Human Vaccines & Immunotherapeutics

ISSN: 2164-5515 (Print) 2164-554X (Online) Journal homepage: http://www.tandfonline.com/loi/khvi20

Economic evaluation of pneumococcal vaccines for adults aged over 50 years in Belgium

Lander Willem, Adriaan Blommaert, Germaine Hanquet, Nancy Thiry, Joke Bilcke, Heidi Theeten, Jan Verhaegen, Herman Goossens & Philippe Beutels

To cite this article: Lander Willem, Adriaan Blommaert, Germaine Hanquet, Nancy Thiry, Joke Bilcke, Heidi Theeten, Jan Verhaegen, Herman Goossens & Philippe Beutels (2018) Economic evaluation of pneumococcal vaccines for adults aged over 50 years in Belgium, Human Vaccines & Immunotherapeutics, 14:5, 1218-1229, DOI: 10.1080/21645515.2018.1428507

To link to this article: https://doi.org/10.1080/21645515.2018.1428507

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2018, VOL. 14, NO. 5, 1218–1229
https://doi.org/10.1080/21645515.2018.1428507

Taylor & Francis
Taylor & Francis Group

RESEARCH PAPER

OPEN ACCESS Check for updates

Economic evaluation of pneumococcal vaccines for adults aged over 50 years in Belgium

Lander Willem[a], Adriaan Blommaert[a], Germaine Hanquet[b], Nancy Thiry[b], Joke Bilcke[a], Heidi Theeten[c], Jan Verhaegen[d], Herman Goossens[e], and Philippe Beutels[a,f]

[a]Centre for Health Economics Research & Modeling Infectious Diseases (CHERMID), Vaccine and Infectious Disease Institute (VAXINFECTIO), University of Antwerp, Antwerp, Belgium; [b]Belgian Health Care Knowledge Centre (KCE), Brussels, Belgium; [c]Center for the Evaluation of Vaccination (CEV), Vaccine and Infectious Disease Institute (VAXINFECTIO), University of Antwerp, Antwerp, Belgium; [d]Department of Clinical Microbiology, Universitair Ziekenhuis Leuven, Leuven, Belgium; [e]Laboratory of Medical Microbiology (LMM), Vaccine and Infectious Disease Institute (VAXINFECTIO), University of Antwerp, Antwerp, Belgium; [f]School of Public Health and Community Medicine, University of New South Wales, Sydney, Australia

ABSTRACT

Streptococcus pneumoniae causes a high disease burden including pneumonia, meningitis and septicemia. Both a polysaccharide vaccine targeting 23 serotypes (PPV23) and a 13-valent conjugate vaccine (PCV13) are indicated for persons aged over 50 years. We developed and parameterized a static multi-cohort model to estimate the incremental cost-effectiveness and budget-impact of these vaccines at different uptake levels. Using three different vaccine efficacy scenarios regarding non-invasive pneumococcal pneumonia and extensive uni- and multivariate sensitivity analyses, we found a strong preference for PPV23 over PCV13 in all age groups at willingness to pay levels below €300 000 per quality adjusted life year (QALY). PPV23 vaccination would cost on average about €83 000, €60 000 and €52 000 per QALY gained in 50–64, 65–74 and 75–84 year olds, whereas for PCV13 this is about €171 000, €201 000 and €338 000, respectively. Strategies combining PPV23 and PCV13 vaccines were most effective but generally less cost-effective. When assuming a combination of increased duration of PCV13 protection, increased disease burden preventable by PCV13 and a 75% reduction of the PCV13 price, PCV13 could become more attractive in <75 year olds, but would remain less attractive than PPV23 from age 75 years onwards. These observations are independent of the assumption that PPV23 has 0% efficacy against non-invasive pneumococcal pneumonia. Pneumococcal vaccination would be most cost-effective in Belgium, when achieving high uptake with PPV23 in 75–84 year olds, as well as by negotiating a lower market-conform PPV23 price to improve uptake and cost-effectiveness.

ARTICLE HISTORY
Received 15 September 2017
Revised 12 December 2017
Accepted 12 January 2018

KEYWORDS
pneumococcal; vaccine; adult; economic evaluation; cost-effectiveness

Introduction

The bacterial pathogen *Streptococcus pneumoniae* (*S. pneumoniae* or pneumococcus) is the most frequent cause of community-acquired pneumonia (CAP) in European adults.[1,2,3,4] More than 90 serotypes are known and distinguished by their unique polysaccharide capsule. The most severe form of pneumococcal disease, invasive pneumococcal disease (IPD), with infection of normally sterile sites (e.g., blood or cerebrospinal fluid) is responsible for meningitis and septicemia, as well as an important part of invasive pneumococcal pneumonia (IPP). Additionally, *S. pneumoniae* also causes non-invasive pneumococcal disease, where infection is limited to the middle ear (otitis media) or the lower respiratory tract, called non-invasive pneumococcal pneumonia (non-IPP) without detectable spread of organisms to the blood stream. Although less severe, non-IPP are much more frequent than IPP, and responsible for three quarters of all hospitalizations for pneumococcal pneumonia.[1] European studies indicated that IPP in elderly cases lead around three times more often to death during 30 days post-diagnosis compared to non-IPP.[5,6]

Since the 1990s, a 23-valent polysaccharide vaccine PPV23 (Pneumovax 23, Sanofi Pasteur MSD) is recommended in Belgium for all elderly above 65 years of age[7] This vaccine covers a high proportion of pneumococcal serotypes causing IPD in this age group (80% of all IPD in 2009–11).[8] PPV23 has shown a moderate efficacy against IPD but inconclusive efficacy against non-IPP. The protection induced by the vaccine is short lived and boosters have been recommended every 5 years.[9,10,11] PPV23 uptake has been around 16% up to 2004 and even decreased to 10% in 2013 in the Belgian population over 65 years.[12] A possible explanation is the lack of confidence of many clinicians in PPV23 due to its limited duration of efficacy and its contested efficacy against non-IPP.[13] In 2015, a 13-valent pneumococcal conjugate vaccine PCV13 (Prevenar 13, Pfizer) was approved for adults based on the CAPITA trial.[14] showing a moderate vaccine efficacy against IPD and non-IPP. There are no studies comparing the direct clinical effect of these two vaccines, but the conjugate vaccine is considered to elicit an immune response that is superior to that of PPV23.[14,15] The immune responses in terms of opsonophagocytic activity (OPA) in 60-64 year olds one month

CONTACT Philippe Beutels philippe.beutels@uantwerpen.be Universiteitsplein 1, 2610 Wilrijk, Belgium.
Supplemental data for this article can be accessed on the publisher's website.

post-vaccination were significantly higher in the PCV13 than in the PPV23 group for 8 of the 12 serotypes common to both vaccines.[16,17] However, there is no established correlate of protection against pneumococcal disease after either PPV23 or PCV13 in adults.[15,16] In 2014, the Belgian Health Council recommended primary vaccination with PCV13, followed by PPV23 after at least 8 weeks for all adults 65–85 years of age.[18] This recommendation was made based on short-term clinical benefit, without consideration of cost-effectiveness, or modeled projections of the comparative effectiveness over time. It remains unclear whether and when revaccination is warranted, and with which vaccine.

Uptake of pneumococcal vaccines remains low in adults, which could also be due to a lack of reimbursement. This absence of government subsidy raises inequity issues since these vaccines' cost is currently paid out-of-pocket, or through complementary private insurance.

In the European Union, pediatric pneumococcal conjugate vaccines covering the 7, 10 and 13 serotypes that most frequently cause IPD (PCV7, PCV10 and PCV13, respectively) have been progressively introduced in the universal childhood vaccination schedule since 2004. Widespread PCV vaccination, implemented at high uptake, provides an indirect effect on non-vaccinated subjects, including the elderly, through a reduction of *S. pneumoniae* carriage and transmission. The indirect effect on the elderly has been well demonstrated for PCV7 vaccination[19,20] but the decline in pneumococcal infections due to PCV7 types has been partly countered by increases in infections due to non-PCV7 types, i.e. so-called "vaccine-induced serotype replacement". This indirect effect is crucial when estimating the benefits of PCV13 in the elderly, as it may decrease the preventable fraction of IPD and non-IPP due to PCV13 serotypes.[15] In Belgium, PCV7 was included in the universal infant vaccination schedule in 2007[21] and replaced by PCV13 in 2013.[22] Two years later, PCV13 was replaced by PCV10 in the Flemish Community and one year later also in the Fédération Wallonie – Bruxelles, each time as the outcome of a tendering process. To our knowledge no effectiveness study exists on the same sequence of PCV use. There is some concern that the switch from PCV13 to PCV10 could lead to a "relapse" in the circulation and incidence (including in adults) of serotypes covered by PCV13 but not by PCV10.

