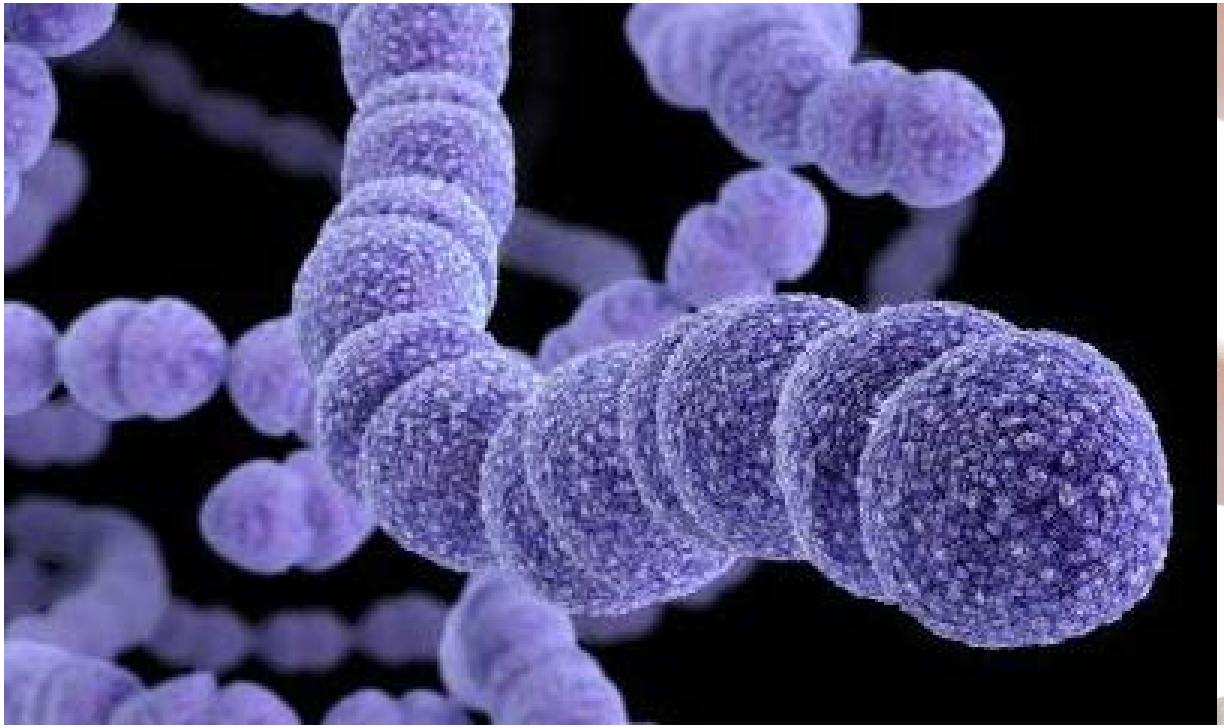
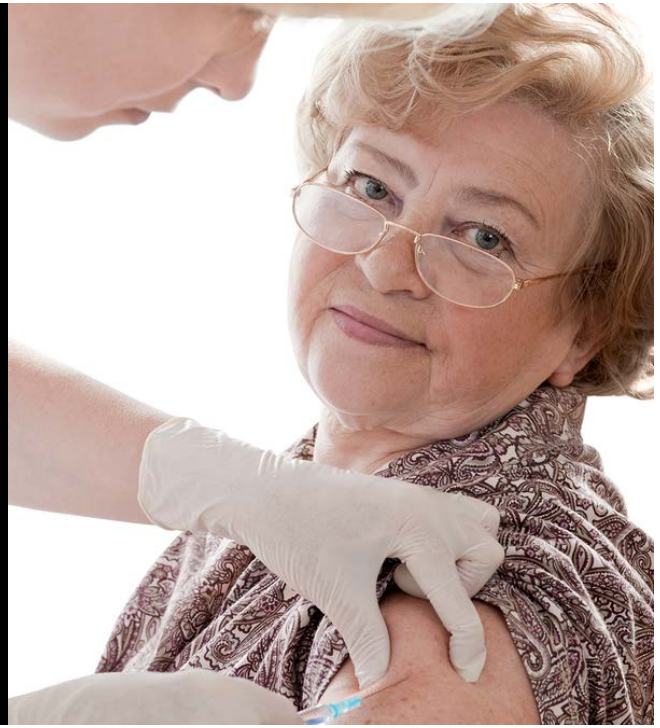
KCE REPORT 274Csh

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SHORT REPORT

USE OF PNEUMOCOCCAL VACCINES IN THE ELDERLY: AN ECONOMIC EVALUATION





KCE REPORT 274Csh
HEALTH TECHNOLOGY ASSESSMENT

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SHORT REPORT

USE OF PNEUMOCOCCAL VACCINES IN THE ELDERLY: AN ECONOMIC EVALUATION

ADRIAAN BLOMMAERT, GERMAINE HANQUET, LANDER WILLEM, HEIDI THEETEN, NANCY THIRY, JOKE BILCKE, JAN VERHAEGEN, PHILIPPE BEUTELS

FOREWORD

Vaccines are much like herbicides: if we fight too selectively against a specific type, other types will immediately fill in the empty niche. Similarly, when we vaccinate infants against specific pneumococcal serotypes, we run the risk to see other serotypes emerging in the population, which may partially cancel the impact of vaccination. But this paradoxical effect is not always easy to predict, and there are further a lot of other uncertainties that make modeling the impact of vaccination a particularly complex and laborious task.

Nevertheless: despite the uncertainties and inaccuracies, it is always enlightening to have an estimate (as accurate as possible) of the advantages and disadvantages of a new vaccine, before taking the decision to offer it in the population and to invest public resources.

The KCE was asked to assess the cost-effectiveness of vaccinating the elderly with the conjugate pneumococcal 13-valent vaccine (PCV13), a relatively new vaccine. Indeed, past experience with such 'modern' vaccines among children seemed to indicate that this is a promising area, and there was thus high expectations from the field. The 23-valent polysaccharide vaccine, marketed for a longer time, could logically serve as a comparator.

But does ‘new’ means ‘best’? In any case, PCV13 is much more expensive than its competitor. In collaboration with our trusted partners from the Universiteit Antwerpen, we thus developped the required cost-effectiveness analysis, and explored numerous hypotheses.

Result: some recommendations for policy makers. But with an extra set of findings that should be of interest to clinicians, if only because they are unexpected.

Hoping to have tickled your curiosity now, we wish you a pleasant reading!

Christian LÉONARD
Deputy general director

Raf MERTENS
General director

SHORT REPORT

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1 RESEARCH QUESTIONS

Streptococcus pneumoniae is responsible for a high disease burden and is a major cause of community acquired pneumonia (CAP), meningitis and septicaemia in the elderly. The polysaccharide capsule of the bacteria is an essential factor of virulence. More than 90 capsular serotypes of S. pneumoniae are known but a limited number of them accounts for most pneumococcal disease. The current pneumococcal vaccines are directed against a limited number of serotypes that are the most prevalent. There are two types of pneumococcal vaccines indicated for the elderly (see also Table 5):

- Pneumococcal conjugate vaccines (PCV) are marketed in Europe (including Belgium) since 2001, but only the 13-valent PCV (PCV13) has been approved in adults, in 2011 against invasive pneumococcal disease and in 2015 against all pneumococcal pneumonia.
- Polysaccharide pneumococcal vaccines (PPV) are available since the 1980s. The current polysaccharide vaccine, PPV23, targeting 23 serotypes, is licensed and recommended in Belgium for all elderly ≥65 years of age since the nineties. However, PPV23 use has always been low in this group.

PPV23 and PCV13 differ in the number of serotypes covered, the corresponding proportion of pneumococcal disease that they prevent, the type of immunity that is conferred and the price.

