 21, 23, 27] The assumed probability of sequelae, given a case of pneumococcal meningitis, ranged from 4%,[15, 21] over 6%-9.7%,[19] to 16%[23, 24, 27] for neurological sequelae ("mental retardation", "brain damage", "seizures", "focal neurological damage") and from 4%,[15] over 15.5%,[19] 14-19%,[24] to 30%[16] for hearing losses.

In the other studies under review, these sequelae were not considered, or not reported in a specific (eg in Claes et al.[16], 20% of pneumococcal meningitis would lead to "multiple sequelae" (excluding hearing losses)) or a transparent way, and hence cannot be reported here.

For non-hospital costs, most studies resorted to expert opinion-based estimates. Since differing levels of severity were defined for OM, and not all studies produced an overall estimate, the costs per case of OM are difficult to compare. Direct medical costs for an uncomplicated OM case were reported to be €11,[15] €48,[17] €66,[16] €76,[25] and €103[93]. In other studies no estimates of OM costs per case (eg, €3 per OM consult[24]), or only estimates with costs of complications included were reported (€213[18]), or it was not clearly stated what the estimates comprised (€114[19] €216[21]).

Table B4: Meningitis unit cost assumptions of published economic evaluations of conjugate pneumococcal vaccines (08/2002 – 01/2006)

Study	Pneumococcal meningitis costs (2002 Euro)					
	Average cost of pneumococcal meningitis		Long-term sequelae of pneumococcal meningitis			
	Item	Cost	Neurological deficit	Cost	Hearing deficit	Cost
Salo et al[28]	Meningitis case (no sequelae)	€7504	NR		Deafness (assumed 13% of productivity losses from death)	€ 89,612
Navas et al[27]	NR	NR	SE (per year)	€ 10,063	Cochlear implant (per procedure)	€ 32,085
Marchetti et al[25]	Meningitis case (no sequelae?)	€7,536 [a]	NR	NR	NR	NR
Butler et al[23]	Meningitis case (no sequelae)	€ 6,356	SE (per year)	€ 4,983	Hearing aid (per unit)	€ 1,526
	Meningitis case (including LT sequelae)	€ 6,356 - € 3,498,915[b]	RC (per year)	€ 47,197	Cochlear implant (per procedure)	€ 16,824
Asensi et al[22]	NR	NR	Yes	NR	Yes	NR
Melegaro et al[24]	Meningitis case (first year)	€ 6,897	Yes	NR	Yes	NR
	Additional LT care (per subsequent year)	€ 210				
Mcintosh et al[19] Mcintosh et al[26]	Meningitis case (including LT sequelae)	€ 6,992	Brain damage (per child)	€ 1,189,806	Deafness (per child)	€ 88,877
Ess et al[93]	Meningitis case (no sequelae)	€ 4,886	RC or SE (per year)	€ 14,717	Yes	NR
	Additional LT health care for sequelae (per year)	€ 736				
	Additional RC or SE for sequelae (per year)	€ 14,717				
Ruedin et al[21]	IPD case (no sequelae)	€ 6,350	SE (per year)	€ 10,135	Cost auditive device (per year)	€ 717
	Additional LT care for sequelae (per case)	€ 19,600				
Claes et al[16]	Meningitis case (no sequelae)	€ 6,870	LT sequelae	€ 47,855	Hearing disorder (per episode)	€ 23,319
	Additional LT health care for sequelae (per episode)	€ 23,319 - € 84,019 [a]	SE (per case)	€ 33,084 - € 82,790 [a]	Cochlear implant (per procedure)	€ 84,019
	Additional RC or SE for sequelae (per episode)	€ 33,084 - € 82,790 [a]				
Bos et al[15]	Meningitis case (uncomplicated)	€ 5,770	SE (per case)	€ 166,215	Hearing disorder (per episode)	€ 4,629
	Meningitis case (complicated)	€ 19,450	RC (per case)	€ 947,008		
Lebel et al[18]	NR	NR	Yes	NR	Yes	NR
De Wals et	Meningitis case (no sequelae)	€ 8,344	Yes	NR	Yes	NR

Study	Pneumococcal meningitis costs (2002 Euro)					
	Average cost of pneumococcal meningitis		Long-term sequelae of pneumococcal meningitis			
	Item	Cost	Neurological deficit	Cost	Hearing deficit	Cost
al[17]						
Moore et al[20]	NR	NR	No		No	

NR: not reported; SE: special education; RC: residential care; LT: long-term;
[a] Price level not adjusted, as original price level not clearly reported
[b]Varies according to the medical condition.

7.4.2.3 Vaccination costs

Where it has been licensed, PCV7 is the most expensive pediatric vaccine to date, with the assumed price of a single dose ranging from €40[15] to €69[23] in this review (Table B1). In Ruedin et al, the cost of a vaccination course (vaccine price plus administration costs) with one dose of a hypothetical PCV9-MenC vaccine was set at €80.[21] Vaccine administration costs varied from €1.6 per dose in Finland [28] (where the PCV7 can jointly be administered with other vaccines) to €15 per dose in England and Wales [19, 24, 26] (where the full cost of a nurse consultation is charged). Three studies assumed the new PCV7 vaccination program would not require any additional administration costs.[18, 20, 25]

7.5 DIFFERENCES IN RESULTS

7.5.1 Universal infants' vaccination

From a (restricted) societal perspective, results for universal infant vaccination with PCV7 varied from total net savings [16, 22] to over €100,000 per discounted QALY gained.[28] From the perspective of the payer (i.e. when only direct medical costs are considered), results ranged from €19,279 [93] per undiscounted QALY gained to €142,033 [17] per discounted QALY gained and €6,394 [26] per undiscounted LYG to over €200,000 [28] per discounted LY gained. Note that ratios with undiscounted health outcomes implicitly assume that a policy maker is indifferent between a life-year saved today, and a life-year saved in the future (be it 5, 30 or 200 years from now).