Here, we estimate the adult burden of disease due to *S. pneumoniae* in Belgium in 2016, and we compare the 2016 situation based on low PPV23 vaccination coverage in the elderly with various options of use of PPV23 and/or PCV13 at different uptake levels, estimating the incremental effectiveness, cost-effectiveness and budget-impact. The results presented in this manuscript were obtained in the context of a health technology assessment coordinated by the Belgian Health Care Knowledge Centre (KCE) to help decision making by national and regional authorities on pneumococcal vaccination policy for the elderly.[23]

Results

Burden

With current low uptake PPV23 vaccination in place, we estimated the average annual disease burden in Belgium of *S. pneumoniae* in 2016 to attain 5905 hospitalizations (with 3606 additional patients treated in ambulatory care), about 428 deaths and 4161 quality adjusted life years (QALY) lost. The health care costs for treatment amount to about €33.7 million. The absolute number of fatalities, and particularly those of pneumonia, is estimated to be higher in older age groups, despite the decreasing size of each age group with increasing age. The number of hospitalizations and especially outpatients decline in the more advanced age groups, which explains also the decreasing trend in costs by age group. Appendix A presents the estimated disease and cost burden into more detail.

Prevented cases

We analyzed the effect of increasing the uptake of PPV23 or introducing PCV13, relative to the "current (2015) situation" in which PPV23 uptake remains relatively low (See Methods and Table 1). This analysis does not incorporate specific risk group vaccination but is applied to the general Belgian population from a health care payer's perspective. We performed our analyses for three different vaccine efficacy assumptions: (1) PPV23 and PCV13 each have fully parameterized baseline efficacy against vaccine-type non-IPP, (2) only PPV23 has no efficacy against vaccine-type non-IPP, (3) both PPV23 and PCV13 have no efficacy against vaccine-type non-IPP. Predictions of one simulation are displayed in Figure 1, showing the prevented IPD and non-IPP cases over time for the different vaccination scenarios and age groups assuming fully parameterized efficacy of PPV23 and PCV13 against non-IPP. This figure shows that PPV23 could prevent more IPD cases up to 5 years compared to PCV13 and the added benefit from revaccination scenarios is clearly visible by an increase in the prevented cases after 5 years. If we focus on prevented non-IPP cases, PCV13 outperforms PPV23 for adults 50–74 years of age.

Cost-effectiveness

We present our results by "cost-effectiveness acceptability frontiers" (CEAFs), which provide for a range of willingness to pay (WTP) values the vaccination strategy with maximum expected net benefit and the probability of that vaccination strategy to be the most optimal among all vaccination scenarios and age groups considered. The CEAFs of all strategies and age groups (see Figure 2) showed, irrespective of the non-IPP efficacy assumption, that the current situation is the most optimal vaccination strategy (highest expected net benefit) for low WTP

Table 1. Vaccination uptake by age in Belgium in 2015 (calculated as the yearly mean of the 2004, 2008 and 2013 five year accumulated up-take) and targeted (re) vaccination programs.

Program	50-64 years	65-74 years	75-84 years	85-105 years
Current (2015) situation with PPV23	0.79%	2.46%	3.01%	2.48%
Program with increased PPV23 and/or PCV13 uptake	25%	50%	60%	40%
Revaccination (PPV23, after 5 years)	15%	25%	25%	20%

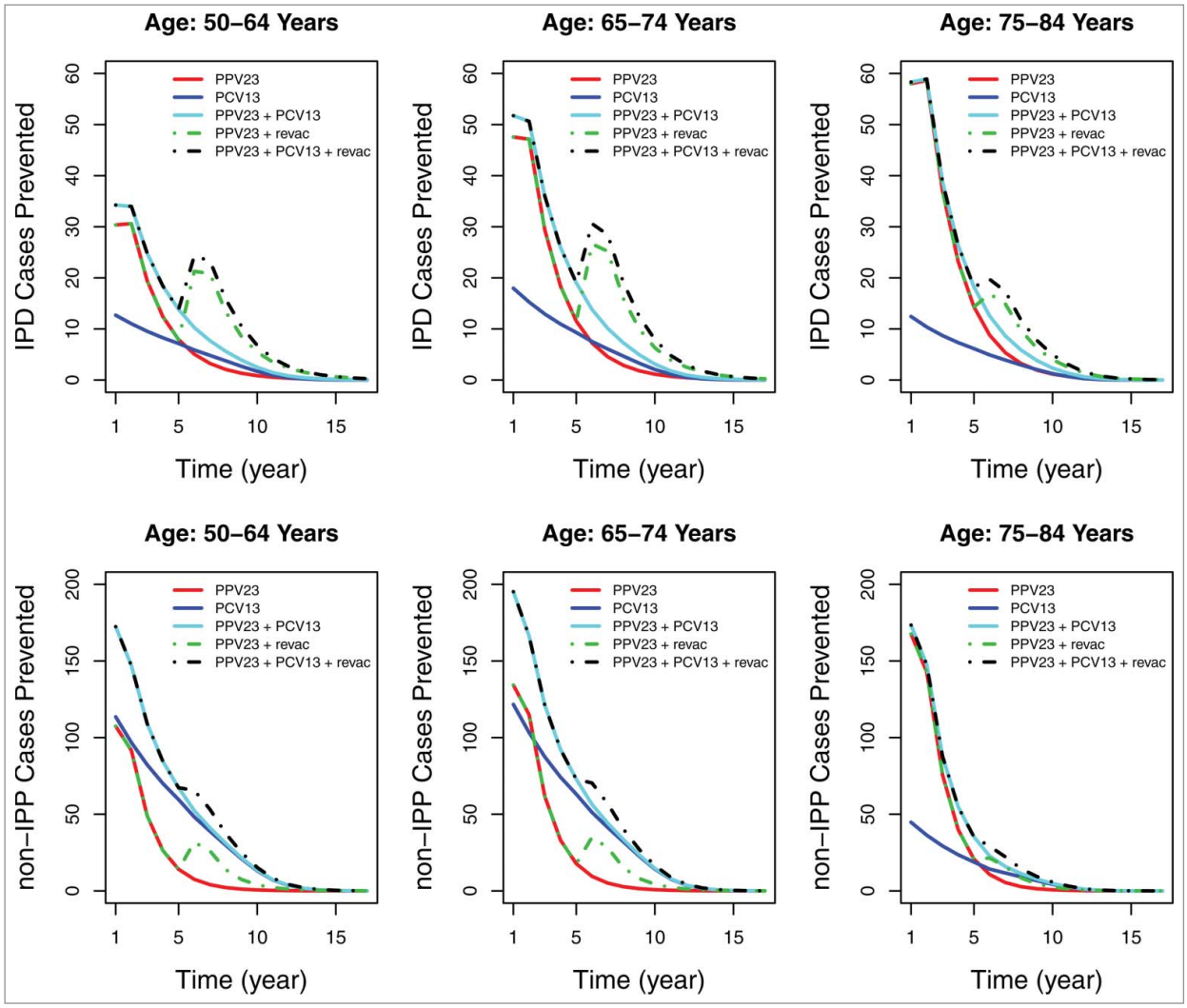

Figure 1. Predicted number of prevented IPD (top) and non-IPP (bottom) cases over time for different vaccination scenarios and age groups (left to right) from one simulation.

values. This means that if each QALY is valued less than €50 000 by a policy maker, the monetary value of QALYs gained by any new strategy is unlikely to surpass the additional vaccination costs minus the health care costs avoided. Strategies targeted at people aged 85 years and older are never selected as the most cost-effective because we concluded through literature review that none of the vaccines has conclusive evidence to show efficacy in that age group.

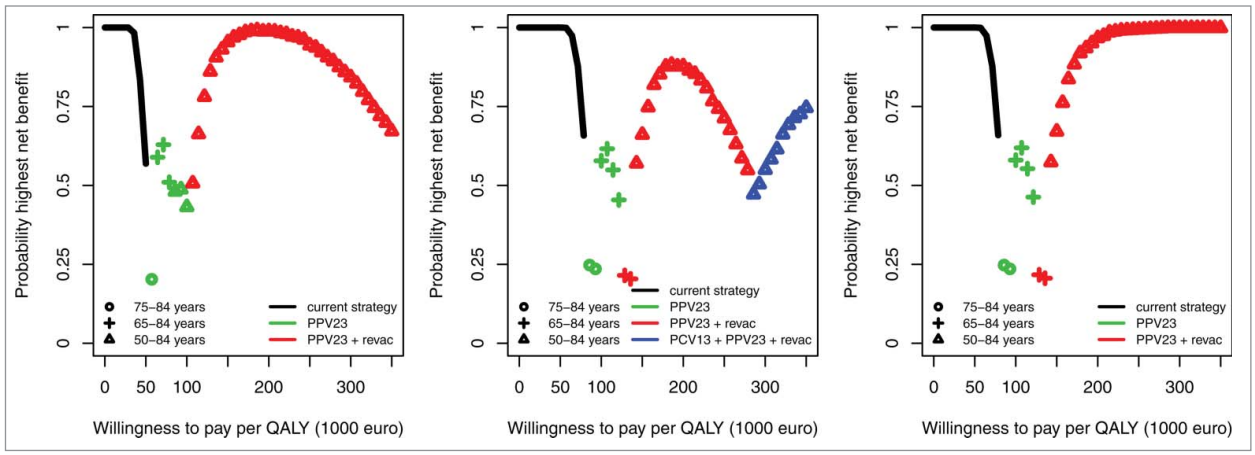

Figure 2. Cost-effectiveness acceptability frontier (CEAFs) for different strategies, with increased uptake of PPV23 or introducing PCV13, relative to the "current (2015) situation" in which PPV23 uptake remains relatively low. We compared all strategies assuming both vaccines have fully parameterized efficacy against non-IPP (left), PPV23 has no efficacy against non-IPP (center) and both PPV23 and PCV13 have no efficacy against non-IPP (right).