In addition, the distribution of circulating PCV13 and PPV23 serotypes changed markedly in recent years as a result of the universal PCV vaccination of infants, through a reduction of *S. pneumoniae* transmission (indirect effect or herd immunity[a]):[1, 2] overall pneumococcal disease rates in elderly have decreased in most settings over time, as a net result of a decrease in disease caused by PCV13 serotypes and a gradual increase in disease caused by non-PCV13 serotypes (including the 11 additional serotypes targeted by PPV23). None of these vaccines are currently reimbursed, but a request for reimbursement has been submitted for PCV13 to the INAMI/RIZIV.

The decision on which vaccine (and schedule) should be preferred in the elderly thus partly depends on the added value of its direct protection of the elderly compared to the indirect effect of the infant PCV vaccination.

This research evolves around an economic evaluation, adopting a health care payer's perspective according to KCE guidelines. The costs and benefits of different vaccination strategies are compared with each other, including the current situation of vaccinating a low proportion of the elderly with PPV23 only. These vaccination strategies involve the administration of PPV23 alone, PCV13 alone, or PCV13 followed by PPV23, with different options for re-vaccination and using different uptake levels (ranging 20-60%) in adults >50 years.

Three main research questions are addressed in this evaluation:

1. What is the clinical impact of the vaccination strategies in terms of number of hospitalizations, outpatient cases,[b] fatalities and long term sequelae due to pneumococcal disease?
2. What is the cost-effectiveness of the vaccination strategies compared incrementally to each other?
3. What is the budget impact of the vaccination strategies?

[a] Herd immunity or community immunity arises when unvaccinated people experience a lower risk of infection thanks to the vaccination of a large or epidemiologically influential group in the population. Children are such an influential group for pneumococcal infections, whereas adults are not.

[b] Outpatient is here defined as a patient who is not hospitalized overnight but who visits a hospital, clinic, or associated facility for diagnosis or treatment.

The three research questions are analysed separately per age group. They are also addressed for an age category younger than the CSS/HGR target age, i.e. all adults from 50 to 64 years of age. This report does not incorporate specific risk group vaccination strategies due to the feasibility of vaccination in the Belgian context and data availability. First, elderly ≥65 years of age with or without comorbidity are vaccinated by the same vaccinators around the same time (for influenza and/or pneumococcal disease); applying separate strategies for high risk groups in this age was considered as an additional burden for the clinicians and would differ from the current CSS/HGR recommendations. Second, there are no data on the numbers of persons with high risk for pneumococcal disease in Belgium. Third, there are no data on PCV13 efficacy in persons with unstable co-morbidities or who are immunocompromised.

2 BURDEN OF PNEUMOCOCCAL DISEASE IN THE ELDERLY

2.1 Incidence of pneumococcal disease

Pneumococcal disease can be divided into invasive pneumococcal disease (IPD) and non-invasive disease (non-IPD). IPD is defined as the isolation or detection of *Streptococcus pneumoniae* from a normally sterile site, most commonly blood, pleural fluid or cerebrospinal fluid.[3] In adults, IPD mostly presents as invasive pneumococcal pneumonia, meningitis or septicaemia, and can lead to septic shock. *S. pneumoniae* is also the first cause of CAP (invasive and non-invasive) in adults.[4-7]

The 2015 incidence of IPD by age has been estimated in Belgium based on the number of strains and samples sent to the National Reference Centre (NRC), corrected for under-reporting (Table 1).[8] IPD incidence rates per 100 000 increase with age, from 14.9 in adults 50-64 years of age to 80.2 in those ≥85 years of age. The distribution of IPD per clinical syndrome and age group has been estimated based on a prospective Belgian study conducted in 2009-11. Invasive pneumonia (including empyema), meningitis and other IPD represented 83-87%, 4-9% and 8-10% of all IPD, respectively.[9] In the Belgian setting, the large majority of IPD are hospitalised and we assumed in this study that all IPD are hospitalised.

In non-invasive CAP, *S. pneumoniae* is not detected in blood or pleural fluid but is identified in sputum, broncho-alveolar lavage or urine. Non-invasive CAP is less severe but much more frequent than invasive CAP; cases may be hospitalised or only seen in an outpatient visit, depending on severity, co-morbidities, age and local policies for admissions. As only scarce Belgian data are available on non-invasive CAP, we derived the proportion of hospitalised pneumococcal CAP that are non-invasive in studies from similar settings. We calculated a pooled estimate based of four studies from similar settings selected for their quality, at 82.7% (95%CI 80-86%).[10-13] The incidence rate for non-invasive hospitalised pneumococcal CAP was then derived from the incidence of invasive pneumococcal pneumonia by applying the corresponding factor. Table 1 indicates that an incidence of pneumococcal CAP as high as 403 per 100 000 is estimated in the oldest age group (≥ 85 years).

Table 1 – Incidence of pneumococcal disease per 100 000 inhabitants estimated in Belgium in 2015, by outcome[c]

Age group	Inpatient IPD*	Inpatient non-invasive pneumococcal CAP**	Total inpatient pneumococcal CAP	Outpatient pneumococcal CAP£
50-64 years	14.9	59.4	71.8	62.9
65-74 years	25.5	105.9	128.0	70.6
75-84 years	36.8	152.7	184.7	105.9
≥ 85 years	80.2	332.8	402.5	158.0

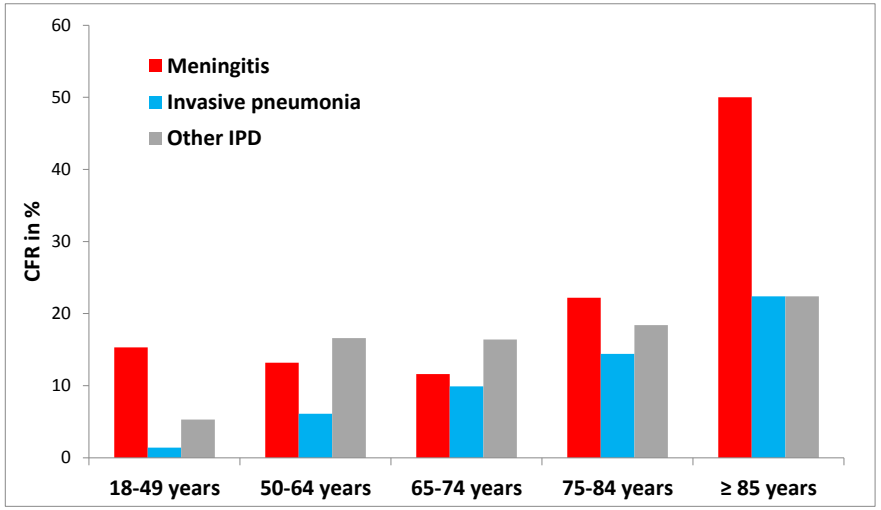
*CAP: Community acquired pneumonia; IPD: Invasive pneumococcal disease, including invasive pneumonia; NRC: National Reference Centre; *: NRC data, corrected for under-reporting; **: by assuming that 82.7% of all hospitalised pneumococcal CAP are non-invasive; £: based on Intego 2013 database, code R81.*

No Belgian data are available on outpatient pneumococcal CAP, because the laboratory determination of the causal pathogen is rarely performed in ambulatory cases. The incidence of outpatient all-cause CAP was estimated based on pneumonia cases identified in the Intego 2013 database (R81), per age group. As the proportion of outpatient all-cause CAP that is due to pneumococcal disease is not known in Belgium, we derived it from a review of studies from similar settings and calculated a pooled estimate at 10.5% (95%CI 7.7-13.2), based on two studies from Denmark and Spain.[14, 15] Table 1 indicates that the estimated outpatient pneumococcal CAP incidence also increases with age, from 63 in 50-64 years to 158 per 100 000 in the ≥85 years.