Table B5: Results of published economic evaluations of conjugate pneumococcal vaccine (08/2002 – 01/2006)

Study	Country	Original currency	Studies' results (2002 Euro): incremental cost-effectiveness ratios (ICER)		
		(year)	Vaccination scenarios	Payer's perspective[a]	Societal perspective[b]
Salo et al[28]	Finland	Euro (2004)	Infants: 4 doses (schedule not stated)	€ 208,570 per disc LYG € 75,922 per undisc LYG € 44,563 per disc QALY gained	€ 133,563 per disc LYG € 23,725 per undisc LYG € 28,536 per disc QALY gained
McIntosh et al[26]	UK	£ (2002)	Infants: 4 doses (2,3,4,12-15m)	€ 6,932 per disc LYG € 6,394 per undisc LYG	NA
Navas et al[27]	Catalonia, Spain	Euro (2000)	Infants: 4 doses (2,3,4,12-15m)	€ 65,929 per disc LYG € 85,727 per disc DALY averted[d]	€ 15,908 per disc LYG € 47,307 per disc DALY averted BCR: 0.59
Marchetti et al[25]	Italy	Euro (2002)[e]	Infants: 3 doses (2,4,6m)	€ 38,286 per disc LYG	€ 26,449 per disc LYG
Butler et al[23]	Australia	$AU (1997-8)	Infants: 4 doses (2,4,6,12m)	€ 175,540 per disc LYG € 92,374 per disc DALY averted	NA
Asensi et al[22]	Spain	Euro (1999) [e]	Infants: 4 doses (2,3,4,12-15m) Infants catch-up: all < 60 months	€ 78,235 per discLYG € 99,773 per disc LYG	Savings Savings
Melegaro et al[24]	England & Wales	£ (2002)	Infants: 3 doses (protected from 4m)	€ 166,060 per disc LYG € 95,792 per undisc LYG € 87,913 per disc QALY gained € 57,087 per undisc QALY gained	NA
Mcintosh et al[19]	England & Wales	£ (2002)	Infants: 4 doses (2,3,4,12-15m)	€ 46,214 per undisc LYG	€ 41,292 per undisc LYG
Ess et al[93]	Switzerland	CHF (2001) [e]	Infants: 4 doses (2,4,6,12-15m) Infants catch-up 1: all <24 months Infants catch-up 2: all <60 months	€ 19,279 per undisc QALY gained € 16,483 per undisc QALY gained € 79,470 per undisc QALY gained	NA
Ruedin et al[21]	Switzerland	Euro (2002)	Infants: 3 doses (2,4,6m) PCV9-MenC	€ 39,000 per disc QALY gained € 34,000 per undisc QALY gained	NA
			Toddler: 1 year - 1 dose of PCV9-MenC	€ 15,000 per disc QALY gained € 13,000 per undisc QALY gained	
Claes et al[16]	Germany	Euro (2002) [e]	Infants: 4 doses (2,3,4,12-15m)	€ 68,201 per disc LYG	Savings[c]
Bos et al[15]	The Netherlands	Euro (2001)	Infants: 4 doses (2,3,4,12-15m)	€ 80,006 per disc QALY gained	€ 71,703 per disc QALY gained

Study	Country	Original currency	Studies' results (2002 Euro): incremental cost-effectiveness ratios (ICER)		
		(year)	Vaccination scenarios	Payer's perspective[a]	Societal perspective[b]
					€ 83,226 per disc LYG
Lebel et al[18]	Canada	$CAN (2000)	Infants: 4 doses (2,4,6,12-15m)	€ 125,469 per disc LYG	€ 63,938 per discounted LYG
De Wals et al[17]	Canada	$CAN (2000)	Infants: 4 doses (2,4,6,12-15m)	€ 152,584 per disc LYG € 142,033 per disc QALY gained	€ 101,452 per disc LYG € 94,148 per disc QALY gained
			Infant catch-up: 3 doses (7-12m)	-	€ 194,788 per disc LYG € 193,165 per disc QALY gained
			Toddler catch-up: 2 doses (12-18m)	-	€ 163,135 per disc LYG € 163,947 per disc QALY gained
			Child catch-up: 1 dose (24-48m)	-	€ 167,943 per disc LYG € 163,947 per disc QALY gained
Moore et al[20]	Canada (British Columbia)	$CAN (2000)	Infants: 4 doses < 18 months	€ 34,528 to € 73,457 per undisc LYG	NA

LYG: life-year gained; QALY: quality-adjusted life year; DALY: disability-adjusted life year; NA: not applicable;
a Including only direct medical costs:
b Including both direct medical costs and indirect productivity costs due to morbidity, unless specified under c
c Societal perspective including also indirect productivity costs due to mortality
d In Navas et al, the authors erroneously refer to "costs per DALY gained". In their table 4, we interpreted the costs per life year saved for society and "provider", as being reversed (as this would be more consistent with the notion that society's perspective produces more attractive ratios than the provider's perspective, ceteris paribus.)
e assumed price level (based on publication year, or other information), as price level not explicitly or not clearly reported

In Finland[28], Australia,[23] England & Wales,[24], The Netherlands [15] and Canada [17] , infant PCV7 vaccination was reported to be not as cost-effective as dialysis and breast cancer screening (Finland); breast or cervical cancer screening (Australia), meningococcal C or influenza vaccination (The Netherlands), adult pneumococcal (with the 23-valent polysaccharide vaccine) or varicella vaccination (Canada). By contrast, universal PCV7 infant vaccination programs were reported to have acceptable cost-effectiveness ratios in Spain,[22], Canada,[18, 20] Germany [16] (more specifically when considering a societal viewpoint in those countries) and in Switzerland.[93] In Spain [22] and in Canada, [18, 20] universal PCV7 infant vaccination was reported to show comparable cost-effectiveness ratios with other local well-accepted interventions (such as hepatitis A and hepatitis B vaccination of children in Spain). McIntosh et al [19] stated that the ICER of universal PCV7 infant vaccination lies at the upper limit of acceptable cost-effectiveness ratios in the UK. Finally, Ruedin et al [21] concluded that, in Switzerland, universal infant vaccination with 3 doses of the combined PCV9-MenC vaccine is more cost-effective than vaccination with MenC alone.