If assuming fully parameterized efficacy for both vaccines (see Figure 2), the best options with increasing WTP for a QALY are to vaccinate the age group 75–84 years with PPV23 only (from WTP €50 000 to €60 000 per QALY), which expands to 65–84 years with PPV23 (up to €80 000 per QALY) and further to 50–84 years with PPV23 (up to €100 000 per QALY), and adding revaccination with PPV23 (up to €350 000 per QALY). In terms of cost-effectiveness, high uptake of PPV23 in 75–84 year olds is more beneficial compared to expanding this strategy to younger age groups. Although introducing high uptake PCV13 + PPV23 vaccination is most effective (PCV13 containing strategies have a higher impact on hospitalizations for pneumococcal pneumonia), this combined strategy has much less to gain versus high uptake PPV23 at relatively high incremental vaccination costs. Therefore, the incremental effectiveness of yet more expansive strategies (e.g. PCV13 + PPV23 with revaccination versus PCV13 + PPV23) is limited.

Taking a different analytical approach, we also assessed the technical efficiency of phased introduction within each age group separately. In 50–64 year olds, introducing PPV23 vaccination with 25% uptake would prevent 14 deaths and gain 288 QALYs versus the current situation over the remaining lifetime of the vaccinated cohorts. Adding 25% PCV13 vaccination would only gain an additional 190 QALYs and avert 194 hospitalizations for pneumococcal pneumonia and 10 deaths at incremental vaccination costs of €48 million. We provide a full overview of the avoided burden in Appendix B. In 65–74 year olds, substantially more IPD cases and deaths can be avoided over the remaining lifetime of the vaccinated cohorts with PPV23 than with PCV13 (both at 50% uptake), and more QALYs can be gained. However, these effects are obtained with twice the vaccine uptake compared to these strategies in the 50–64 year olds (Table 1). In 75–84 year olds, with 10% higher uptake than in the previous age group, the prevented burden of disease increases and the balance tips further in favor of PPV23. The uncertainty on the pneumococcal pneumonia hospitalizations and outpatient cases averted is higher for both vaccines compared to the 50–64 year olds. The incremental cost-effectiveness ratio (ICER) is greater for PCV13 containing strategies and lower for PPV23 containing strategies, in comparison to the previous age groups. Higher uptake PPV23 vaccination of both 65–74 and 75–84 year olds would prevent 764 hospitalizations and 80 deaths compared to the current situation. PCV13 at the same uptake would prevent 545 hospitalizations and 43 deaths.

For the two other vaccine efficacy scenarios, a similar order of preferred strategies with increasing WTP is found, except that expanding PPV23 to 50–84 years is never the preferred strategy, and higher uptake for 75–84 years with PPV23 only becomes preferred at a higher WTP, at about €75 000 per QALY gained (Figure 2). Also, if we assume that PPV23 has 0% efficacy against non-IPP (while that of PCV13 is maintained), the PCV13 + PPV23 with revaccination emerges as the most beneficial in the highest region of WTP shown here. Assuming no PPV23 protection against non-IPP makes PCV13 containing strategies in the 50–64 year and 65–74 year age groups the most beneficial when WTP per QALY exceeds €250 000 and €200 000, respectively. When the efficacy of both vaccines against non-IPP is assumed to be 0%, an important advantage of PCV13 over PPV23 disappears. PPV23 with revaccination in 50–84 year olds is the strategy with the highest net benefits when WTP exceeds about €130 000, and none of the PCV13 containing scenarios then attains the highest net benefit up to a WTP of €350 000 (Figure 2).

Sensitivity analysis

In addition to parametric sensitivity, we also explored uncertainty in relation to other assumptions through uni- and multivariate sensitivity analysis. Unless stated otherwise, results presented below are obtained with fully parameterized vaccine efficacy against non-IPP for both PCV13 and PPV23. We highlight here the main results of univariate (or one-way) sensitivity analyses, including the influence of PCV13 price reductions. Detailed results are provided in Appendix C.

We varied the level and duration of efficacy of both vaccines extensively. For instance, considering a maximum duration of PCV13 protection (9 years fixed protection followed by slow waning to no protection at 20 years), the WTP level at which strategies with PCV13 are retained lowers in 50–74 year olds to about €250 000 – €275 000 per QALY. Assuming PCV13 efficacy is age-independent in 50–84 year olds (as reported in the CAPITA study 14) and has 0% efficacy in ≥85 year olds, makes PCV13 unlikely to be the most cost-effective option at any age or WTP level considered. In the 65–74 year age group there is a clear impact of assuming an age-independent PCV13 vaccine efficacy. The tilting point of age-dependence is 72 years (i.e. the average age in the CAPITA study), meaning that 65–72 year olds have a lower and 73–74 year olds have a higher PCV13 vaccine efficacy without than with age-dependence. The 65–72 year olds however dominate the result of the 65–74 year old, meaning that PCV13 scenarios become less attractive when assuming an age-independent PCV13 vaccine efficacy. For 75–84 year olds, the improved (age-independent) efficacy estimate increases the uncertainty by which the PPV23-only strategies dominate PCV13 containing strategies over the range of WTP considered. PCV13 + PPV23 with revaccination then becomes the strategy with the highest expected net benefits when WTP exceeds €400 000.

Assuming five years of PPV23 protection without waning followed by instant loss of protection makes this vaccine in the age groups 65–74 and 75–84 years an attractive strategy from a WTP of €40 000 per QALY. Two years of complete PPV23 protection followed by no protection, requires the WTP to exceed €90 000 for any PPV23 vaccination strategy to become cost-effective. There is no change in the relative attractiveness of the different strategies.

Assuming a double baseline incidence of pneumococcal pneumonia hospitalizations, due to potential ICD coding misclassification, makes the PPV23 scenario likely to be cost-effective at a WTP value of €50 000 per QALY gained for 50–84 year olds. This is specifically the case in the 75–84 year and 65–84 year age groups from about €25 000 and €30 000 per QALY gained, respectively. If a higher percentage of pneumococcal pneumonia in outpatient CAP is assumed (27% 1 instead of 10.5%), all vaccination options show a more favorable cost-effectiveness ratio, especially if they include PPV23 use.

We also assumed different levels of indirect effects from infant vaccination. Assuming a minimum indirect effect on vaccine serotypes, with a declining PCV13 serotype incidence of 10% per year and 76.3% replacement by non-PCV13 serotypes (see "Model Design" in the Methods section for more details) makes vaccination options slightly more cost-effective. Pneumococcal vaccination using PPV23 for ages 65–84 years remains the most beneficial from a WTP of about €45 000 per QALY. In 50–64 year olds, vaccination becomes likely beneficial from about €70 000 with PPV23 and from about €220 000 with PCV13 + PPV23 with revaccination (€200 000 for 65–74 year olds). For 75–84 year olds, none of the PCV13 containing strategies are selected as the most cost-effective. A maximum indirect effect on vaccine serotypes with a PCV13 serotype incidence decline of 20% per year and 76.3% replacement echoes our baseline analyses.

Assuming a quick relapse of the incidence of serotypes included in PCV13 but not in PCV10 (following the recent switch to PCV10 infant vaccination) in which PCV13 serotype incidence returns to its 2015 value within 7 years, makes all vaccination options more attractive. In particular PCV13 containing options and PPV23 revaccination strategies become more beneficial. PCV13 + PPV23 with revaccination in <75 year olds would be cost-effective from WTP of about €130 000 per QALY. For 75–84 year olds, the most beneficial strategy is PCV13 + PPV23 with revaccination from a WTP of €230 000 per QALY. Assuming slow serotype relapse with PCV13 incidence returning to its 2015 value within 15 years, PCV13-only strategies are never selected, but PCV13 + PPV23 with revaccination becomes the most beneficial in the age groups 50–74 year olds (from €175 000).

Vaccine price

Reductions of 25% to 50% of the PCV13 vaccine price make little difference to the overall picking order of age groups and strategies. Reductions of 75% do have an effect when we simultaneously assume that PPV23 has 0% efficacy against non-IPP. In that case, especially for the age groups 50–64 and 65–74 years, PCV13 containing strategies are more likely selected. The minimum WTP level at which PCV13 containing strategies are favored given a price reduction of 75% is about €55 000 for 50–64 year olds and about €50 000 for 65–74 year olds. None of the price reductions expect a PCV13 containing strategy in 75–84 year olds to have the highest benefit below a WTP of €250 000 per QALY. In the age group 75–84 years, a price reduction of 75% and assuming no protection of PPV23 against non-IPP, still only leads to the selection of PPV23 based strategies, with PCV13 + PPV23 with revaccination as the only PCV13 containing strategy having the highest expected net benefits when WTP attains about €250 000.