2.2 Mortality of pneumococcal disease

The mortality due to *S. pneumoniae* is substantial in older adults. The case fatality ratio (CFR) of IPD in Belgium was calculated based on hospital deaths in cases matched between the NRC (containing IPD only) and the Hospital database (RHM/MZG) in years 2007-12 (Figure 1). It increased with age, and was generally higher in meningitis (15% overall, up to 50% in ≥85 years) and other IPD (18%) than in invasive pneumonia (12%).

Figure 1 – Case fatality ratio (CFR) of IPD by clinical syndrome in cases matched in RHM/MZG (ICD9 primary diagnosis) and NRC, 2007-12



RHM/MZG: Résumé Hospitalier Minimum/Minimale Ziekenhuis Gegevens; NRC: National reference centre.

In the absence of reliable CFR data on non-invasive CAP in Belgium (hospitalised or outpatient), we conducted a literature search. All studies on hospitalised pneumococcal CAP suggest a higher mortality for invasive (or bacteraemic) cases compared to non-invasive (non-bacteraemic) ones. The study most suited to inform Belgian CFR was a large Spanish prospective study focusing on pneumococcal CAP, which estimated an adjusted mortality hazard ratio of 2.8 (95%CI 1.6-5.1) for bacteraemic versus non-

[c] These values may differ from the current burden estimated by the model as they are based on mean values while the model sampled values from the confidence interval.

bacteraemic hospitalised pneumococcal CAP.[16] CFR of non-invasive hospitalised cases were estimated by applying the inverse of this factor to the CFR of invasive pneumococcal CAP (Table 2). No mortality data in outpatient pneumococcal CAP was found from European studies and studies on outpatient all-cause CAP were used as proxy. A Spanish cohort study was selected as best reference since it was prospective and primary care based. CFR of outpatient CAP was 1.7% in this study (Table 2).[17]

Table 2 – Case fatality ratio of pneumococcal disease (%) estimated in Belgium in 2015, by outcome

Age group	Inpatient IPD*	Inpatient non-invasive pneumococcal CAP**	Outpatient pneumococcal CAP£
18-49 years	3.5%	0.5%	1.7% (no data by age)
50-64 years	10.7%	2.2%	
65-74 years	12.6%	3.5%	
75-84 years	16.4%	5.1%	
≥ 85 years	22.8%	8.0%	

*CAP: Community acquired pneumonia; IPD: Invasive pneumococcal disease, including invasive pneumonia; *: hospital deaths in cases matched in NRC and RHM/MZG; RHM/MZG : Résumé Hospitalier Minimum/Minimale Ziekenhuis Gegevens; NRC : National reference centre; **: by applying a factor of 1/(2.8) - based on the hazard ratio - to the case fatality ratio of invasive pneumococcal CAP to derive the case fatality ratio of non-invasive CAP; £: based on Vila-Corcoles et al.[17]*

2.3 Sequelae

Sequelae of pneumococcal disease have been described following meningitis in 25.7% of adult survivors in a meta-analysis in high-income countries.[18] A review of five recent EU studies suggests an equal share of hearing loss and other neurological sequelae (e.g. 20-26% and 22% respectively).[19-22] Among cases of hearing loss (i.e. loss >30dB), one third and two third were unilateral and bilateral respectively. Sequelae of pneumococcal empyema may reduce the quality of life in survivors, due to thoracic pain and dyspnoea, but data describing their impact are scarce and studies are biased towards the most severe cases, which hampers adequate quantification of this rare event.

2.4 Serotype distribution

Pneumococcal serotypes are not routinely detected in IPD cases in Belgium, only the serogroup is determined at the NRC.d We estimated the serotype distribution of IPD cases in Belgium by applying the distribution of vaccine serotypes within serogroups from a recent German adult study to the 2015 Belgian serogroup data.[23] Table 3 indicates that PCV13 serotypes accounted for 25% of adult IPD cases and PPV23 for 66% of them; 42% of the cases have serotypes included in PPV23 but not in PCV13 (see Table 5 for vaccine serotypes). A third of all IPD cases in that age group has a serotype that is not included in any vaccine.

Serogroup or serotype data on non-invasive disease are not available in Belgium. A literature review in recent studies from similar settings and vaccine history (with infant PCV7 followed by PCV13) indicated that the serotype distribution of IPD and non-invasive pneumococcal disease (mostly pneumonia) differs in terms of vaccine serotype coverage.[11, 24-27] We only found one study (Benfield et al) that was conducted in a vaccination setting similar to Belgium, i.e. Denmark, with universal infant PCV7 followed by PCV13 at high uptake, and with a similar IPD serotype distribution in adults as observed in Belgium.[9, 24] In this 2013 study, the proportion of non-invasive CAP was 33% for PCV13 serotypes, 57% for PPV23 serotypes and 43% of the serotypes were not included in any vaccine. We updated the serotype distribution of non-invasive disease of this study to 2015, assuming that it experienced the yearly IPD serotype changes from the SpIDnet network (see section 3), and used it as an approximation of the serotype distribution for non-invasive cases in Belgium (Table 3).

d Serotypes that are related to each other by their cell surface antigens are included together in one serogroup. There are at least 40 serogroups, For instance, serogroup 19 include serotypes 19A and 19F.

Table 3 – Serotype distribution in IPD and non-invasive CAP among adults (≥50 years) estimated in Belgium in 2015

Serotype groups	Proportion of vaccine serotypes in IPD in Belgium, NRC (estimated counts)*	Proportion of vaccine serotypes in non-invasive CAP (estimated counts)**
Serotypes in common for PCV13 and PPV23 (12 serotypes)§	24.4% (242)	26.6% (69)
Serotypes covered by PPV23 but not by PCV13 (11 serotypes)†	41.8% (415)	24.4% (64)
Serotype covered by PCV13 but not by PPV23 (serotype 6A)	1.0% (10)	0.3% (1)
All PCV13 serotypes	25.3% (251)	26.9% (70)
All PPV23 serotypes	66.2% (657)	51.1% (133)
Non-vaccine serotypes	32.9% (326)	48.7% (127)
Total	100% (993)	100% (260)

**: Counts are estimated by applying the Van der Linden (Germany) serotype distribution to 2015 NRC serogroup counts; **: Based on Benfield et al 2013,[24] extrapolated to 2015 based on annual serotype changes in IPD from SpIDnet network; §: serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F; †: Serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F; CAP: community acquired pneumonia; IPD: Invasive pneumococcal disease; NRC: National Reference Centre.*

In contrast in the Netherlands where infant PCV7 was followed by PCV10, the placebo arm of the CAPITA study (see PCV13 efficacy under 0) showed a higher proportion of PCV13 serotypes in non-invasive CAP (69%) compared to IPD (50%) and compared to studies from PCV13 countries in the same period (9-44%).[11, 24, 27, 28] The three PCV13 serotypes that are not included in PCV10 amounted to 32% of non-invasive cases compared to 14% in IPD, mostly dominated by 19A (16%). This may reflect a lack of indirect effect of the PCV10 infant vaccination on these serotypes (see also section 3. Indirect effect of infant PCV vaccination).[28]

2.5 Costs of pneumococcal disease

Costs for hospitalised episodes of pneumococcal disease were based on cases with an ICD9 pneumococcal code in the clinical and financial hospital databases (RHM/MZG and SHA/AZV) and matched to NRC database in 2007-12. Mean costs estimated per clinical syndrome and age group are shown in Table 4. They were generally higher for meningitis (range €6973-€9103) than for pneumonia and septicaemia (range €2990-€8114). The costs of pneumococcal septicaemia are used as an approximation for the costs of other IPD.

Table 4 – Mean costs of pneumococcal disease, per clinical syndrome (ICD9 primary diagnosis) in cases matched in RHM/MZG-SHA/AZV and NRC, 2007-12

Age groups	Meningitis	Septicemia	Pneumonia
50-64 years	€ 7686	€ 8114	€ 5669
65-74 years	€ 8900	€ 6317	€ 5909
75-84 years	€ 9103	€ 5003	€ 4747
≥85 years	€ 6973	€ 3137	€ 2990

RHM/MZG: Résumé Hospitalier Minimum/Minimale Ziekenhuis Gegevens; SHA/AZV: Séjour Hospitalier Anonyme/Anoniem Ziekenhuis Verblijf; NRC : National reference centre.