It is interesting to note that this divergence between the studies' conclusions also occurs for studies pertaining to the same country. In Canada, Lebel et al [18] and Moore et al [20] were more favourable to universal infant PCV7 vaccination than De Wals et al.[17] Without getting into much detail, it seems that this divergence between the studies' conclusions mainly stems from different estimates of the costs of each disease stage and/or of the incidence rate of invasive pneumococcal disease (Lebel et al's [18] model resulted in a much higher number of pneumococcal meningitis cases per birth cohort than De Wals et al[17], whereas Moore et al [20] 's estimate of invasive pneumococcal disease incidence for British Columbia appeared to be higher than Canada in

general). A detailed discussion of these Canadian studies can be found in Beutels [12]. Also, for England and Wales, McIntosh et al [19] reported more favourable results than Melegaro et al.[24], presumably because McIntosh et al [19] estimated a higher burden of disease in the absence of vaccination than Melegaro et al. [24] It is also of note that McIntosh et al are employed by Wyeth, whereas Melegaro & Edmunds are employed by the Health Protection Agency, a British public body. Irrespective of such independency issues, these variations in assumptions and results highlight the need for consistent definitions in assessments of both clinical and economic input data.[12]

7.5.2 Catch-up vaccination

Three studies assessed the efficiency of supplementing the introduction of universal infant PCV vaccination with catch-up PCV vaccination [17, 93, 22]. In these scenarios healthy children up to 24 [93, 22] or 60 months [93] of age are all caught up with at the start of the program, or alternatively, more gradually, through the vaccination of infants (7-12 months), toddlers (12-18 months) and children (24-48 months), until the first cohort of vaccinated infants has reached their age (i.e. 7, 12 or 24 months, respectively). In 2 studies, the ICERs for catch-up vaccination were found to be less favourable than for universal infants' vaccination alone (irrespective of the age of the catch-up group).[17, 22] In Ess et al [93], additional catch-up vaccination of all infants < 24 months when universal infant vaccination starts, was found to be more attractive than universal vaccination of younger infants alone (€16,483 versus €19,279 per undiscounted QALY gained).

7.6 CONCLUSION

Given the lack of consensus between the studies' results for both the perspectives of the payer and society, it is difficult to draw solid conclusions about the cost-effectiveness of universal infant vaccination with a PCV7. It seems unlikely, however, that PCV7 vaccination will be cost saving for the health care payer. A key assumption determining the economic attractiveness of universal PCV7 vaccination is the cost of the vaccine. Indeed, given its large budget impact, all studies have identified the cost of the vaccine as one of the most influential variables determining the efficiency of PCV7 vaccination. Some studies have also reported that a substantial reduction in the cost of the vaccine could bring the ICERs within an acceptable range. For example, without herd immunity impact, the price of the PCV7 would have to be reduced to a third of its current value for the ICER to be lower than the £30,000 (€44,000) per QALY gained threshold for acceptable interventions in England and Wales.[24] Note that a previous review of PCV7 economic evaluations published before August 2002 concluded, in line with the current findings, that the attractiveness of PCV7 vaccination hinges on the potential for price reductions and the willingness for decision makers to adopt a societal perspective.[13]

Many studies have also pointed out the difficulty of assessing with much precision the efficiency of PCV7 vaccination due to uncertainties related to the current burden of pneumococcal disease, the duration of vaccine protection and the long-term effects of vaccination on the epidemiology of pneumococcal disease. Indeed, pneumococcal conjugate vaccines have the potential to decrease nasopharyngeal carriage, thereby reducing transmission of pneumococci by herd immunity in the pediatric and adult population. Such indirect protection of the population with infant pneumococcal conjugate vaccination has been observed in Northern California [10] and the USA in general [8, 30] and this could potentially also have an impact on the cost-effectiveness of the current pneumococcal vaccination strategies in adults. However, after the introduction of the vaccination, non-vaccine serotypes may well replace vaccine serotypes, leading to a smaller reduction in disease burden over time. This raises various questions related to the potential long-term population effects

In many European countries and in the United States, the recommended vaccination schedule for the pneumococcal conjugate vaccine (PCV) requires four doses per vaccinee. The infant immunization programme in Denmark, Finland, Italy, Norway, and Sweden is based on primary vaccinations at 3 and 5 months, and a third dose at 11 or 12 months of age, whereas in most other European countries the primary immunization schedule consists of 4 doses (three <1y, and one ≥1y). The use of a simplified schedule including 3 doses of PCV7 administered concomitantly with the routine primary infant vaccinations at age 3, 5 and 11 or 12 months has been shown to confer an equivalent antibody level for any of the vaccine serotypes compared to the four-dose PCV7 scheme.[15,17] These findings are valid for both pre-term and full term infants, and confirm earlier results demonstrating that the immune response induced by PCV7 using the

simplified schedule is no different from that induced by the four-dose schedule. Kayhty et al [2] showed that the administration of two doses of PCV7 induced satisfactory antibody response, except for the serotypes 6B and 23F. However, at month 13, after the booster dose, the pneumococcal antibody concentrations were comparable with those observed with the four dose schedule.[2] Moreover, the important increase of antibody concentration after the administration of the third dose in the reduced schedule, suggests that two doses of PCV7 may induce a sufficient immunological memory. Additional data from the United States show that a remarkable decline in invasive pneumococcal disease among young children is seen despite vaccine shortages and with only a minority of children having received a fourth dose of PCV7 vaccine.[10] Another option is to postpone the final dose of PCV7 to at least age 2 years, and replace it by a dose of pneumococcal polysaccharide vaccine (as these vaccines are not effective before age 2 years). Pneumococcal polysaccharide vaccines cover more serotypes (though not all the 7 serotypes from PCV7) and are currently much cheaper than the PCV7 vaccine.

These findings provide important information for PCV7 vaccine introduction in countries routinely using three doses in the infant immunization schedule and could lead to substantial cost reductions (in terms of vaccine costs, vaccine supply and administration) at no apparent loss in effectiveness.