Price reductions of PPV23 are most influential for strategies that use multiple vaccine doses, but single dose PPV23 vaccination remains the most cost-effective option in 75–84 year olds. The incremental cost-effectiveness of PPV23 with revaccination is optimal in 65–74 year olds. With a 75% reduction in vaccine price, the mean ICERs for PPV23 strategies with and without revaccination become €20 000 – €37 000 and €37 000 – €48 000 per QALY gained, respectively, depending on the inclusion of a vaccine effect on non-IPP.

Multivariate sensitivity analysis

Potential price reductions are key for the cost-effectiveness but also assumptions on the duration of protection and serotype relapse are important. The incidence of pneumococcal pneumonia is influential, but less so than these other three, unless in combination with other disease burden changes, such as all incidences and death rates. Risk group analysis showed that using QALY impact of a medium risk group (i.e. those with unstable co-morbidities or immunocompromised) and doubling all incidences is sufficient to make PPV23 cost saving at a WTP of €35 000 per QALY for all age groups <85 years. This is only the case if we assume PPV23 to provide (partial) protection against non-IPP. Such savings also occur for PCV13, if simultaneously the vaccine price decreases by at least 50%.

For PCV13, decreasing vaccine prices and faster and more extensive relapse scenarios are most important to make it preferable to PPV23. By assuming an increase in the in-hospital death rate of 50%, the relative advantage of PPV23 over PCV13 remains constant for people up to 74 years of age, but increases for 75–84 year olds. The addition of a serotype relapse scenario makes PCV13 in these circumstances clearly preferable to PPV23, except in the 75–84 year olds where PPV23 still yields the highest net benefits. The multivariate sensitivity analyses also showed that the assumed WTP threshold per QALY is also highly influential. More results of this multivariate sensitivity analysis are described in Appendix C.

Budget impact

We performed a budget impact analysis of the increased PPV23 uptake program, assuming baseline efficacy against non-IPP. The estimated avoided treatment costs over 10 years (estimated at <€10 million for all ages), benefiting mainly the national health insurer RIZIV/INAMI and patients, is much lower than the required vaccination costs (>€104 million for 50–84 year olds), expected to be mainly incurred by the regional governments (Flanders, Wallonia, Brussels) and patients. This results in a low (<10%) return on investment and in net costs in excess of €95 million. There is little difference between 5 or 10-year time spans because the change in uptake under a change in vaccination policy is modeled as having the largest impact in the first year of the introduction. Also, we performed a budget-impact of a high PCV13 uptake versus the current situation using the baseline retail price and uptake levels for single dose PCV13 vaccination and assuming baseline efficacy against non-IPP. This showed that the avoided treatment costs (<€6.3 million for all ages) in combination with the required vaccination costs (>€229 million for 50–84 year olds) results in a lower (<3%) return on investment and higher net costs of €224 million. The budget-impact of PCV13 is more sensitive to vaccine price compared to vaccine uptake. When reducing the PCV13 price by 75% and keeping baseline uptake, the highest return on investment is in the age group 65–74 years at 9% after 5 and 10% after 10 years. More information on the budget-impact can be found in Appendix D.

Discussion

The analyses presented in this paper were complex because of different levels of uncertainty. There is uncertainty on all aspects that have a major influence on cost-effectiveness: the effectiveness and price of both PPV23 and PCV13, the preventable burden of disease under the influence of the changing childhood vaccination program, and the WTP for a QALY in Belgium. Yet through elaborate literature reviews and uncertainty analyses, we can draw some clear conclusions from these analyses. We found a strong preference for using PPV23 over PCV13 in all age groups at WTP levels below €300 000 per QALY, which was the most consistent for those aged over 75 years. Versus the current situation, high uptake PPV23 vaccination would be, depending on the age group, about 2 to 6 times more efficient at gaining QALYs than PCV13 vaccination. Indeed, PPV23 vaccination would cost on average about €83 000, €60 000 and €52 000 per QALY gained in 50–64, 65–74 and 75–84 year olds, whereas for PCV13 this is significantly higher at about €171 000, €201 000 and €338 000, respectively.

The recent switch from PCV13 to PCV10 in the Belgian infant vaccination program could cause a relapse in the PCV13 serotype incidence in the elderly. Although the sequence of changing from PCV7 to PCV13 and to PCV10 remains to our knowledge unique to Belgium, in Finland the introduction of PCV10 was associated with a relative increase in serotype 19A (which is a PCV13 serotype) 5 years later.[24] We ran various scenarios to explore the potential impact of such a relapse on the cost-effectiveness.

However, the preference for PPV23 would only change when joint changes would occur in PCV13 vaccine price, in PCV13-type specific disease burden caused by PCV13 and in the duration of PCV13 protection. Although a combination of such changes from our baseline assumptions could make PCV13 more attractive in age groups <75 years, a preference for PCV13 over PPV23 remains highly unlikely for the age groups over 75 years. These observations are independent of whether we assume that PPV23 has 0% efficacy against non-IPP or has some positive (uncertain) efficacy against it, as measured in observational studies.[25,26]

In view of the above, if we are going to increase the use of these vaccines, cost-effectiveness analyses indicate that we should use PPV23 in people between 50 and 75 years of age, and neither vaccine in elderly >84 years. Note that we can expect individual heterogeneity in those over 85 years, and that along with equity concerns, this may be an argument to use PPV23 in this group selectively based on physicians' clinical judgment of overall fitness.

A more fundamental question relates to allocative efficiency: should we use pneumococcal vaccines in older adults at all. This depends entirely on the WTP for a QALY. We have shown that when WTP levels are in the lower – likely more acceptable magnitude ranges – of the levels we explored (mainly €0 to €350 000, but up to €5 million in analyses not shown), use of PPV23 could be considered cost-effective, particularly in the age group 75–84 years, where the fully parameterized baseline puts the average cost-effectiveness at around €50 000 per QALY. For the age group 65–74 years and 50–64 years, the WTP for a QALY has to be higher, and the certainty by which PPV23 is cost-effective at a given WTP level, is also more sensitive to the uncertainties we have explored.

We have shown that PPV23 price reductions, more in line with PPV23 prices observed in other EU countries, would further improve the cost-effectiveness of PPV23 containing strategies. The 2015 retail price of PPV23 (€28.46 per dose) in Belgium was markedly higher than e.g. in France (€12.46 per dose). Furthermore, large PPV23 price reductions, combined with higher estimates of pneumococcal disease incidence and a more optimistic parameter choice for PPV23 vaccine efficacy would bring more expansive use of single dose PPV23 below an average of €35 000 per QALY gained in all age groups. It would also bring the ICER of revaccination with PPV23 down to about €15 000 per QALY gained in 65–74 year olds. Our budget-impact analysis also showed that PPV23 requires a much lower investment upfront compared to PCV13, and yields a superior return on investment for the health care system. Still, the return on investment yielded by higher uptake PPV23 remains less than 11% and the additional vaccination costs required to achieve this are around €21 million over a 5 year period.

Other published economic analyses on pneumococcal vaccination have also used the results of the CAPITA study for the Netherlands,[27] England,[28] Germany,[29] and the US.[30] Mangen et al,[27] and Van Hoek et al,[28] only assessed PCV13, as PPV23 was either not considered as an option to prevent pneumococcal disease in the elderly (the Netherlands) or was already implemented (England). The English study found that the introduction of PCV13 in the elderly would cost the health care payer as much as £257 771 per additional QALY gained[28] which was considered highly cost-ineffective. This study has a number of assumptions and methodological choices in common with our study, i.e. waning of vaccine immunity, assumed indirect effect of infant vaccination program on elderly disease (though no replacement scenarios), the use of a health care payer perspective, and it also did not consider a targeted risk group vaccination.

The Dutch study[27] concluded that single dose PCV13 vaccination at 64–82% (uptake according to risk level), is highly cost-effective in the Netherlands with a cost per QALY gained as low as €12 922 for >65 year olds under a societal perspective. The main difference with our study is that Mangen et al,[27] focused on risk group vaccination assuming a high burden of disease in the medium and high-risk group, while assuming PCV13 would protect people with a medium and high-risk profile, albeit with a lower efficacy in the high-risk group compared to healthy persons. In terms of parameters, Mangen et al,[27] used costs for hospitalized cases (IPD and CAP) at least twice as high as costs we estimated from Belgian databases. Depending on age group and clinical syndrome, this ranged from €11 000 – €18 000 for IPD in Mangen et al,[27] versus €1 700 – €9 000 in our study. For inpatient CAP the prices ranged from €6 500 – €10 500 versus €1 700 – €5 900 in our study. Furthermore, the remaining PCV13 burden was higher than in Belgium (e.g. 38–46% of all IPD vs. 25%) and the indirect effect of PCV13 infant vaccination was not considered, because only PCV7 and PCV10 have been used in the infant program in the Netherlands (PCV10 since 2011). In addition, rates of outpatient pneumonia were estimated much higher (5 to 9 times)

than we observe in Belgium. Focusing on vaccinating low risk elderly 65–74 years of age, they found that PCV13 would cost €50 184 per QALY gained versus no vaccination.

