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# The cost-effectiveness of pneumococcal vaccination in healthy adults over 50: An exploration of influential factors for Belgium

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ABSTRACT

*Background:* A recent trial demonstrated the 13 valent conjugate pneumococcal vaccine (PCV13) to be effective against invasive and non-invasive pneumococcal disease in healthy adults. PCV13 might therefore be considered as an alternative to the 23 valent polysaccharide vaccine (PPV23).
*Aim:* To explore the cost-effectiveness of vaccinating healthy adults over 50, with either PCV13 or PPV23 alone, or with a combined strategy using both PCV13 and PPV23.
*Methods:* A static multi-cohort model was developed simulating the consequences of pneumococcal vaccination in adults over 50 from a health care payer's perspective, for different scenarios of duration of vaccine protection and serotype evolution.
*Results:* At currently expected prices, PCV13 vaccination of healthy adults over 50 is unlikely to be cost-effective either compared with no vaccination or in combination with PPV23 versus PPV23 only.
*Conclusion:* Further research is needed on vaccine efficacy of the combination strategy and of risk groups, as well as the duration of vaccine protection. Serotype evolutions under the influence of the childhood PCV program should be closely monitored.



## 1. Introduction

Pneumococcal infection can cause invasive pneumococcal disease (IPD: meningitis and septicemia, pneumonia with bacteremia) and non-invasive disease (non-IPD: otitis media, pneumonia without bacteremia), both most severely in infants, the elderly and particular risk groups [1]. Two pneumococcal vaccines are available for adults. The 23-valent polysaccharide vaccine (Pneumovax23™, henceforth called PPV23), is weakly immunogenic and protects against IPD caused by 23 serotypes [2,3]. Although it has been in use for decades, its effectiveness against non-IPD has not been shown conclusively. The 13-valent pneumococcal conjugate vaccine (Prevenar13™, henceforth called PCV13) provides protection against 13 serotypes [4,5].

The recent CAPITA trial showed PCV13 to be effective against both IPD and non-bacteremic pneumonia in the elderly [5]. Due to high pneumonia incidence in the elderly [6], PCV13 is being considered to replace PPV23 or to be given in addition to it. In Belgium, the Superior Health Council recommends one dose of PPV23 or, in line with the US recommendations of the Advisory Committee on Immunization Practices, one dose of PCV13 followed by one dose of PPV23 in healthy adults above 65, with revaccination after 5 years [7,8].

Pneumococcal conjugate vaccines containing fewer (PCV7 and PCV10) or the same number of serotypes (PCV13) are also being used in childhood. Herd immunity arising from childhood PCV vaccination reduces vaccine serotype circulation across all age groups, with part of the disappearing vaccine serotypes being replaced by other serotypes [9–12]. This implies that successful childhood PCV vaccination lowers the potential utility of pneumococcal vaccines

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in older age groups. Belgium experienced PCV7 market entrance in 2004, introduced a universal childhood PCV7 program in 2007, switched to PCV13 in 2011, and is currently (2015–2016) in the process of replacing PCV13 by PCV10 (see Supplement S2).

Due to the recent evidence on PCV13's efficacy in the elderly and on indirect effects arising from childhood PCV vaccination, the cost-effectiveness of pneumococcal vaccination in the elderly requires revision. To our knowledge there are no cost-effectiveness analyses comparing both vaccines in the elderly using the CAPITA trial data and accounting for potential indirect effects such as herd immunity and serotype replacement. We therefore assess the cost-effectiveness of PCV13 or PPV23 versus no vaccination as well as both PCV13 and PPV23 versus PPV23 only in healthy adults over 50, while accounting for the uncertainties arising from the vaccination costs and the indirect effects.

## 2. Methodology

### 2.1. Model structure

We developed and applied an age-structured static multi-cohort model to simulate the costs and effects of adult pneumococcal conjugate vaccination strategies (see Fig. S1 in supplement). Single year age cohorts between 50 and 90 years of age are simultaneously followed from the moment of vaccination until death of the last survivor in the youngest cohort. The vaccines (PCV13, PPV23 or both), their timing, uptake and the applied scenario of duration and waning of vaccine-induced protection, determine each cohort's vaccine effectiveness (VE). This VE together with the background serotype-evolution (influenced mainly by the children's PCV13 program), determine the population at risk at each age, separate for IPD and non-IPD, and per serotype category (see Section S1.1.1 in supplement). Age specific incidences are then applied to calculate IPD (pneumonia with bacteremia, meningitis and septicemia) and non-IPD (pneumonia without bacteremia) and their associated costs, deaths and Quality-Adjusted Life Years (QALYs) lost. Long-term consequences of meningitis (hearing loss or neurological sequelae) are also taken into account. For details on the model structure see Section S1.1 in supplement.