The possible effect of herd immunity and of complete substitution of vaccine serotype with non-vaccine ones on the cost-effectiveness of PCV7 universal vaccination was investigated by Melegaro et al.[24] As expected, their base-case cost-utility ratio (€87,913 per discounted QALY gained) decreased dramatically when indirect protection to the unvaccinated was included (€7,352 per discounted QALY gained). But the inclusion of complete serotype replacement increased substantially this ratio (€39,132 per discounted QALY gained, still substantially lower than the base-case ratio). As was noted by these authors, there is as yet little quantified information on the magnitude of herd immunity and serotype replacement effects (i.e., the extent to which replacement occurs, and the severity of disease caused by non-vaccine types as opposed to vaccine types). Recently, at least two additional studies have explicitly considered the impact of herd immunity, and concluded that PCV7 vaccination in childhood would be cost-effective. McIntosh et al [26] concluded that 4 doses of PCV7 at €6,394 per life-year gained would be "highly cost-effective" in the UK, whereas Beutels et al [31] found (at A$14,645 (about € 8500) per DALY averted in the baseline) three doses of PCV7 to be of comparable or better cost-effectiveness as routine meningococcal C conjugate vaccination in Australia, for varying time spans and assumptions regarding herd immunity and serotype replacement.

The divergences in the studies' conclusions are showing the difficulties with obtaining reliable burden of disease data. When observed herd immunity effects from the US are included, and a three dose schedule can be assumed to be similarly effective as a four dose schedule, childhood PCV7 vaccination, at the current vaccine price, is likely to be judged as relatively cost-effective to the health care payer, and potentially cost-saving to society. At the same time, it remains to be seen whether the net effects on antimicrobial use and resistance, serotype replacement and cross reactivity are detrimental or beneficial to the overall cost-effectiveness of the program. It is encouraging that current evidence from the US indicates the latter.[10, 34-36, 30] This enforces the observation, that at least in the short term, the cost-effectiveness can be viewed as attractive.

8 APPENDIX C: BESCHRIJVING PROCEDURE GEGEVENSVERZAMELING CM

8.1 BESCHRIJVING VAN DE METHODE

In onderstaande tekst beschrijven we de gegevens die de CM reeds verzamelde voor deze studie op het ogenblik van het schrijven van dit rapport en op welke manier deze werden bekomen. Merk op dat dit steeds onder toezicht gebeurde van een adviserend geneesheer. Enkel geanonimiseerde gegevens worden overgemaakt aan Prof. Beutels.

8.1.1 Identificatie van de CM-leden

In eerste instantie werd er aan 48 labo's (verspreid over heel België) per e-mail de toelating gevraagd om de gegevens betreffende hun patiënten met een invasieve pneumokokkeninfectie (die dus een cultuur positief op pneumokokken hadden) op te vragen bij het referentielabo van Prof. Verhaegen. De gegevens van de 27 labo's die hierop tegen 07/02/2006 positief hadden geantwoord werden gebruikt voor de identificatie van de CM-leden die in de studie werden opgenomen. Alle labo's die positief hadden geantwoord kregen een brief (Appendix C1) waarin officieel werd gevraagd - krachtens artikel 26 van het KB nr 35 van 20/07/67 over het statuut van de adviserend geneesheer (Appendix C2) - naar bijkomende inlichtingen over de CM-leden waarvoor zij een staal stuurden naar het referentielabo van Prof. Verhaegen.

De gegevens die we van het referentielabo ontvingen bevatten informatie over 5532 stalen (echter niet alleen afkomstig van CM-leden vermits hier geen gegevens beschikbaar waren over het ziekenfonds van aansluiting) die sinds 1994 door de desbetreffende labo's naar het referentielabo werden opgestuurd. In deze bestanden waren o.a. de volgende velden aanwezig: labo-code, naamveld met naam en voornaam (in hetzelfde veld en niet altijd correct, volledig of consistent ingevuld - soms werd hier een code gebruikt specifiek voor een labo of de initialen), geboortedatum, postcode, gemeente, isolatiebron en isolatiedatum.

Om in deze gegevens specifiek de CM-leden te identificeren werd er een extractie gedaan uit de databanken van de CM waarbij er gezocht werd naar de volgende nomenclatuurnummers geattesteerd sinds 1994:

- 549010 en 549021: Aërobe hemocultuur met identificatie van de geïsoleerde kiemen.
- 549555 en 549566: Microscopisch microbiologisch onderzoek na dubbele kleuring van cerebrospinaalvocht.
- 550373 en 550384: Aerobe kweek van etter , exsudaten, punctievloeistoffen en biopten
- 550336 en 550340: Aërobe kweek van expectoraties, bronchiale aspiraten of monsters bovenste luchtwegen, exclusief keeluitstrijk.

Vervolgens werd deze extractie gekoppeld met de gegevens van de stalen van het referentielabo volgens de twee volgende selectiemethoden:

- Selectie van de CM-leden waar de achternaam letterlijk werd herkend in het naamveld van het referentielabo met overeenkomst van geboortedatum en labo.
- Selectie van de CM-leden met waar de achternaam niet letterlijk werd herkend in het naamveld van het referentielabo maar waar er minder dan vier dagen verschil was tussen de isolatiedatum (volgens gegevens referentielabo) en de prestatiedatum (volgens de CM-gegevens) eveneens met overeenkomst van geboortedatum en labo.

De CM-leden die resulteerden uit deze koppeling werden daarna nog aan een manuele controle onderworpen (waarbij b.v. en indien mogelijk of van toepassing werd gekeken naar overeenkomst van initialen of naar overeenkomst van voornaam en - voor de tweede selectie - achternaam) waarbij nog een aantal leden met een onzekere koppeling werden verwijderd uit de selectie.

Door deze procedure konden we uiteindelijk 1718 stalen identificeren afkomstig van 1664 CM-leden.

8.1.2 Enquête

Uit de groep van 1664 leden hierboven geïdentificeerd werden diegenen geselecteerd die op het moment van de extractie nog in leven waren en waarvan het regionaal ziekenfonds van aansluiting was gekend. Deze leden (915 in totaal) werden aangeschreven door de geneesheer-directeur van CM in het kader van de enquête. De brief die hiervoor werd gebruikt is te vinden in Appendix C3. Merk op dat er in deze brief tevens een informed consent aanwezig was dat moest worden ondertekend vooraleer de enquête werd afgenomen. De coördinatie van deze enquête gebeurde door een lid van de dienst onderzoek en ontwikkeling van de CM die in deze materie reeds zeer ruime ervaring had.