The mean cost of outpatient pneumonia episodes was sourced from the GRACE study, which involved observational studies of adults with lower respiratory infections.[29] Eight Belgian outpatient pneumonia cases were identified in the database and patient medications were cost based on Belgian tariffs (http://beta.bcfi.be). The mean cost per patient amounted to €80.9 per pneumonia episode.

The cost of follow-up treatment of sequelae was based on literature review for the frequency of specific sequelae (see 2.3) and INAMI/RIZIV reimbursement rules for treatment costs. We assumed that half of the survivors with meningitis sequelae (26%) would present hearing loss (one third unilateral and two third bilateral) and the other half would have other neurological sequelae. We assumed that all cases of hearing loss ranging

30-90 dB (around three quarter of all hearing loss) would require hearing aid(s) and all those with a loss >90 dB (one quarter) would have a cochlear implant in accordance with INAMI/RIZIV reimbursement rules.[19, 21] The cost of hearing aid was estimated based on INAMI/RIZIV data.[30] The mean cost of a hearing loss case was estimated at €11 619 in the first year and €1498 in the following years. The mean cost of a patient with other neurological sequelae was estimated at €35 000 per year.[31]

2.6 Quality of life

We searched for data on the impact of pneumococcal disease on the health-related quality of life in adults in the published and unpublished literature. We prioritize studies describing health states with the EQ-5D, with values collected in Belgium or based on settings similar to Belgium, and preferably related to pneumococcal infections rather than to any bacterial infection.

No Belgian data could be identified in the literature search. Therefore the French study database PNEUMOCOST (unpublished), set up to estimate the treatment costs and quality of life impact of hospitalised pneumococcal pneumonia was analysed and used to inform the QALY estimates in our study. It collected EQ-5D scores and utilities at 1, 3, 6 and 12 months after diagnosis on 523 hospitalised pneumococcal pneumonia patients (mostly ≥50 years of age), bacteraemic and non-bacteraemic. We used post-hospitalisation observations collected in a subset of 323 low risk patients to derive QALY estimates after hospital discharge. The total QALY loss of a disease episode was calculated by taking the difference between the estimated quality of life measurement at each month and the average age-specific quality of life values of the French population (French population norm). Age-specific quality of life data for susceptible individuals and survivors of pneumococcal disease without sequelae were taken from the French population norms.[32] The final estimates of QALY loss over a year for IPD and non-IPD are:

- In patients 50-64 years of age: 0.0203 and 0.0491, respectively[e]
- In patients ≥65 years of age: 0.1741 and 0.0679, respectively

The Galante et al study, identified in the literature search, was used to inform utility weights for ambulatory pneumonia (0.508 applied during 8.5 days), hearing loss and neurological sequelae (0.635 and 0.319 respectively, assumed to last lifelong).[33] As per the Belgian guidelines on economic evaluations, QoL losses of caregivers, which are unlikely large for the target groups we consider, were not included.[34]

[e] Based on QALY loss estimates in 0-64 years of age.

3 INDIRECT EFFECT OF INFANT PCV VACCINATION

In Belgium, PCV7 was available in pharmacies in 2004 and included in the infant vaccine schedule in 2007, to be then replaced by PCV13 in 2012 and by PCV10 in 2015-16 (July 2015 in the Flemish Community and May 2016 in the Fédération Wallonie-Bruxelles).[35] In EU countries, the indirect effect of this vaccination on the elderly has resulted in declines in vaccine serotypes and increases in non-vaccine types due to vaccine-induced serotype replacement.[f, 36-39] The indirect effect tends thus to decrease the preventable fraction of IPD and CAP disease due to PCV13 and PPV23 serotypes.[40]

Three studies from similar settings described changes in elderly IPD after 4 years of universal infant PCV13. They all showed a reduction in overall IPD in the elderly (ranging -9 to -25%) after PCV13 compared to the PCV7 period. This was the result of a gradual decline of the PCV7 serotypes and the six PCV13 serotypes not included in PCV7 (PCV13non7), of 68-89% and 20-64% respectively,[37, 39, 41] and gradual increases in non-PCV13 types, up to +53% in a EU multicentre study (Figure 2).[39] The literature review also highlighted that more replacement by non-PCV7 and non-PCV13 types occurred in the EU compared to the US.[36, 39] One UK study showed comparable indirect effects between IPD and non-IPD, with a stabilization of PCV7 incidence evolution and an average annual decline of 13% for the six additional PCV13 types.[41]

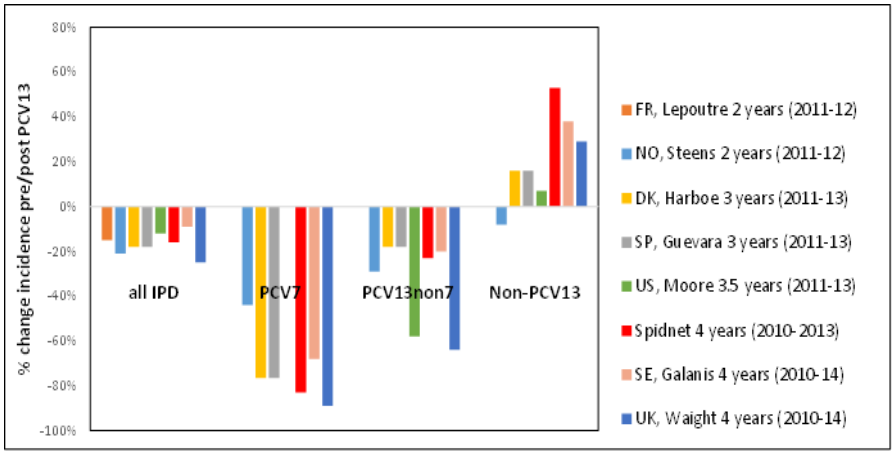
Reporting of PCV10 indirect effects varies by country and by time. Two EU countries that used exclusively PCV10 (Finland and the Netherlands) did not observe a decline in overall IPD incidence in the elderly during the first 2-4 years after PCV10 use,[42, 43] as gradual decreases in PCV10 serotypes were compensated by rapid non-PCV10 types increases. In Finland, IPD incidence even increased in 2015 in the elderly, five years after PCV10 introduction, due to continued increase in non-PCV10 serotypes, serotype 19A in particular.[44] Early changes in non-invasive CAP following two years of infant PCV10 were described in one Dutch study, along with the suggestion that relative IPD changes can be extrapolated to non-invasive CAP.[45]

However, no study could be found from a country with the same infant PCV history than Belgium, i.e. PCV7 followed by PCV13 and then PCV10.

The SpIDnet project, which included five EU countries with high PCV13 uptake in infants in 2015 (France, Ireland, Scotland, Norway and Denmark), was selected to provide parameters for serotype changes in Belgium under infant PCV. It showed an average 16% yearly decline in PCV13non7 serotypes and an average 4% rise of non-PCV13 types per year. In view of the recent shift to PCV10 in the infant schedule (after parameters have been set), we added a sensitivity analysis simulating relapses (rapid or slow) in PCV13 IPD, as observed in Finland after PCV10 introduction.

[f] Vaccine-induced serotype replacement occurs when serotypes that are covered by the vaccine are less and less being transmitted and causing disease, but at the same time serotypes not covered by the vaccine are being more and more transmitted and causing disease. In that case the non-vaccine serotypes (usually partially) replace the vaccine serotypes that dominated before the vaccine was used on a large scale.