In the economic evaluation for Germany,[29] vaccination with PPV23 clearly dominates PCV13 strategies. One-time vaccination with PPV23 would prevent more deaths and hospitalizations at lower costs than one-time vaccination with PCV13. The estimated cost per QALY gained of PPV23 vaccination, ranging €14 400 – €15 700, was much lower than in our study. This might be partly explained by their high vaccine efficacy of PPV23 for IPD and non-IPP of 75% and 66% respectively, in contrast with our baseline PPV23 efficacy of 56% and 30.8%, respectively. Also, the average (direct + indirect) disease costs per case were assumed to be higher: €8 581 for IPD and €3 178 for CAP and inpatient treatment, respectively.

The US study by Stoecker et al,[30] concluded that PCV13 + PPV23 vaccination has a mean cost-effectiveness ratio of $62 065 from a societal perspective, though increased herd protection by childhood vaccination may dramatically increase the cost per QALY after only a few years. They assumed PPV23 provides no protection against non-IPP and that its efficacy against IPD declines to 0% in 15 years time. Waning immunity of PCV13 is much slower with a decrease of 10% each 5 years. Interestingly, the QALY loss per disease episode for IPD is ten-fold smaller compared to the England[28] or our study. The included costs per case, ranging from $27 097 to $40 161 for IPD and $23 300 to $35 000 for non-IPP, were two to four times higher than our estimated costs from a health-care payer perspective.

In contrast to other studies, we used a multi-cohort approach with age-dependent and waning vaccine efficacy, included the possibility of a relapse of PCV13 serotypes, compared more strategies and explored many more aspects of the uncertainty. To extend the explorative analysis for Belgium by Blommaert et al,[31] we used the most up-to-date Belgian and international data and made more aspects age-dependent.

A limitation in this study was the lack of sufficient data on risk group vaccination. This, combined with the questionable feasibility of risk group vaccination in the Belgian context, made us focus on age, rather than risk group vaccination. Another limitation was the absence of an explicit WTP threshold in Belgium.[32] Using a WTP threshold, we could focus the analyses and perform efficient threshold analyses on price differentials between PCV13 and PPV23. We also ignored herd immunity from vaccinating 25% to 60% of age groups >50 years additional to that of childhood vaccination. Elderly adults are not core transmitters of the pathogen hence at these levels of vaccine uptake we expect a limited underestimation of the benefits of adult PCV13 vaccination. A dynamic transmission model of both the childhood and adult pneumococcal vaccination programs would substantially increase the complexity of the analyses as well as the uncertainty of the estimates since many aspects of pneumococcal transmission and carriage have not been quantified yet by age. Also, we assumed the direct vaccine impact on acute otitis media to be negligible in adults. Finally, the analyses are restricted by the limitations of the data. The incidence of pneumococcal pneumonia and other aspects of the attributable disease burden remain difficult to quantify and the effectiveness of the vaccines by age and over time against each outcome is uncertain. Nonetheless, through extensive sensitivity analyses, we believe that we have made the most of the available data.

Vaccination with PPV23 was found to be more cost-effective than PCV13 in all age groups at WTP levels below €300 000 per QALY. It will be essential to detect any change in the epidemiology to customize and expand the conclusions from the present study.

Methods

Health economics framework

We evaluated the incremental effectiveness, cost-effectiveness and budget-impact of various options of use of PPV23 and/or PCV13 in elderly at different uptake levels, compared to the 2015 situation with low PPV23 vaccination uptake (Table 1). The improved uptake estimates were based on the average seasonal influenza uptake in Belgium. We adopted the health care payer's perspective (i.e. morbidity and mortality-associated productivity losses to society were excluded) and used a discount rate of 0.03 and 0.015 for costs and health outcomes, respectively. All costs are expressed in euro and updated to 2015 values using consumer price indices (Eurostat) where needed. The analytical time horizon ran over the remaining life span of all cohorts, until the last intervention cohort had died. In the absence of an explicit willingness to pay (WTP) threshold in Belgium, we present cost-effectiveness results over a wide WTP range from €0 to €350 000.

Model design

We used a static model consisting of single year age cohorts above 50 years of age that are simultaneously followed from the moment of vaccination until death. Cohort sizes over time were informed by age-specific all-cause mortality and life expectancy, which were assumed to be independent of explicit pneumococcal-specific mortality (this assumption was tested and had no significant influence on the outcomes). Figure 3 presents the health-states we included in de model. This analysis does not incorporate specific risk group vaccination strategies due to the lack of data in this group and the KCE's viewpoint based on expert opinion that strategies differing by risk groups would not be feasible to implement in the Belgian context. Vaccine uptake and efficacy determine the part of the population that is susceptible for IPD and non-IPP for each cohort at each age. Given a projected serotype evolution and related burden of IPD and non-IPP, we calculated the number of IPD and non-IPP cases, respectively. Serotype categories were "onlyPPV23" with the serotypes in PPV23 but not in PCV13, "onlyPCV13" with the serotypes in PCV13 but not in PPV23; "both" with the serotypes in both vaccines combined and "none" with all serotypes, except those covered by the vaccines. A detailed list of the serotypes included in each vaccine is provided in Appendix E. Vaccine protection is modeled to act differently against IPD and non-IPP, according to initial vaccine efficacy and waning over time.

We accounted for indirect (herd) effects of infant vaccination on adult pneumococcal disease with respect to serotype

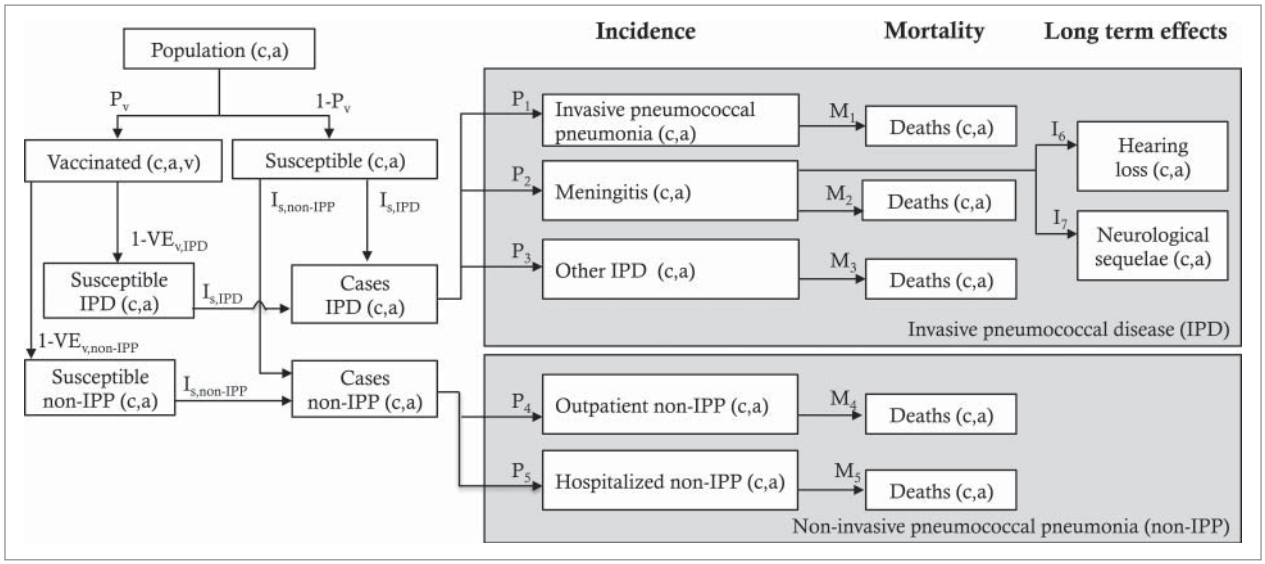

Figure 3. Model compartments and transitions regarding IPD and non-IPP incidence, mortality and long-term effects. Health states are presented for cohort *c* at age *a* with P_v the uptake of vaccine *v*, $VE_{v,IPD}$ the vaccine efficacy of vaccine v against IPD related vaccine serotypes, $VE_{v,non-IPP}$ analogous for non-IPP, $I_{s,IPD}$ the incidence rate of IPD related vaccine serotype s; $I_{s,non-IPP}$ analogous for non-IPP, P_i the prevalence of disease type i among all cases and M_i the mortality rate of disease type i. All transition rates are age-specific. All IPD cases are hospitalized. Background mortality is not presented.

distribution. The serotype replacement due to the childhood vaccination program (PCV10 or PCV13) was calculated as the relative increase of non-PCV13 serotypes divided by the relative decline of PCV13 serotypes. Based on SPIDNET data, we assumed a yearly increase of 4% of non-PCV13 types (that represented 75.3% of 2015 IPD incidence in Belgium) and an average decline of 16% of PCV13 types (24.7% of 2015 Belgian IPD incidence). This results in a yearly PCV13 serotype replacement of (4%*75.3%)/(16%*24.7%) = 76.3%.