Vervolgens werden deze 915 leden verdeeld tussen en telefonisch gecontacteerd door een team van 11 adviserend verpleegkundigen onder toezicht van de adviserend geneesheer waarbij moest worden getracht om - per verpleegkundige - bij ongeveer 15 leden een afspraak te maken om bij hen thuis een enquête af te nemen. De enquête (met bijhorende Bijlagen I en II) is te vinden in Appendix C4. De bedoeling was om per lid en per kostensoort (zie Bijlage I) een inventaris te maken van het aantal eenheden, de eigen bijdrage en de RIZIV kost dit zowel binnen het eerste jaar na de infectie als later (zie Bijlage II).

Op het ogenblik van het schrijven van dit rapport waren er reeds gegevens van ongeveer 150 enquêtes beschikbaar die na het afsluiten van de enquête, de nodige verwerking en anonimisatie zullen worden overgemaakt aan Prof. Beutels.

8.1.3 Matching

Vermits we slechts bij een 150-tal leden een enquête konden afnemen, hebben we de (geheel of gedeeltelijk terugbetaalde) gezondheidskosten vanaf 1994 van alle 1664 leden volgend uit de hierboven beschreven koppeling opgezocht in de CM-databanken. Al deze kosten werden ingedeeld volgens de kostensoort (zie Appendix C5) en volgens het aantal maanden voor of na de eerste isolatiedatum. Telkens waren het aantal prestaties, het terugbetaalde bedrag en de persoonlijke tussenkomst van de patiënt beschikbaar. Bovendien hebben we het aantal hospitalisatiedagen rond de eerste isolatiedatum opgezocht (gedefinieerd als hospitalisaties waarvan de isolatiedatum in het tijdsinterval lag bepaald door de opnamedatum - 7 dagen en de ontslagdatum + 3 dagen).

Om een idee te krijgen wat de gezondheidskosten zouden geweest zijn indien er geen pneumokokkeninfectie was geweest, hebben we de 915 patiënten, die potentieel hadden geënquêteerd kunnen worden, gematcht met een willekeurig lid dat op het moment van de extractie nog in leven was met bovendien hetzelfde geslacht, behorende tot dezelfde hoofdgemeente en dezelfde sociale categorie (waarbij de categorieën en regelingen werden gebruikt waarin de patiënt recht heeft op terugbetaling grote risico's) en met een minimaal verschil in leeftijd (dat niet groter mocht zijn dan 12 maanden). Voor 881 van de 915 leden hebben we een willekeurig lid gevonden dat aan deze criteria beantwoordde. Voor deze 881 willekeurige leden hebben dezelfde gegevens opgezocht in de CM-databanken als voor de leden met een pneumokokkeninfectie.

8.1.4 Voorschrijfgedrag antibiotica artsen Intego-netwerk

Om een schatting te kunnen maken van de kosten geassocieerd aan het antibioticaverbruik voor pneumokokkeninfecties in de ambulante praktijk hebben we de het aantal geassocieerde consultaties en frequentie van antibioticavoorschriften voor otitis media en pneumonie opgevraagd bij de huisartsenpeilpraktijken Intego via Prof. Frank Buntinx (Academisch centrum voor Huisartsgeneeskunde K.U.Leuven). Om de kosten gerelateerd aan antiobioticavoorschriften te kunnen extrapoleren naar de algemene huisartsenpraktijk, hebben we de gegevens van 2004 i.v.m. alle antibioticavoorschriften (voorschriften voor medicatie met ATC-code beginnend met 'J01') voor CM-leden door 54 Intego-artsen (RIZIV-nrs ter beschikking gesteld door Prof. Buntinx) uit de CM-databanken geëxtraheerd en vergeleken met de gegevens van alle andere huisartsen (RIZIV-nr eindigend op 003 of 004). Dit voorschrijfgedrag werd gerelateerd aan het aantal consultaties gepresteerd door de desbetreffende huisartsen. De vergelijking werd gedaan per geslacht en per leeftijd van de patiënt.

8.1.5 Bepalen diagnose via 727-formulieren

Uit de enquête bleek dat de isolatiebron (veelal ging het over hemoculturen) opgegeven in de bestanden van Prof. Verhaegen in vele gevallen niet representatief was voor het type van infectie dat was opgetreden. Omdat we een kostenplaatje willen maken per type pathologie is er, in samenwerking met de regionale ziekenfondsen, getracht om voor een groot deel van de 1664 patiënten met een pneumokokkeninfectie het werkelijke infectietype (pneumonie, meningitis, otitis media, …) te achterhalen via de formulieren bij de beëindiging van een hospitalisatie (727-formulieren - hierop zijn diagnose en nevendiagnose weergegeven). Dit gebeurde eveneens onder toezicht van adviserend geneesheren. Merk op dat dit een zeer arbeidsintensieve opdracht is vermits deze formulieren in vele gevallen manueel in archieven moeten worden opgezocht waarbij de diagnose vervolgens moet worden overgetypt. Deze gegevens werden pas beschikbaar op 22 mei 2006 voor 453 CM leden, wat gezien de finale deadline van de studie (2 juni 2006), niet meer mogelijk maakte deze gegevens op een kwantitatieve manier te gebruiken in onze berekeningen.

8.2 APPENDIX C1: INHOUD VAN DE BRIEF AAN DE DEELNEMENDE LABO'S.

Geachte collega,

In het kader van een studie in opdracht van het Federaal Kenniscentrum over de kosteneffectiviteit van het pneumokokkenvaccin, wensen wij over een aantal bijkomende inlichtingen te beschikken met betrekking tot onze leden voor wie u een cultuur hebt uitgevoerd. Het artikel 26 van het KB nr 35 van 20/07/67 over het statuut van de adviserend geneesheer voorziet in de mogelijkheid van een dergelijke procedure.

Meer specifiek vragen wij u van de CM leden voor wie u na 1994 een staal stuurde naar het referentielaboratorium van de K.U.Leuven (Prof. Jan Verhaegen) de oorsprong van dat staal en het serotype te preciseren.