Figure 2 – Changes in IPD incidence in ≥65 years in EU and US studies after PCV13 infant vaccination programme compared to PCV7 period, by serotype group



4 PNEUMOCOCCAL VACCINES

The main characteristics of the two pneumococcal vaccines indicated for all elderly ≥65 years and for adults with chronic conditions in Belgium are described in Table 5

and further detailed in the sections below. Between 1993 and 2013, the CSS/HGR recommended to administer PPV23 to all elderly above 60 years of age, with or without underlying disease.[46]

Despite this recommendation, PPV23 uptake has always been low in this group and tended to decline between 2004 and 2013 in the 65-80 year olds.[47] The CSS/HGR currently recommends to use PCV13 followed by PPV23 in all healthy adults 65-85 years of age, in those at high risk of pneumococcal infection aged 19-85 years and those with comorbidity aged 50-85 years (Table 5).[48] These two vaccines are not funded or reimbursed.

Table 5 – Characteristics of the two pneumococcal vaccines indicated in the elderly

Characteristics	23-valent polysaccharide vaccine or PPV23	13-valent conjugate vaccine or PCV13
Commercial name, manufacturer	Pneumovax 23, Sanofi Pasteur MSD	Prevenar 13, Pfizer
Indications authorised in adults according to the European Medicines Agency label (date)	Prevention of pneumococcal infections due to vaccine serotypes in subjects ≥2 years of age presenting an increased risk of mortality and morbidity due to pneumococcal infections (last update 2015)	Active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in adults ≥18 years of age and the elderly (2015)
Serotypes included (bold: serotype not in the other vaccine)	1, **2**, 3, 4, 5, 6B, 7F, **8**, **9N**, 9V, **10A, 11A, 12F**, 14, **15B**, **17F**, 18C, 19A, 19F, **20, 22F**, 23F, **33F**	1, 3, 4, 5, **6A**, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F
Retail price in Belgium[35]	€31.93 per dose*	€74.55 per dose
Vaccine uptake (2013)	50-64 years: 3.6% 65-84 years: 10.0% ≥85 years: 11.2%	Non relevant, recommendation not available in 2013
% IPD covered by vaccine serotypes (2015)	66%	25%
Recommended schedule in Belgium (CSS/HGR, 2014)[48]	*1. Adults 19-85 years of age with high risk of pneumococcal infection:* • Primovaccination PCV13 followed by PPV23 after minimum 8 weeks • Those previously vaccinated with PPV23: one PCV13 vaccination, at least 1 year after the last PPV23 dose • Re-vaccination with PPV23 every 5 years *2. Adults 50-85 years of age with comorbidity, and healthy adults 65-85 years of age:* • Primovaccination PCV13 followed by PPV23 after minimum 8 weeks • Those previously vaccinated with PPV23: one PCV13 vaccination, at least 1 year after the last PPV23 dose • Booster : to be evaluated, based on supplementary data and the epidemiology after 5 years *3. Adults >85 years of age:* • On an individual basis, taking into account the risk of pneumococcal infection and the evaluation of the immune response to the vaccine, the clinician may vaccinate a person above 85 years according to the recommended schedule (as above).	

** The 2015 price (€28.46 per dose) has been used in this study (that started in 2015).*

4.1 Vaccine efficacy and effectiveness

There are no studies comparing the direct effect on clinical disease of both vaccines.

4.1.1 PCV13 efficacy

The CAPITA clinical trial in the Netherlands followed 84 496 subjects ≥65 years of age during 4 years (2008-13) and provided PCV13 efficacy estimates against invasive and non-invasive disease.[28] However, included subjects were not fully representative of the general population, as they were younger and less likely to be female, did not include patients with unstable comorbidities or immunocompromised and only 3.5% of them were aged 85 years or older.[49] Eighty-two subjects who became immune-deficient or suppressed before disease onset were included in the modified intention-to-treat analyses (mITT) but excluded from the per protocol (PP) analyses.

Efficacy against any IPD and any pneumococcal CAP was significant, at 48.5% and 22.4% respectively, and efficacy against non-invasive pneumococcal CAP was not significant at 17.4% (mITT analysis, Table 6). As expected, efficacy against vaccine serotypes were systematically higher than efficacy against disease due to any serotype. Efficacy estimates against IPD were based on low numbers of cases, e.g. 8 in vaccine group vs. 33 in placebo group for vaccine-type IPD.

No published effectiveness study was available up to July 2016, with the exception of a small study presented at a conference. There is no data on PCV13 efficacy against outpatient pneumococcal pneumonia.

Further analysis of CAPITA data showed a significant decline in efficacy against vaccine type disease (IPD/CAP) with increasing age at vaccination, with an Hazard Ratio 1.057, 95%CI 1.008–1.109 in mITT analysis and no efficacy after 85 years of age.[50]

Table 6 – PCV13 efficacy against pneumococcal disease in the elderly, by outcome for a first episode[29]

Clinical syndrome	VE (95%CI) against any serotypes	VE (95%CI) against vaccine serotypes
Invasive pneumococcal disease	mITT: 48.5% (20.9 to 67.0) PP: 51.8% (22.4 to 70.7)	mITT: 75.8% (46.5 to 90.3) PP: 75.0% (41.4 to 90.8)
All-cause CAP	mITT: 5.1% (-5.1 to 14.2)	Not available
Pneumococcal CAP	mITT: 22.4% (2.3 to 38.5) PP: 30.6% (9.8 to 46.7)	mITT: 37.7% (14.3 to 55.1) PP: 45.6% (21.8 to 62.5)
Non-invasive pneumococcal CAP	mITT: 17.4% (-10.2 to 38.2) PP: 24.1% (-5.7 to 45.8)	mITT: 41.1% (12.7 to 60.7) PP: 45.0% (14.2 to 65.3)

CAP: community acquired pneumonia; mITT: modified intention-to-treat analysis, includes all confirmed IPD with onset at least 14 days after vaccination, including subjects who became immune-deficient or suppressed before disease onset; PP: per protocol analysis; VE: vaccine efficacy/effectiveness.

4.1.2 PPV23 efficacy and effectiveness

The recent meta-analyses of clinical trials were not retrieved in our literature review, because they either mixed valences of vaccines (from 2-valent to 23-valent), age, and outcomes for IPD and/or included many old studies and/or trials were conducted in very different settings and populations.[51-54] In the observational studies that we selected, PPV23 effectiveness against PPV23 types IPD ranged 24-39% in studies using an indirect cohort design,[55-58] while case-control studies and the Cochrane meta-analysis provided systematically higher values (≥70%).[51, 59, 60] Effectiveness was not significant in subjects ≥85 years of age. Effectiveness in healthy adults was (non-significantly) higher than the estimates among immunocompromised subjects, in which it was low and not significant (except in one study).

We selected the Andrews et al study to inform our parameters.[55] This study used an indirect cohort design, with the advantage of controlling for biases in ascertainment between cases and controls, and matched controls to cases in terms of risk factors, age and periods. Due to its large sample size, it stratified VE by age group and time after vaccination, and the setting (England & Wales) presents very similar pneumococcal epidemiology and vaccine history as Belgium. The full review can be found in the scientific

report. PPV23 effectiveness against PPV23 serotype IPD was significant at 24% overall (all age risk groups confounded, Table 7), declined by age, and was not significant in those ≥85 years of age. This value is conservative, as most recent observational studies and meta-analyses present higher effectiveness values.[g]

Table 7 – PPV23 effectiveness against PPV23 type IPD by age at diagnosis and risk group in Andrews et al[55]

Risk group / age group (age at diagnosis)	Vaccine effectiveness[#]			
	65-74 years	75-84 years	≥85 years	All ages
N cases/controls	369/343	523/524	378/405	1270/1272
All	28% (1 to 47)	25% (3 to 43)	18% (-11 to 39)	24% (10 to 36)
No risk	56% (24 to 75)	27% (-16 to 52)	14% (-40 to 47)	34% (12 to 50)
High risk immuno-competent	21% (-46 to 57)	23% (-23 to 52)	11% (-51 to 48)	20% (-9 to 41)
Immuno-compromised	-17% (-96 to 3:	38% (3 to 43)	35% (-15 to 64)	22% (-5 to 42)

#: crude estimates (matching was by age and year of illness) because adjusted vaccine effectiveness estimates were similar to non-adjusted ones.