On the estimated IPD and non-IPP cases, we applied the age-specific yearly proportion of the different hospitalized disease categories (invasive pneumococcal pneumonia, meningitis, other IPD and non-IPP) and outpatient non-IPP incidence among all cases and their consequences in terms of deaths and long-term effects (Figure 3). We assumed that all IPD cases are hospitalized. The distinction between different disease categories was made based on ICD9 coding of classified hospitalized patients in administrative databases. For outpatient cases, only pneumococcal pneumonia was included because we considered the direct vaccine impact on acute otitis media negligible in adults. We considered hearing loss and neurological sequelae as long-term consequences of meningitis. Parameter values and distributions can be found in Appendix E.

The static cohort model was coded in R[33] using a modular design, making it easily adaptable for scenarios analyses. Calculations were performed on Intel® Xeon® E5-2680 v2 2.80GHz CPU's (release Q3'13) and required around 2.5 minutes per scenario tested with 1000 stochastic realizations.

Outcome and uncertainty

Key outputs include: averted hospitalized invasive pneumococcal pneumonia, meningitis, other IPD, hearing loss and neurological sequelae from meningitis, outpatient and hospitalized non-IPP cases and fatalities. Direct medical costs and QALYs associated with these outcome categories were used to compare the different options. Where appropriate, uncertainty around input parameter estimates were specified in terms of probability distributions. To assess uncertainty, we conducted Monte-Carlo sampling with 1000 draws taken from each input distribution assuming independence of the uncertain inputs. Results are aggregated by appropriate age groups for each outcome, and subsequently summarized by taking means and medians.

Results are presented by the incremental cost-effectiveness ratio (ICER) and cost-effectiveness acceptability frontiers (CEAFs). The latter provides for a range of WTP values the vaccination strategy with maximum expected net benefit and the probability of that vaccination strategy to be the most optimal among all vaccination scenarios and age groups considered. The net benefit is calculated as the monetary difference between the incremental cost of implementing a vaccination scenario and the QALYs gained valued at the corresponding WTP.

The baseline vaccine efficacy of PPV23 is assumed to be 0.56 during the first 2 years after vaccination, followed by exponential waning with a half-life of 1.5 years.[34] PCV13 is assumed to provide full protection for 5 years[14] followed by a logistic waning with a half-life of 10 years. As none of the vaccines had conclusive evidence to show general efficacy in people aged 85 years and older, we assumed that vaccinating people in this age group would have little or no effect on health outcomes and an infinitely high cost-effectiveness ratio. We have included their vaccination costs in the budget-impact analysis, as they could still be considered as part of the target group for reasons of equity.

We performed our analyses for three different vaccine efficacy scenarios: (1) PPV23 and PCV13 each have fully parameterized baseline efficacy against vaccine-type non-IPP, (2) only PPV23 has no efficacy against vaccine-type non-IPP, (3) both PPV23 and PCV13 have no efficacy against vaccine-type non-IPP. While we show results for all three explorations, we believe the likelihood of the first scenario is much higher than that of the second, which in turn is much more likely than the third.[25,26] Recent estimates of PPV23 effectiveness against

vaccine type non-IPP confirmed our estimates based on Andrews et al.[34] We therefore strongly emphasize our results under the first scenario.

In addition to probabilistic sensitivity analysis and scenario analysis on vaccine efficacy, we also explored the impact of uncertainty in other assumptions (e.g., serotype relapse and replacement scenarios, waning immunity, vaccine price reductions, etc.) through uni- and multi-variate sensitivity analysis.

Input data

We informed our model as much as possible by Belgian data. When Belgian data were not available, we used data sources of acceptable quality that would be the most suitable for the Belgian context. We also performed uncertainty analysis on data sources, where multiple sources existed. A complete overview of vaccine, epidemiological and demographic parameters is provided in Appendix E together with details on costing, QALY estimations and discounting. Disease incidence and mortality rates are also provided next to the parameter distributions for the probabilistic sensitivity analysis and their plausible range for additional scenario analyses.

We derived the serogroup distribution of IPD cases in Belgium in 2015 from the National Reference Centre (NRC, based on 100% coverage). Since the NRC does not routinely test for serotypes, we had to convert serogroup to serotype based on a recent German study[35] in adults. This large-scale study contained sufficient details on specific serotypes and was suited for our purpose given the similar PCV history between Germany and Belgium. As such, we estimated that PCV13 serotypes account for about 25.3% of IPD cases, and PPV23 serotypes for 66.2%. About 42% of the serotypes found in IPD in this age group are exclusively covered by PPV23, whereas a third is not covered by either of the vaccines.

To obtain the distribution of non-IPP serotypes, we reviewed studies published after the introduction of PCV10 or PCV13 in the infant vaccination schedule in settings similar to Belgium, that describe the serotype distribution of non-invasive pneumococcal pneumonia in adults including elderly $\geq$ 65 years of age. The Danish study by Benfield et al.[36] was the most recent and most comparable to Belgium in terms of past vaccine history and uptake i.e. PCV7 followed by PCV13 at high uptake, and IPD serotype distribution in adults. The serotype distributions of non-IPP were updated to the 2015 situation based on annual serotype changes in IPD from SPIDNET network to account for the effect of more infant PCV13 years. We estimated that PCV13 serotypes account for about 24.7% of non-IPP cases, PPV23 serotypes for 51.1% and 48.7% is not covered by either of both vaccines.

Outpatient pneumonia cases were identified from a large primary care network (Intego) using its specific code for all-cause pneumonia. We estimated the outpatient pneumonia incidence per age group by dividing numbers of cases in 2013 per age group by the total practice population of general practitioners included in the Intego-network.

The case fatality ratio of IPD in Belgium was calculated based on hospital deaths in IPD cases matched between the NRC and the national (census) Hospital database (MZG/RHM), per clinical syndrome. The case fatality ratio of IPD was 12.2% overall in all $\geq$ 18 years, increased with age up to 23% in $\geq$ 85 years, and was generally higher in meningitis (16% overall, up to 50% in $\geq$ 85 years) and septicemia (16% overall) compared to invasive pneumonia (9% overall). It should be noted that hospital deaths due to pneumonia might underestimate the case fatality ratio as they do not cover pneumonia patients in long-term facilities (such as nursing homes) that are at higher risk of pneumonia with a fatal outcome, and rarely hospitalized.

PCV13 vaccine efficacy and effectiveness was derived from the CAPITA study,[14] which measured the efficacy against CAP and IPD in persons $\geq$ 65 years of age. This study involved all confirmed IPD/non-IPP cases with onset at least 14 days after vaccination. PCV13 efficacy against a first occurrence of vaccine type non-IPP and against IPD was 41.1% (95%CI 12.7 to 60.7). The post-hoc analysis[37] of CAPITA data showed a significant decline in vaccine efficacy against vaccine type IPD/non-IPP with increasing age. This study also supports our assumption of no vaccine protection after 85 years of age. We applied a declining vaccine efficacy for both IPD and non-IPP with age using a hazard ratio of 1.058 (1.008-1.109) per year of age and analyzed the effect of an age in-dependent scenario in the sensitivity analysis. Bonten et al.[14] conclude that efficacy persisted throughout the duration of the trial, i.e. around 4 years, without evidence of waning. We assumed no waning over 5 years, followed by logistic reduction to 50% after 10 years.

We based our estimates of PPV23 vaccine efficacy against IPD on Andrews et al.[34] which shows a gradient of effectiveness by age and risk group, with a 56% point estimate among 65–74 years of age with no risk. The vaccine efficacy ratio of non-IPP on IPD ranged in the literature between 0.55-0.77.[38] We applied the lowest and most trustworthy of these ratios (55% from Ochoa-Gondar et al.[39]), to derive the vaccine efficacy against non-IPP of 30.8% (22%-37%). We assumed a constant PPV23 vaccine efficacy by age and no protection in those $\geq$ 85 years of age.[34] We implemented PPV23 waning for IPD and non-IPP by assuming 2 years of fixed vaccine protection, followed by exponential waning with a half time value of 1.5 years (i.e. reducing vaccine protection to 15% over the course of 3 years). The duration of PPV23 protection is varied between 2 and 5 years in sensitivity analysis. Figure 4 presents the vaccine efficacy and effective efficacy of PCV13 and PPV23 over time. The efficacy of PCV13 is higher and wanes slower, but if we take also serotype coverage into account, the difference in protection over time is much smaller and/or PPV23 performs better the first years.