Deze informatie zal strikt en uitsluitend voor de doelstelling van deze studie gebruikt worden. Voor de betrokken patiënten is er geen enkele consequentie aan verbonden in termen van terugbetaling of rechten. Wel zullen wij achteraf een aantal van onze leden contacteren om na hun schriftelijke toestemming een optimale inschatting van de lange-termijn kosten die een invasieve pneumokokkeninfectie meebrengt te kunnen maken.

U dankend voor uw medewerking, zend ik u inmiddels mijn vriendelijke groeten.

Dr. Michiel CALLENS — Dr. Yves Van houte

Adviserend geneesheer — Geneesheer directeur

8.3 APPENDIX C2: ARTIKEL 26 VAN HET KB NR 35 VAN 20/07/67 OVER HET STATUUT VAN DE ADVISEREND GENEESHEER.

Article 26 du Statut, barème et agréation des médecins-conseils

Le médecin-conseil exerce sa mission en liaison avec le médecin traitant.

Il examine avec celui-ci les possibilités de préciser le diagnostic et d'améliorer la thérapeutique et, le cas échéant, le moyen de diminuer les frais de traitement sans réduire en rien l'efficacité de la thérapeutique.

Le médecin-conseil est tenu de répondre à toute demande de renseignements formulée par le médecin traitant à l'occasion d'une décision qu'il a prise.

Il peut communiquer aux instances médicales, sanitaires et médico-sociales tous renseignements statistiques susceptibles d'aider à l'accomplissement de leur mission.

Il aide l'assuré et le médecin traitant à obtenir en faveur de l'assuré toute intervention d'un organisme médical ou social qu'il estime justifiée.

8.4 APPENDIX C3: INHOUD VAN DE BRIEF GESTUURD AAN DE CM-LEDEN ALS VOORBEREIDING VAN DE ENQUÊTE.

Onderzoek uitgaven pneumokokkeninfectie

Geachte mevrouw

Geachte heer

Onze adviserend geneesheer heeft vastgesteld naar aanleiding van terugbetaalde onderzoeken dat u of uw kindje vermoedelijk door een pneumokokkeninfectie werd getroffen. We weten dat de gevolgen daarvan ernstig kunnen zijn. Sinds enkele maanden bestaat tegen deze ziekte een vaccin. Vooraleer het ter beschikking te stellen, wil de overheid het terugbetalingsdossier met een wetenschappelijke studie onderbouwen. Hiervoor rekent ze ook op de CM. U kunt ons nuttige informatie bezorgen over de uitgaven die met de pneumokokkeninfectie gepaard gingen of nog zullen gaan. Daarom doen wij via deze weg een beroep op uw medewerking.

Eventueel zal een verpleegkundige van de CM eerstdaags telefonisch met u contact opnemen met de vraag of u aan het onderzoek wilt deelnemen. Moest uw telefoonnummer niet in de officiële telefoongidsen te vinden zijn, vragen wij u vriendelijk zelf met ons contact op te nemen op het nummer……

Deelnemen aan het onderzoek neemt een half uur in beslag. Een CM-medewerker zal enkele vragen stellen over uw uitgaven n.a.v. de pneumokokkeninfectie en de uitgaven die u nog verwacht. Hij zal ook nagaan of u gebruik maakt van alle sociale voordelen waarop u recht hebt.

De verwerking van de gegevens heeft uiteraard een vertrouwelijk karakter en gebeurt onder het toezicht van de adviserend geneesheer. Indien u aan het onderzoek deelneemt, zal de CM medewerker u bij zijn bezoek vragen onderstaande machtiging in te vullen.

Wij hopen op uw bereidwilligheid te mogen rekenen.

Met dank en vriendelijke groeten

Dr. Yves Van houte

Geneesheer-directeur

Machtiging

De heer/mevrouw: ……

Nummer SIS-kaart: ……

Vader/moeder/voogd van: ……

geeft de CM de toestemming om de uitgaven gedaan of nog te doen n.a.v. een pneumokokkeninfectie te verwerken. .

Handtekening:

8.5 APPENDIX C4: ENQUÊTE (MET BIJLAGEN I EN II) AF TE NEMEN DOOR ADVISEREND VERPLEEGKUNDIGEN.

VRAGENLIJST PNEUMOKOKKENINFECTIE

VOORBEREIDING ENQUÊTE

Zelf de **uitgavenstaat uit weblid** en **hospitalisatiedatum uit konhos** halen en uitprinten om mee te nemen naar het interview.

Op basis van uitgavenstaat, konhos en isolatiedatum: **interview reeds voorbereiden**. Uitgavenstaat al eens overlopen en op voorhand al een overzicht maken van gezondheidskosten die gemaakt zijn. Belangrijk om hier reeds een overzicht van te hebben voor het interview!!!

Vergeet tijdens of na het interview zeker niet om achter een ondertekende **informed consent** te vragen (onderaan de brief die de mensen ontvangen hebben)!!!! Dit is juridisch belangrijk voor ons.

Zowel op deze vragenlijst die je invult als op exceldocument met overzicht kosten steeds het **lidnummer** vermelden. Dit is heel belangrijk om achteraf een koppeling tussen de gegevens te kunnen maken.

ENQUÊTEURGEGEVENS

Datum enquête

_ _ / _ _ / _ _ _ _

Beginuur

_ _ uur _ _ minuten

Lidnummer respondent (terug te vinden op uitgavenoverzicht van deze patiënt LIDNUM)

_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Initialen verpleegkundige

_ _ _ _

!!!!! In cursief: Informatie of vragen voor ondervraagde !!!!!

!!!!! Onderlijnde tekst is bedoeld voor verpleegkundige !!!!!

INLEIDING

De Christelijke Mutualiteit voert momenteel een onderzoek uit naar de gezondheidsgevolgen van een pneumokokkeninfectie en naar de kosten daarvan.

Om hier een goed beeld van te krijgen voeren we momenteel een aantal interviews uit bij mensen die een pneumokokkeninfectie doormaakten of waarvan hun kind een dergelijke infectie doormaakte. Daarom willen we ook graag uw verhaal horen.