In the three PPV23 studies on CAP retrieved from the literature review, effectiveness against all pneumococcal CAP in subjects ≥65 years of age ranged 32-53% and was again higher in case-control studies (37-53%) compared to cohort studies (32% not significant).[11, 61, 62] PPV23 effectiveness against bacteraemic pneumococcal CAP was systematically higher than VE against non-bacteraemic CAP although 95%CI overlapped. Trends of effectiveness by age are not consistent across studies.

No single study seemed sufficient to provide PPV23 effectiveness parameters against pneumococcal CAP and values vary substantially across design and settings. We favoured cohort studies due to the likely overestimation of effectiveness values in case-control studies and the more robust design, but the most complete and recent cohort study, Ochoa-Gondar et al, used a different concept of exposure in the main analyses (i.e. considering as vaccinated only those within 5 years before study start and as unvaccinated those vaccinated >5 years before study start).[11] As three analyses indicated a relatively homogeneous ratio in the effectiveness against non-bacteraemic versus bacteraemic CAP, ranging 0.55-0.77, we applied this ratio on the effectiveness against IPD (0.55 in baseline and 0.77 in univariate sensitivity analysis).

No study demonstrated significant PPV23 effectiveness against outpatient or inpatient all-cause pneumonia, despite the availability of some large studies.[11, 63]

No efficacy or effectiveness data are yet available on schedules combining PCV13 followed by PPV23.

4.1.3 Duration of protection

PCV13 duration of protection is not known beyond the four years of the CAPITA trial. No efficacy estimates by period after vaccination is provided, but authors stated that the efficacy persisted throughout the duration of the trial, without evidence of waning.[28] In an unpublished post-hoc analysis, efficacy by cumulative period of time (up to 5 years) after vaccination did not show a clear decline.[64] One immunogenicity study covered the 5-year period after initial PCV13 vaccination of adults ≥50 years and showed a marked decline in immunological markers of protection (OPA GMT) in the vaccinated group for each vaccine serotype, to titres 4 to 20 times lower after 5 years.[65]

In the model, we assumed a 5-year period of protection after PCV13 administration as reported by the CAPITA trial, followed by immunity waning according to a logistic function in which the efficacy is reduced to 50% of the initial VE after 10 years following vaccination. Several variations in both the duration of full protection and the speed of waning were also modelled. We assumed the same waning function against IPD and non-invasive CAP.

[g] For instance, the last Cochrane meta-analysis presented (Moberley et al) estimated a pooled efficacy at 74% against IPD.

PPV23 duration of protection was assessed in four studies measuring VE against IPD over time after vaccination.[55-58] Three studies show a decline in VE over time, with highest effectiveness estimates against IPD in the first 2 years, significant and lower in the 2-5 years and non-significant after 5 years (except in one study).[55-57] No PPV23 study on pneumococcal CAP stratified VE by time after vaccination, but the Ochoa-Gondar cohort study found higher VE point estimates against pneumococcal outcomes in those vaccinated within the five years before study start compared to subjects vaccinated at any time.[11] However, confidence intervals are wide and overlapping.

In the model, we assumed 2 years of fixed PPV23 protection with the initial protection at 56% (95%CI 40 to 68) according to the Andrews et al value estimated in the 65-84 years of age, followed by exponential waning reducing the 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. We also assumed the same waning function against IPD and non-invasive CAP.

4.1.4 Comparison between PCV13 and PPV23 protection

Overall, PCV13 seems to provide more protection against IPD than does PPV23: PCV13 showed 76% efficacy against PCV13 type IPD compared to 24% for PPV23 against PPV23 type IPD in Andrews et al (Table 6 and Table 7) or 29-77% in other PPV23 retrieved studies.

The differences in efficacy/effectiveness against pneumococcal CAP is difficult to establish due to overlapping 95%CI, but PCV13 did not show higher point estimates: efficacy against all pneumococcal CAP was 22.4% (significant) for PCV13 in CAPITA and effectiveness was 32% (not significant) for PPV23 in Ochoa-Gondar et al, or 37-53% (significant) in other retrieved studies. Likewise, efficacy/effectiveness against any bacteraemic pneumococcal CAP was 48.5% for PCV13 vs. 44-66% for PPV23. Finally, efficacy/effectiveness against non-bacteraemic CAP was 17.4% for PCV13 and 29-42% for PPV23. However, any comparison between studies is hazardous due to differences in study population, analyses, design and proportion of serotypes covered by these vaccines. The CAPITA study has a maximum follow-up period of 5 years and has important advantages and limitations inherent to a randomised trial design with specific inclusion criteria (only 3.5% subjects above 85 years of age, no immuno-compromised subjects at entry). We only selected PPV23 effectiveness studies, which included all kinds of subjects, a sizeable proportion of immunocompromised subjects and subjects ≥85 years of age, and covered longer periods of time after vaccination. These are factors that should a priori lower the observed effectiveness for PPV23 versus PCV13, though most PPV23 studies, that are observational studies, provide by design less reliable estimates than we can expect from a randomised controlled study such as CAPITA. This is further complicated as we cannot make a comparison between the two vaccines for similar groups or follow-up periods because the CAPITA study did not yield separate estimates for IPD and pneumococcal CAP outcomes by age and time. For IPD estimates, the proportion of cases covered by PPV23 serotypes is also larger than those covered by PCV13, and this difference has increased over time under the previous influence of universal infant PCV7 and PCV13 vaccination, and will likely continue to evolve similarly under PCV10 vaccination, and other higher-valent PCV vaccines for infants in years to come. Since the uncertainty in terms of efficacy against non-IPD is large, we elaborated three "base case" calculations for efficacy (see under Methods).

4.2 Vaccine safety

The frequency of local reactions and systemic adverse events was similar by age groups after PPV23 and PCV13 vaccination.[28, 66-69] Local reactions at injection site are reported in 35-50% of vaccinees ≥65 years of age, consist mostly of mild side effects (pain, erythema, and swelling) and usually resolve within 2-5 days following vaccination.[28, 70] Vaccine-related systemic adverse reactions following vaccination ranged 20-35% in those ≥50 years of age and the most common ones were asthenia/fatigue, myalgia and headache. The frequencies of newly diagnosed chronic medical conditions, serious adverse events, or deaths did not show significant differences between vaccinated and placebo arms for both vaccines. No vaccine-related serious adverse events were reported. For both vaccines, a lower frequency of adverse reactions is observed in older age (>65 years of age) compared to younger adults.

Earlier studies have shown a higher frequency of injection site reactions after PPV23 revaccination than after primary vaccination.[71] However, these

reactions were mild, resolved within 5 days and more recent studies in older adults indicate that a second vaccination given five or more years after a first vaccination is well tolerated.

In one study, the administration of PCV13 followed by PPV23 was followed by mild local reactions, whose frequency was lower compared to subjects receiving two doses of PPV23 but tended to be higher compared to subjects receiving one PCV13 dose only.[72] Mild fever (<38.5°C) was observed in 5% of subjects and no severe fever was reported. The frequency of other systemic reactions was not significantly higher compared to subjects receiving one PCV13 dose only.

Quality of life losses for vaccine-related adverse reactions were not included in our study.