QALY loss of disease episodes was derived from the French PNEUMOCOST[40] database containing data on 523 hospitalized pneumococcal pneumonia patients (mostly >50 year old patients), distinguishing between bacteraemic and non-bacteraemic pneumonia cases. EQ-5D descriptive scores (using French tariffs)[41] and utilities were obtained at different time intervals: 1 month, 3 months, 6 months and 12 months after diagnosis. To estimate the total QALY loss of a disease episode for a patient, we took the difference between the estimated quality of life measurement at each month and the age-specific French population norm. Data on low risk patients were selected in view of the strategies evaluated in this analysis, which target in the first place healthy adults using vaccines with limited evidence of effectiveness in high and medium risk groups. In the univariate sensitivity analysis, we

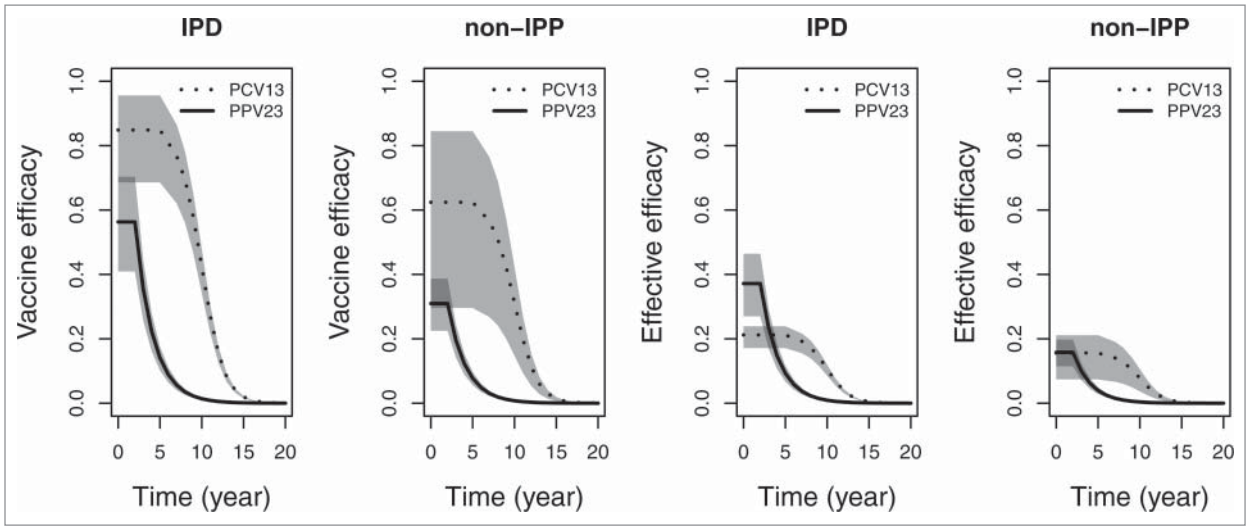

Figure 4. Vaccine efficacy and effective efficacy (= vaccine efficacy * serotype coverage) against IPD and non-IPP of PCV13 and PPV23 over time. The modeled median values are presented for people aged 50 years together with the 95% confidence interval (shaded area). For PPV23, we assumed the same efficacy profile for people aged 50–84 years. For PCV13, we assumed a decreasing efficacy by age (see main text).

included a scenario using the average estimates, based on the proportions of these risk groups in France. QALY loss estimates for IPD and non-IPP where 0.0491 and 0.0203, respectively, for adults aged <65 years and 0.0679 and 0.1741 for adults aged ≥ 65 years. Uncertainty around QALY estimates were obtained through bootstraps of the PNEUMOCOST database and the population norms and are described in Appendix E. Quality of life utility weights for ambulatory pneumonia, hearing loss and neurological sequelae, were based on the study by Galante et al,[42] which report the QALYs for 6 different health states related to pneumococcal infections in adults using the generic EQ-5D instrument. The weight for ambulatory pneumonia was 0.508 (95%CI 0.442-0.575) and was applied during 8.5 days. The utility weights for hearing loss and neurological sequelae following meningitis were 0.635 (95%CI 0.578-0.691) and 0.319 (95%CI 0.252-0.386), respectively, and were assumed to last lifelong. We incorporated uncertainty for each parameter based on a normal distribution using the mean and confidence intervals reported in Galante et al.[42] Quality of life losses for vaccine-related adverse reactions and life losses for caregivers (e.g. next of kin) were not included.

Disclosure of potential conflicts of interest

A university chair in CHERMID at the University of Antwerp was supported in 2009–2016 by a gift from Pfizer. There is no connection between either Pfizer or the research of the chair holder (Niel Hens) and this article. HT currently conducts a research study on carriership of pneumococcus in Belgium (2016-2019), a study co-financed by an unrestricted grant from Pfizer. Her participation at an international congress on HPV in 2015 was co-financed by Sanofi Pasteur MSD.

Acknowledgments

We thank all contributors (experts and validators) of the Health Technology Assessment (HTA) for the Belgian Health Care Knowledge Centre (KCE), KCE Reports 274 D/2016/10.273/79. We also thank Annick Mignon (Pfizer), Marc Bonten and Cornelis Van Werkhoven (UMC Utrecht) for providing original data that contributed to define model parameters. We are also grateful to Raymond Oppong and Joanna Coast (University of Birmingham) of the GRACE project "Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe" (DG Research, 2005) for giving access to Belgian cost data on pneumococcal pneumonia. We are indebted to Gérard de Pouvourville (ESSEC) for giving access to data on Quality of Life in pneumococcal patients in France. We also thank the Flemish Supercomputer Center (VSC), funded by the Research Foundation – Flanders (FWO) and the Flemish Government (department EWI) to provide computational resources and services. The authors acknowledge the Antwerp Study Centre for Infectious Diseases (ASCID) at the University of Antwerp.

Funding

This study was co-funded by the Belgian Health Care Knowledge Centre (KCE), a Belgian government agency. LW is supported by the FWO, project G043815N. JB is supported by a postdoctoral grant from the FWO. With the exception of KCE, which has standard processes in place to facilitate data collection and organize external peer review, the funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. Said MA, Johnson HL, Nonyane BA, Deloria-Knoll M, Katherine L, Team AAPBS, Andreo F, Beovic B, Blanco S, Boersma WG, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. PLoS ONE. 2013;8(4):e60273. doi:10.1371/journal.pone.0060273. PMID:23565216.
2. Torres A, Blasi F, Peetermans W, Viegi G, Welte T. The aetiology and antibiotic management of community-acquired pneumonia in adults in Europe: a literature review. Eur J Clin Microbiol Infect Dis. 2014;33(7):1065–1079. doi:10.1007/s10096-014-2067-1. PMID:24532008.
3. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax. 2012;67(1):71–79. doi:10.1136/thx.2009.129502. PMID:20729232.
4. Rozenbaum M, Pechlivanoglou P, Van Der Werf T, Lo-Ten-Foe J, Postma M, Hak E. The role of Streptococcus pneumoniae in community-acquired pneumonia among adults in Europe: a meta-analysis. Eur J Clin Microbiol Infect Dis. 2013;32(3):305–316. doi:10.1007/s10096-012-1778-4. PMID:23242464.
5. Garcia-Vidal C, Fernández-Sabé N, Carratalà J, Díaz V, Verdaguer R, Dorca J, Manresa F, Gudiol F. Early mortality in patients with community-acquired pneumonia: causes and risk factors. Eur Resp J. 2008;32(3):733–739. doi:10.1183/09031936.00128107.