Dit gesprek zal echter geen enkel gevolg hebben voor de terugbetaling en is ook geen controle. Integendeel, indien tijdens het gesprek zou blijken dat u recht heeft op zaken waarvan u geen weet had, dan zal dit met u besproken worden.

ALGEMENE OMSCHRIJVING VAN DE PNEUMOKOKKENINFECTIE

Kan u me zeggen wat uw band is met de persoon die de pneumokokkeninfectie heeft doorgemaakt? (omcirkel juiste antwoord)

1: ikzelf heb de pneumokokkeninfectie doorgemaakt

2: ouder

3: voogd

4: partner

5: grootouder

6: broer of zus

7: tante / nonkel

8: andere (gelieve te specifiëren) _

Uit onze informatie blijkt dat de pneumokokkeninfectie werd vastgesteld in het jaar _ _ _ _ (verpleegkundige: vul aan) *en dat het om de volgende vorm ging* _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ (verpleegkundige: vul aan)

Kan u me zeggen hoe de pneumokokkeninfectie juist is begonnen en hoe het geëvolueerd is?

(geef zo volledig mogelijk het verhaal van de persoon weer)

_ _
_ _
_ _
_ _
_ _
_ _
_ _

Heeft de pneumokokkeninfectie gezorgd voor blijvende gezondheidsgevolgen?

1: neen (indien neen, ga onmiddellijk naar vraag 9)

2: ja (ga naar vraag 8)

Kan u specifiëren om welke gezondheidsgevolgen het hier juist gaat?

(meerdere antwoorden mogelijk)

(omcirkel juiste antwoord(en))

1: doofheid

2: neus-keel-oor problemen (bv sinusitis)

3: neurologische problemen (bv verlammingen, hersenletsels, coördinatiestoornissen…)

4: buikvliesontsteking

5: oogproblemen

6: ademhalingsproblemen

7: problemen met het hart

8: problemen met het beendergestel of gewrichten

9: mentale achterstand (bv leerstoornissen)

10: andere (gelieve te specifiëren) _

OVERZICHT KOSTEN GEZONDHEIDSTRAJECT

Inventariseer ALLE kosten (in vraag 9 tot 11) die betrekking hebben op pneumokokkeninfectie in de EXCEL file in Bijlage II met als titel "Invuldocument kosten patiënt". Gebruik daartoe in kolom 1 de categoriecodes vermeld in Bijlage I met als titel "Categorieën van mogelijke kosten van de pneumokokkeninfectie".

Vraag steeds of het gaat om kosten die gemaakt zijn binnen het eerste jaar na de infectie of later (kolom 2 in Bijlage II – gebruik hier enkel cijfer 1 of 2). Gebruik twee verschillende lijnen met een opsplitsing van de kosten (dus een lijn met het cijfer 1 in kolom 2 en een lijn met cijfer 2 in kolom 2) indien de kost zich uitstrekt over het eerste jaar en de daaropvolgende jaren.

Vraag naar het aantal opnamedagen bij hospitalisaties en probeer voor andere categorieën het aantal eenheden te bekomen (bv aantal consultaties bij een huisarts). Zie Bijlage I voor de definitie van de eenheden in de verschillende categorieën.

Vraag ook naar de eenheidsprijs (bv prijs van 1 consultatie) voor de eigen bijdrage als het voor het bedrag terugbetaald voor het RIZIV.

Vermenigvuldig het aantal eenheden met de eenheidsprijs om zowel de eigen bijdrage als het bedrag terugbetaald door het RIZIV te bekomen. Bereken vervolgens de totale kost (eigen bijdrage + RIZIV bijdrage).

Indien je geen aantallen van de persoon kan bekomen of indien er in Bijlage I geen eenheden zijn gedefinieerd, gelieve dan tenminste de totale kost te noteren. Dit geld ook indien er geen opsplitsing kan gemaakt worden in eigen bijdrage en RIZIV bijdrage. Probeer het gebruik van '?' te vermijden.

Eventuele commentaar bij een bepaalde rij kan je vermelden door in de kolom "commentaar" een nummer in te geven en dit dan op de achterkant van het formulier te specifiëren.

U kan in de EXCEL file van Bijlage II steeds rijen toevoegen indien nodig of u kan meerdere afdrukken maken van deze bijlage (gelieve deze dan te nummeren per patiënt).

Spontaan verhaal van de persoon

We zouden graag een overzicht maken van alle kosten waar u beroep op heeft gedaan omwille van de pneumokokkeninfectie. Het kan hier zowel gaan om medische kosten (zoals hospitalisaties, doktersbezoeken, medicatiegebruik) als om niet-medische of persoonlijke kosten (zoals speciaal onderwijs, aanpassingen woning, transport, loopbaanonderbreking). Let wel op dat u in uw

overzicht enkel die zaken vermeldt die een gevolg waren van de penumokokkeninfectie. Eventuele dokterconsultaties of hospitalisaties die met andere aandoeningen te maken hadden, mogen we niet opnemen in dit overzicht. We zullen de periode overlopen die begint vanaf het moment van de pneumokokkeninfectie en die loopt tot op vandaag.

Verpleegkundige:Laat de persoon eerst zijn/haar verhaal doen over de mogelijke kosten die met de pneumokokkeninfectie te maken had. Indien mogelijk begin reeds met het invullen van Bijlage II. U mag tijdens het spontane verhaal van de patiënt de uitgavenstaat (zie vraag 10) reeds zelf consulteren om een idee te hebben over de exacte kosten waarover de patiënt spontaan vertelt.

Verder specifiëren aan de hand van de uitgavenstaat

Als mutualiteit beschikken we over een beperkt aantal gegevens van zaken waar u beroep op heeft gedaan. U heeft er reeds een aantal zelf opgenoemd. Ik zou graag met u nu een aantal zaken overlopen die in dit overzicht staan, maar die u niet vermeld heeft. We zullen dan nagaan of deze met een andere aandoening te maken hadden of dat u deze bent vergeten te vermelden. Het kan ook zijn dat ik over bepaalde zaken die u wel vermeldt heeft een aantal bijkomende vragen stel aan de hand van dit overzicht.