4.3 Vaccine uptake

No data on the use of PCV13 in adults are available as the recommendation is very recent. PPV23 uptake data from the Health Interview Surveys show a decline in uptake in most ages >60 years between 2004 and 2013. In 2013, PPV23 uptake over the previous 5 years was 3.6% (2.5-4.8) in all subjects 50-64 years of age, 10.0% (8.1-11.9) in the 65-84 years and 11.2% (6.1-16.3) in the ≥85 years of age.[47]

4.4 Cost of vaccine and vaccine administration

Based on expert opinion, the cost of one vaccine administration is estimated at half a GP visit (€23.32/2), under the assumption that half the vaccine recipients in the target age groups over 50 years would take the opportunity to consult the vaccinating physician on other issues relating to their health (e.g. administration of influenza vaccination), without being charged extra for the pneumococcal vaccination. The costs of the vaccines per dose are based on the 2015 retail prices in Belgium (Table 5).[35]

5 METHODS FOR ECONOMIC EVALUATION

5.1 Model and analytical approach

A static closed age-structured multi-cohort model was developed and applied to the Belgian population aged 50 years and more. Since adults over 50 years are not core transmitters of pneumococcal infections (in contrast with children), herd immunity effects induced by vaccinating relatively small proportions of this age group are likely to be negligible.[73] Ignoring herd immunity effects by using a static model for this analysis therefore implies that there might be a small underestimation of the benefits of vaccination, rendering this analysis conservative in this respect. Single year age cohorts above 50 years of age are simultaneously followed from the moment of vaccination until death of the last survivor in the youngest cohort. Cohort sizes over time are informed by standard demography, including age specific all-cause mortality and life-expectancy.

The vaccines (PCV13, PPV23 or both), their timing and the applied scenario of duration and waning of vaccine-induced protection determine each cohort vaccine effectiveness at every age in years post-vaccination, for both IPD and non-IPD.

Due to the large uncertainty in terms of efficacy against non-IPD for both vaccines, we present analyses for three base cases: one in which PPV23 and PCV13 each have baseline (fully parameterised) efficacy against non-IPD, one in which only PPV23 has no efficacy against non-IPD (i.e. PPV23 is then assumed to have 0% efficacy against non-IPD, with certainty) and for comparison one (less plausible case) in which both PPV23 and PCV13 have no efficacy against non-IPD.

A *serotype change* module is used to simulate the impact of childhood vaccination (herd immunity or indirect effects) and trends in serotype distribution in adults. It calculates a correction factor for the decay in PCV13 type incidence per year and for non-PCV13 type incidence increases. The same correction factor is applied for invasive and non-invasive disease as the few available data do not suggest different indirect effects in invasive and non-invasive disease. In view of the 2015-2016 change to infant PCV10

vaccination, we also explore scenarios in which there is a "relapse" in incidence of the serotypes included in PCV13. These scenarios intend to mimick the "comeback" of PCV13 serotypes for which PCV10 vaccine in infants does not provide sufficient indirect protection in adults, as observed with 19A in Finland.

The vaccination coverage together with the vaccine efficacy and serotype evolution determine the population susceptible to acquire invasive or non-invasive pneumococcal disease for each cohort, at each age in years. On these people, we apply age- and serotype-specific yearly incidence rates of the different disease categories. Possible long-term consequences of meningitis (hearing loss or neurological sequelae) are also taken into account.

The main outcome for the cost-effectiveness analysis is the incremental cost-effectiveness ratio (ICER), in this report defined, unless stated otherwise, as the incremental direct costs per QALY gained. We also report impact on health outcomes separately, as well as budget-impact analyses. The considered time horizon for the simulations is the remaining life span of the cohorts. Future life-years lost due to pneumococcal-attributable mortality were discounted at an annual rate of 1.5%, and future costs were discounted at an annual rate of 3%.[34]

These and other standard methodological choices are in accordance with Belgian guidelines.

All costs are expressed in Euro from the year 2015.

5.2 Accounting for uncertainty

To assess parametric uncertainty of the ICERs, we conducted Monte-Carlo sampling with 1000 draws (i.e. probabilistic sensitivity analysis or PSA). These results are summarised by means, medians with their 95% uncertainty interval, and are available under an extensive range of univariate and multivariate sensitivity analyses accounting for non-parameterised uncertainty (see Scientific report for details).

Furthermore cost-effectiveness acceptability frontiers (CEAFs) and cost-effectiveness planes (CE planes, see Scientific report) were constructed. CEAFs have the attractive feature of summarizing parameter uncertainties in the ICERs in relation to a range of willingness to pay values.[h]

5.3 Vaccination strategies to compare

The vaccination strategies were defined in discussion with the study expert committee and the Vaccination subcommittee of the Superior Health Council in Belgium (Table 8). Uptake levels of the more expansive strategies (2 to 7) were informed by influenza vaccine uptake levels by age and were assumed to be lower in those ≥85 years of age based on the expert opinion regarding medical practice in primary care. All incremental strategies in Table 8 are compared versus each other to select the strategy with the highest probability to be cost-effective versus all the other strategies, at a given willingness to pay for a QALY (represented as CEAFs). Uptake values are for the whole target group, i.e. not focused on risk groups, and for previously unvaccinated individuals. They are based on the 2013 Health interview and other surveys for recent vaccine uptakes (e.g. influenza).[47]

[h] The willingness to pay for a QALY is the maximum amount society would be willing to pay in order to gain an additional year of life in perfect health.

Table 8 – Vaccination strategies defined by vaccine choice, schedule, and uptake in different age groups

Vaccination comparison	50-64 years	65-74 years	75-84 years	≥85 years
(1) *Reference strategy:* ***"current situation":*** PPV23 at current uptake[a]	0.7% PPV23	2.0% PPV23	2.0% PPV23	2.2% PPV23
(2) Higher uptake PPV23 only once versus option (1): **"PPV23"**	25% PPV23	50% PPV23	60% PPV23	40% PPV23
(3) PCV13 only once versus option (1): **"PCV13"**	25% PCV13	50% PCV13	60% PCV13	40% PCV13
(4) PCV13 followed by PPV23 once in the same year versus options (1), (2) and (3): **"PPV23+PCV13"**	25% PCV13, 25% PPV23	50% PCV13, 50% PPV23	60% PCV13, 60% PPV23	40% PCV13, 40% PPV23
(5) as in (2), with PPV23 revaccination once after 5 years versus option (2): **"PPV23+ revac PPV23"**	15% revaccination	25% revaccination	25% revaccination	20% revaccination
(6) as in (3) with PCV13 revaccination once after 5 years versus option (3): **"PCV13+ revac PCV13"**	15% revaccination	25% revaccination	25% revaccination	20% revaccination
(7) as in (4), with PPV23 revaccination once after 5 years versus option (4) **"PPV23+PCV13+revac PPV23"**	15% revaccination	25% revaccination	25% revaccination	20% revaccination

[a]: *"Current uptake" for the purpose of the analysis defined in these comparisons as PPV23 only once at the low uptake as observed in 2013. The uptakes for strategy (1) are the 5-year uptake rates reported in section 4.3, divided by 5. The uptakes in options 2-7 are assumed conditional on these options being funded (hence higher uptake).*

5.4 Summary of model parameters

Table 9 presents an overview of the model parameters and their sources, along with the report section where they are described in detail.