### 2.2. Model parameters

Tables 1 and 2 contain the input parameters used in the model. In this subsection, we clarify our main assumptions made.

Serotype-specific incidence (to calculate $Q_\tau(a, c)$ see Section S1.1.1 in supplement) in adults is influenced by previous childhood (PCV13 and PCV7) vaccination. In the absence of Belgian studies on herd effects in adults, we used the same yearly decay of circulating PCV7 serotypes as observed in 2–4 year olds over the period 2003–2008 and assumed the decay proportion was the same every year (i.e. exponential decay with 24% yearly decline [11]), while illustrating the impact of varying this decline (from 0% over 12% to 24% per year). Defining the maximum decline at 24% per year based on the decline in PCV7 types observed during 2003–2008 can be seen as favouring PCV13, because PCV7 uptake in children was low until 2007 (see supplementary information). The annual decline of 24% is almost identical to the PCV13 type specific incidence reduction recently reported for England and Wales (−64% over 4 years, [23]). The extent of serotype replacement, assumed equal for IPD and non-IPD, was varied between 0% and 100% (results shown with 50%, unless specified otherwise).

In the absence of empirical evidence and for ease of comparison we conservatively show results assuming PCV13 and PPV23 produce equal durations of vaccine protection of 5 years.

PPV23's protection against non-bacteremic pneumonia is assumed zero and the combination of PCV13 and PPV23 is assumed to yield the per-serotype best protection of the two vaccines.

Where appropriate, uncertainty around input parameter estimates is specified in terms of probability distributions used for probabilistic sensitivity analysis, assuming independence between inputs.

In order to facilitate the interpretation of the results, we used a pragmatic cost per quality-adjusted life year (QALY) gained threshold of €35,000. This amount has been used before as a benchmark for Belgium [24–27].

### 2.3. Sensitivity analysis for PCV13 or PPV23 versus no vaccination

Since the duration of vaccine efficacy and the decline in PCV13 serotype specific incidence under the influence of the children's vaccination program are both highly uncertain, we studied these two factors in sensitivity analysis for the vaccination of 75% of each target group with either PCV13 or PPV23 compared to no vaccination. Given a limited follow up period of vaccine efficacy, we considered two distinct waning scenarios: In the first ("no waning scenario") we assumed no vaccine waning and a constant vaccine efficacy over the assumed duration of protection (varied between 4 and 15 years). In the second ("exponential waning scenario") we assumed 5 years of no waning (period of complete vaccine protection) followed by an exponential decay with its half-life varied between 0 and 10 years. PCV13 serotype change was expressed as a proportional decline and was varied from 0 over 12% to 24%, the observed PCV7 decline. Compensation of this PCV13 incidence reduction, by serotype replacement, is assumed proportional to the current incidence of non-PCV13 serotypes and varied between none and complete PCV13 specific incidence compensation.

At each draw from the input distribution, we recalculate the vaccine price for which the incremental cost-effectiveness ratio (ICER) equals our defined threshold of €35,000 and summarize its distribution by taking the mean, median and 95% range. Since vaccine price and ICER have a strictly monotone relationship, the median threshold price (and other order statistics) can be interpreted as the price for which the median ICER equals €35,000. This median price was taken as dependent variable in sensitivity analysis, to investigate the plausible impact of price competition through tendering.

### 2.4. Sensitivity analysis for PCV13 and PPV23 versus PPV23 alone

In addition to studying the cost-effectiveness of various vaccination scenarios against no vaccination, we study possible conditions of incremental cost-effectiveness of adding a dose of PCV13 to an existing PPV23 program. The main added value of PCV13 vaccination lies in the demonstrated efficacy against non-bacteremic pneumonia. Therefore, we explore the impact of model assumptions regarding the proportion of outpatient pneumonia cases caused by pneumococcus and of non-bacteremic hospitalised pneumonia. Furthermore, model assumptions on the duration of vaccine protection and the evolution of the circulating serotypes causing pneumococcal disease are explored.

## 3. Results

### 3.1. Assuming equal uptake and duration of effectiveness for PPV23 and PCV13

Table 3 lists the incremental costs and effects of vaccinating 75% of the population per age group with either PCV13 or PPV23, assuming an equal duration of complete vaccine protection of 5 years without waning for both vaccines. This shows the clear advantage of PPV23 vaccination, for all age groups, in preventing IPD, indicated