Verpleegkundige: Ga aan de hand van de uitgavenstaat expliciet na of de respondent bepaalde kosten nog niet vernoemd heeft. Indien dit het geval is, ga dan met de respondent na of dit ook in verband stond met de pneumokokkeninfectie. Noteer alles in Bijlage II.

Afchecken van mogelijke andere kosten (niet-terugbetaalde medische kosten, persoonlijke kosten, toekomstige kosten)

Er zijn echter nog een heleboel andere zaken waar men beroep op kan doen en waarover de mutualiteit geen gegevens heeft. Tot slot zal ik daarom met u nu een aantal van deze zaken overlopen die u niet vermeld heeft. Het kan zijn dat u op deze zaken geen beroep op heeft gedaan, maar het kan ook zijn dat u deze bent vergeten te melden.

Op deze manier bekomen we een zo compleet mogelijk beeld van al de zaken waar u beroep op heeft gedaan en van de bijhorende kosten die u daarvoor heeft moeten maken.

Verpleegkundige: Neem Bijlage I erbij (categorieën van mogelijke kosten) en ga na welke zaken men niet heeft vermeldt.

Einduur

_ _ uur _ _ minuten

BIJLAGE I:CATEGORIEEN VAN MOGELIJKE KOSTEN VAN DE PNEUMOKOKKENINFECTIE

Categorie		Eenheid
MEDISCHE KOSTEN		
1	*- Consultatie huisarts*	*Aantal*
2	*- Hospitalisatie*	*Aantal dagen*
	- Consultatie specialist:	
3	*- pediater*	*Aantal*
4	*- internist*	*Aantal*
5	*- neuroloog*	*Aantal*
6	*- neus-keel-oorarts*	*Aantal*
7	*- andere specialist*	*Aantal*
	- Consultaties andere gezondheidsberoepen:	
8	*- kinesist*	*Aantal*
9	*- logopedie*	*Aantal*
10	*- andere gezondheidsberoepen*	*Aantal*
11	*- Technische onderzoeken (bloedtesten, X-rays)*	*Aantal*
12	*- Medicatie (antibiotica, pijnstillers)*	*Aantal verpakkingen*
13	*- Verzorgingsproducten (zalven, verzorgende pleisters ontsmettingsmateriaal)*	*Aantal verpakkingen*
14	*- Technisch fysische hulpstukken (prothese, hoorapparaat, rolstoel)*	*Aantal*
15	*- Verpleging door medische professionelen (bv thuisverpleging)*	*Aantal bezoeken*
16	*- Voorziene toekomstige medische kosten*	
17	*- Andere medische kosten*	
NIET-MEDISCHE OF PERSOONLIJKE KOSTEN		
18	*- Transport van/naar de dokter, hospitaal, kinesist*	*Aantal km*
19	*- Plaatsing/revalidatie*	*Aantal maanden*
20	*- Speciaal onderwijs*	*Aantal maanden*
21	*- Speciale voeding (bijvoeding, voedingssupplementen, sondevoeding, voedingspomp)*	*Aantal verpakkingen*
22	*- Hulpverlening aan huis (gezinshulp, poetsdienst, boodschappendienst maaltijddienst)*	*Aantal maanden*
23	*- Hulpmateriaal om comfortabel en mobiel te blijven binnenshuis (loopbrug, lift, speciale inrichting badkamer)*	*Aantal*
24	*- Hulpmateriaal om comfortabel en mobiel te blijven buitenshuis (aangepast auto, aangepaste fiets)*	*Aantal*
25	*- Verlof*	*Aantal dagen*
26	*- Loopbaanonderbreking*	*Aantal maanden*
27	*- Werkduurvermindering*	*Aantal maanden*
28	*- Verhuis*	*Aantal*
29	*- Voorziene toekomstige persoonlijke kosten*	
30	*- Andere persoonlijke kosten*	

BIJLAGE II

Naam verpleegkundige: _ Lidnummer patiënt: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ Datum: _ _ / _ _ / _ _ _ _

Categorie Zie bijlage I	**1: Minder dan 1 jaar na infectie 2: Meer dan 1 jaar na infectie**	**Aantal eenheden** Zie bijlage I	**Eigen bijdrage (per eenheid)**	**Eigen bijdrage Totaal**	**RIZIV (eenheid)**	**Totaal RIZIV**	**Totaal kost**	**Commentaar** (noteer hier nr en comm op achterkant)

8.6 APPENDIX C5: CATEGORIEËN VAN DE VERSCHILLENDE KOSTEN

Code	Omschrijving
1	Heelkunde
2	Medische beeldvorming
3	Reanimatie
4	Anesthesie
5	Verloskunde
6	Nierdialyse
7	Inwendige geneeskunde
8	Dermato-venerologie
9	Kinesitherapie - Fysiotherapie
10	Klinische Biologie
11	Wachtdienst en toezicht
12	Pathologische anatomie en genetische onderzoeken
13	Algemene speciale verstrekkingen en puncties
14	Tandheelkunde
15	Radio- en radiumtherapie / nucleaire geneeskunde
16	Bandagisten, opticiens, orthopedisten, gehoorporthesen
17	Synthesemateriaal - implantaten
18	Ligdagen
19	Patientensupplementen zonder ziv-tussenkomst
20	Geneesmiddelen
21	Technisch geneeskundige verstrekkingen
22	Revalidatie
23	Aanwezig. Arts anesth. - Operatieve hulp
24	Raadpleging en bezoeken
26	Weefsels van menselijke oorsprong
27	Gipsbanden en ander gipsmateriaal
28	Plaatsing en reiskosten - PA preventoria
29	Forfaitair remgeld technische gen. Prestaties
30	Regularisatie
31	Zorgen thuisverpleging
32	Zorgen in het buitenland
33	Forfait chronische zieken / incontinentie
34	Medisch tehuis
35	Logopedie
36	Producten en diensten van de mutualiteit
37	Codes Solimut en MAF
38	Codes complementaire verzekering

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37 HTA of Magnetic Resonance Imaging. D/2006/10.273/34.
38 Cervical Cancer Screening and Human Papillomavirus (HPV) Testing. D/2006/10.273/37.
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