6. Capelastegui A, Zalacain R, Bilbao A, Egurrola M, Iturriaga LAR, Quintana JM, Gomez A, Esteban C, España PP. Pneumococcal pneumonia: differences according to blood culture results. BMC Pulm Med. 2014;14 (1):128. doi:10.1186/1471-2466-14-128. PMID:25096919.
7. Bachcz P, Peleman R, Vanatoru J, Van Laethem Y, Struelens M, Verhaegen J. Belgian consensus on pneumococcal vaccine. Acta Clin Belg. 1996;51(5):350–356. doi:10.1080/22953337.1996.11718529. PMID: 8950842.
8. Verhaegen J, Flamaing J, De Backer W, Delaere B, Van Herck K, Surmont F, Van Laethem Y, Van Damme P, Peetermans W. Epidemiology and outcome of invasive pneumococcal disease among adults in Belgium, 2009–2011. Euro Surveill. 2014;19(31):14–22. doi:10.2807/1560-7917.ES2014.19.31.20869. PMID:25138972.
9. Kraicer-Melamed H, O'Donnell S, Quach C. The effectiveness of pneumococcal polysaccharide vaccine 23 (PPV23) in the general population of 50 years of age and older: A systematic review and meta-analysis. Vaccine. 2016;34(13):1540–1550. doi:10.1016/j.vaccine.2016.02.024. PMID:26899372.
10. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2008;1(1). doi:10.1002/14651858.CD000422.pub2. PMID: 18253977.
11. Schiffner-Rohe J, Witt A, Hemmerling J, von Eiff C, Leverkus FW. Efficacy of PPV23 in preventing pneumococcal pneumonia in adults at increased Risk–A systematic review and meta-analysis. PLoS ONE. 2016;11(1):e0146338. doi:10.1371/journal.pone.0146338. PMID: 26761816.
12. Drieskens S, Charafeddine R, Demarest S, Gisle L, Tafforeau J, Van der Heyden J. Health Interview Survey, Belgium, 1997 - 2001 - 2004 - 2008 - 2013: Health Interview Survey Interactive Analysis. Brussels: WIV-ISP. https://hisia.wiv-isp.be/.
13. Van De Vyver N, Govaerts F, Pilaet A. Preventie van ernstige pneumokokkeninfecties bij volwassenen. Aanbeveling voor goede medische praktijkvoering Huisarts Nu. 2005;34:588–96.
14. Bonten MJ, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, van Werkhoven CH, van Deursen AM, Sanders EA, Verheij TJ, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015;372(12):1114–1125. doi:10.1056/NEJMoa1408544. PMID:25785969.
15. Musher DM, Rodriguez-Barradas MB. Why the recent ACIP recommendations regarding conjugate pneumococcal vaccine in adults may be irrelevant. Hum Vaccin Immunother. 2016;12(2):331–335. doi:10.1080/21645515.2015.1098794. PMID:26606172.
16. Jackson LA, Gurtman A, Rice K, Pauksens K, Greenberg RN, Jones TR, Scott DA, Emini EA, Gruber WC, Schmoele-Thoma B. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in adults 70 years of age and older previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Vaccine. 2013;31(35):3585–3593. doi:10.1016/j.vaccine.2013.05.010. PMID:23688527.
17. Juergens C, de Villiers PJ, Moodley K, Jayawardene D, Jansen KU, Scott DA, Emini EA, Gruber WC, Schmoele-Thoma B. Safety and immunogenicity of 13-valent pneumococcal conjugate vaccine formulations with and without aluminum phosphate and comparison of the formulation of choice with 23-valent pneumococcal polysaccharide vaccine in elderly adults: A randomized open-label trial. Hum Vaccin Immunother. 2014;10(5):1343–1353. doi:10.4161/hv.27998. PMID:24576885.
18. Conseil Supérieur de la Santé. Guide de vaccination: Vaccination antipneumococcique - adultes, Bruxelles, CSS 9210. 2014
19. Vestrheim DF, Høiby EA, Bergsaker MR, Rønning K, Aaberge IS, Caugant DA. Indirect effect of conjugate pneumococcal vaccination in a 2 + 1 dose schedule. Vaccine. 2010;28(10):2214–2221. doi:10.1016/j.vaccine.2009.12.054. PMID:20056192.
20. Miller E, Andrews NJ, Waight PA, Slack MP, George RC. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study. Lancet Infect Dis. 2011;11(10):760–768. doi:10.1016/S1473-3099(11)70090-1. PMID:21621466.
21. Beutels P, Van Damme P, Oosterhuis-Kafeja F. Effects and costs of pneumococcal conjugate vaccination of Belgian children. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2006. KCE reports 33CD/2006/10273/54.
22. Beutels P, Blommaert A, Hanquet G, Bilcke J, Thiry N, Sabbe M, et al. Cost-effectiveness of 10-and 13-valent pneumococcal conjugate vaccines in childhood. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2011. KCE reports 155CD/2011/10273/21.
23. Blommaert A, Hanquet G, Willem L, Theeten H, Thiry N, Bilcke J, et al. Use of pneumococcal vaccines in the elderly: an economic evaluation. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2016;274. KCE Reports 274 D/2016/10273/79.
24. Jokinen J, Rinta-Kokko H, Siira L, Palmu AA, Virtanen MJ, Nohynek H, Virolainen-Julkunen A, Toropainen M, Nuorti JP. Impact of ten-valent pneumococcal conjugate vaccination on invasive pneumococcal disease in Finnish children–a population-based study. PLoS ONE. 2015;10(3):e0120290. doi:10.1371/journal.pone.0120290. PMID:25781031.
25. Domínguez À, Soldevila N, Toledo D, Torner N, Force L, Pérez MJ, Martín V, Rodríguez-Rojas L, Astray J, Egurrola M, et al. Effectiveness of 23-valent pneumococcal polysaccharide vaccination in preventing community-acquired pneumonia hospitalization and severe outcomes in the elderly in Spain. PLoS ONE. 2017;12(2):e0171943. doi:10.1371/journal.pone.0171943. PMID:28187206.
26. Suzuki M, Dhoubhadel BG, Ishifuji T, Yasunami M, Yaegashi M, Asoh N, Ishida M, Hamaguchi S, Aoshima M, Ariyoshi K, et al. Serotype-specific effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumococcal pneumonia in adults aged 65 years or older: a multicentre, prospective, test-negative design study. Lancet Infect Dis. 2017;17(3):313–321. doi:10.1016/S1473-3099(17)30049-X. PMID:28126327.
27. Mangen MJJ, Rozenbaum MH, Huijts SM, van Werkhoven CH, Postma DF, Atwood M, van Deursen AM, van der Ende A, Grobbee DE, Sanders EA, et al. Cost-effectiveness of adult pneumococcal conjugate vaccination in the Netherlands. Eur Respir J. 2015;46(5):1407–1416. doi:10.1183/13993003.00325-2015. PMID:26160871.
28. van Hoek AJ, Miller E. Cost-Effectiveness of Vaccinating Immunocompetent ≥ 65 Year Olds with the 13-Valent Pneumococcal Conjugate Vaccine in England. PLoS ONE. 2016;11(2):e0149540. doi:10.1371/journal.pone.0149540. PMID:26914907.
29. Falkenhorst G, Remschmidt C, Harder T, Wichmann O, Glodny S, Hummers-Pradier E, Ledig T, Bogdan C. Background paper to the updated pneumococcal vaccination recommendation for older adults in Germany. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2016;59(12):1623–1657. doi:10.1007/s00103-016-2466-9. PMID:27885449.
30. Stoecker C, Kim L, Gierke R, Pilishvili T. Incremental cost-effectiveness of 13-valent pneumococcal conjugate vaccine for adults age 50 years and older in the United States. J Gen Intern Med. 2016;31 (8):901–908. doi:10.1007/s11606-016-3651-0. PMID:26976292.
31. Blommaert A, Bilcke J, Willem L, Verhaegen J, Goossens H, Beutels P. The cost-effectiveness of pneumococcal vaccination in healthy adults over 50: An exploration of influential factors for Belgium. Vaccine. 2016;34(18):2106–2112. doi:10.1016/j.vaccine.2016.03.003. PMID: 26988257.
32. Cleemput I, Neyt M, Thiry N, De Laet C, Leys M. Threshold values for cost-effectiveness in health care. Health technology assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE). 2008. KCE reports 100C D/2008/10.273/96.
33. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing. 2016. https://www.R-project.org/
34. Andrews NJ, Waight PA, George RC, Slack MP, Miller E. Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. Vaccine. 2012;30(48):6802–6808. doi:10.1016/j.vaccine.2012.09.019. PMID:23000122.
35. van der Linden M, Falkenhorst G, Perniciaro S, Imöhl M. Effects of infant pneumococcal conjugate vaccination on serotype distribution in invasive pneumococcal disease among children and adults in

Germany. PLoS ONE. 2015;10(7):e0131494. doi:10.1371/journal.pone.0131494. PMID:26132078.
36. Benfield T, Skovgaard M, Schønheyder HC, Knudsen JD, Bangsborg J, Østergaard C, Slotved HC, Konradsen HB, Thomsen RW, Lambertsen L. Serotype distribution in non-bacteremic pneumococcal pneumonia: association with disease severity and implications for pneumococcal conjugate vaccines. PLoS ONE. 2013;8(8):e72743. doi:10.1371/journal.pone.0072743. PMID:24009703.
37. van Werkhoven CH, Huijts SM, Bolkenbaas M, Grobbee DE, Bonten MJ. The impact of age on the efficacy of 13-valent pneumococcal conjugate vaccine in elderly. Clin Infect Dis. 2015;61(12):1835–1938. doi:10.1093/cid/civ686. PMID:26265498.
38. Vila-Corcoles A, Salsench E, Rodriguez-Blanco T, Ochoa-Gondar O, de Diego C, Valdivieso A, Hospital I, Gomez-Bertomeu F, Raga X. Clinical effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumonia in middle-aged and older adults: a matched case–control study. Vaccine. 2009;27(10):1504–1510. doi:10.1016/j.vaccine.2009.01.013. PMID:19171174.
39. Ochoa-Gondar O, Vila-Corcoles A, Rodriguez-Blanco T, Gomez-Bertomeu F, Figuerola-Massana E, Raga-Luria X, Hospital-Guardiola I. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against community-acquired pneumonia in the general population aged ≥ 60 years: 3 years of follow-up in the CAPAMIS study. Clin Infect Dis. 2014;58(7):909–917. doi:10.1093/cid/ciu002. PMID:24532544.
40. Saba G, Andrade LF, Gaillat J, Bonnin P, Chidiac C, Illes HG, Laurichesse H, Messika J, Ricard JD, Detournay B, et al. Costs associated with community acquired pneumonia in France. Eur J Health Econ. 2017;p. 1–12. doi:10.1007/s10198-017-0900-z. PMID: 28547724
41. Chevalier J, de Pouvourville G. Valuing EQ-5D using time trade-off in France. Eur J Health Econ. 2013;14(1):57–66. doi:10.1007/s10198-011-0351-x. PMID:21935715.
42. Galante J, Augustovski F, Colantonio L, Bardach A, Caporale J, Marti SG, Kind P. Estimation and Comparison of EQ-5D Health States' Utility Weights for Pneumoccocal and Human Papillomavirus Diseases in Argentina, Chile, and the United Kingdom. Value Health. 2011;14(5):S60–S64. doi:10.1016/j.jval.2011.05.007. PMID:21839901.

Supporting information

[Appendix A]

Estimated burden of disease and costs in Belgium by S. pneumoniae in 2016

[Appendix B]

Avoided burden and cost-effectiveness

[Appendix C]

Sensitivity analysis

[Appendix D]

Budget-impact analysis

[Appendix E]

Parameter values and distributions