Table 9 – General overview of assumptions and model input parameter values

Parameter	Values and distribution	Source / Reference	Section where described
Vaccine parameters			
Current vaccine uptake (2013)	Varying from 1% to 20% by age group (Table 8)	Health Interview Survey data[47]	4.3. Vaccine uptake
Targeted vaccine uptake (for new unvaccinated cases)	See Table 8	Expert committee	Table 8 in 5.3. Vaccination strategies to compare
PCV13 efficacy against PCV13 types	1. Initial VE (≤5 years), 50-84 years: - IPD: 75.8% (46.5%-90.3%) - Non-invasive CAP: 41.1% (12.7%-61%) 2. Waning over time: 5 years fixed protection, followed by logistic function reducing to 50% of initial VE after 10 years	CAPITA[28] Waning: assumptions based on CAPITA,[28] Frenck et al,[65] and expert opinion	4.1.3. Duration of protection
PCV13 efficacy age dependence	Decline with hazard ratio f_{HR}= 1.058 (1.008 to 1.111) per year of age for both IPD and non-IPD In <65 years: same VE as 65 year olds In ≥80 years: VE assumed at 0% (≥85 years for IPD)	Van Werkhoven et al[50]	4.1.1. PCV13 efficacy
PPV23 efficacy against PPV23 types	1. Initial VE (≤2 years): IPD: in 50-84 years: 56% (40 to 68); in ≥85 years: assumed at 0%. Non-IPD: in 50-84 years: 30.8% (22 to 37); in ≥85 years: assumed at 0%. 2. Waning: 2 years fixed protection, followed by exponential waning reducing VE to 15% over 3 years	IPD: Andrews et al[55] Non-IPD: Andrews et al, scaled at a 0.55 ratio for VE non-IPD/IPD according to Ochoa-Gondar[11] Waning assumption: VE by time in Andrews et al[55]	Initial VE: 4.1.2. PPV23 efficacy and effectiveness Waning: 4.1.3. Duration of protection
Cost of vaccine administration	€11.7 (half a GP visit or €23.32/2)	Tariff of one GP visit	4.4. Cost of vaccine and vaccine administration
Cost per PCV13 dose	€74.55 current retail price, reduced prices explored in sensitivity analyses (25% stepwise reductions)	Belgisch centrum voor farmacotherapeutische informatie.[35]	4.4. Cost of vaccine and vaccine administration and Table 5
Cost per PPV23 dose	€28.46 2015 retail price*, reduced prices explored in sensitivity analyses		
Epidemiological and demographical parameters			
Size target group	Non-random, 2015	Eurostat 2015 population data	Not available
Incidence of outpatient pneumococcal disease	Table 1: from 57 to 143 per 100 000 according to age group	INTEGO 2013 R81 for all-cause pneumonia % outpatient CAP due to pneumococcus: pooled estimate from Capelastegui and Holm[14, 15]	2.1. Incidence of pneumococcal disease
Incidence of hospitalised invasive pneumococcal disease	Table 1: from 15 to 80 per 100 000 according to age group All IPD assumed to be hospitalized	NRC 2015 and Verhaegen et al for clinical syndromes[9]	2.1. Incidence of pneumococcal disease

Incidence of hospitalised non-invasive pneumococcal CAP	Table 1: from 59 to 332 per 100 000 according to age group	NRC for IPD incidence data. Pooled estimate of 4 studies for the % of non-invasive in hospitalised pneumococcal CAP[10-13]	2.1. Incidence of pneumococcal disease
Proportion of long term consequences of meningitis	- % hearing loss in meningitis survivors: 12.9% in base case, 20% in sensitivity analysis - % neurological sequelae in meningitis survivors: 12.9% in base case, 22% in sensitivity analysis	% meningitis sequelae: Jit[18] % neurological and hearing loss sequelae: Ostergaard,[20] Weisfelt;[21] Worsoe et al for sensitivity analysis for hearing loss[22]	2.3. Sequelae
Vaccine serotype coverage	- IPD: PCV13: 25%; PPV23: 66% - Non-IPD: PCV13: 27%; PPV23: 51%	IPD: NRC 2015 data and Vanderlinden et al[23] Non-IPD: Benfield et al[24]	Table 3, 2.4. Serotype distribution
Case fatality ratio of IPD	Table 2	RHM/MZG deaths during hospitalisations, in matched IPD cases NRC-RHM/MZG	2.2. Mortality of pneumococcal disease
Case fatality ratio (CFR) in outpatient pneumonia	2/118 (1.7%) All ages (mean age study=74 years)	Vila Corcoles et al 2009[17]	2.2. Mortality of pneumococcal disease
Ratio CFR invasive versus non-invasive pneumonia	Adjusted hazard ratio for invasive versus non-invasive pneumonia 2.8 (1.6-5.1)	Capelastegui et al 2014[16] To inform CFR non-invasive pneumonia	2.2. Mortality of pneumococcal disease
Indirect effect of PCV infant vaccination on PCV13 disease	PCV13: Yearly decline of 16% (base case) Sensitivity analyses: min. -10%, max. -20%	SPIDNET 2010-15 analysis[39]	3. Indirect effect of infant PCV vaccination
Serotype replacement due to infant vaccination	76.3% of PCV13 decline (compensated by the non-PCV13 serotype increases) Sensitivity analyses: slow or quick relapse	SPIDNET 2010-15 analysis[39]	3. Indirect effect of infant PCV vaccination
Life expectancy	Belgian national institute of statistics (2014)	STATBEL†	Not available
Background mortality	Belgian national institute of statistics (2014)	STATBEL†	Not available
Costs of treatment			
Hospitalisation cost	Table 4	RHM/MZG-SHA/AZV linked with NRC	2.5. Costs of pneumococcal disease
Out of hospital for inpatients	Not included	Non relevant	Non relevant
Cost of outpatient pneumonia	€80.9 per outpatient episode Sensitivity analysis: €104.2 (adding a 2nd GP visit)	GRACE project, personal communication, Raymond Oppong, 2015[29]	2.5. Costs of pneumococcal disease
Cost of long term consequences of meningitis	- Hearing loss: average €11 619 1st year; €1498 / year in following years - Neurological sequelae: €35 000 /year	KCE report n° 231[30]	2.5. Costs of pneumococcal disease
QALY / Utilities			
QALY loss for hospitalised cases	QALY loss until 12 months after hospitalisation - In 50-64 years: 0.0203 for IPD and 0.0491 for non-IPD - In ≥65 years: 0.1741 for IPD and 0.0679 for non-IPD	PNEUMOCOST survey France, personal communication of Gerard de Pouvourville, ESSEC, 2016[33]	2.6. Quality of life

QALY loss for non-hospitalised pneumonia	Utility value QoL: 0.508 (0.442 – 0.575), applied during 8.5 days	Galante et al[33]	2.6. Quality of life
QALY loss long term consequences of meningitis	Utility weight hearing loss: 0.635 (lifelong) Utility weight neurological sequelae: 0.319 (lifelong)	Galante et al[33]	2.6. Quality of life
UK population norms (to use with Galante et al)	0.93	Age group 25-35 years from Kind et al[74]	2.6. Quality of life
Discounting			
Discount rate for costs	3%	Cleemput et al[34]	Not available
Discount rate for health outcomes (life years, QALYs)	1.5%	Cleemput et al[34]	Not available

*SHA/AZV: Séjour Hospitlier Anonyme / Anoniem Ziekenhuis Verblijf; RHM/MZG: Résumé Hospitalier Minimum / Minimale Ziekenhuis Gegevens; NRC : National Reference Centre; † : http://statbel.fgov.be/nl/statistieken/cijfers/bevolking/sterfte_leven/tafels/); *: The current (2016) retail price is €31.93 per dose.*

6 RESULTS

6.1 Current disease burden

Table 10 shows the current annual burden by age estimated from our model, i.e. with current PPV23 vaccination recommendations in place. We expect about 5800 hospitalisations and 3600 additional patients treated in ambulatory care, as well as about 430 deaths and about 4150 QALYs lost. The health care costs for treatment amount to about €33 million. The number of fatalities, and particularly those due to pneumonia, are higher in older age groups, despite the decreasing size of each age group with increasing age. The number of hospitalisations and especially outpatients decline in the more advanced age groups (also due to decreasing cohort size), which also explains the decreasing trend in costs by age group.

Table 10 – Current annual disease and cost (€2015) burden related to *S. pneumoniae* in adults ≥50 years (mean (median) of 1000 simulations, rounded to the nearest unit)

Age	50-64 years	65-74 years	75-84 years	85-105 years	Total (age ≥50 years)
Age group size	2 233 358	1 022 444	720 255	288 423	4 264 480
Meningitis cases	29 (29)	11 (11)	12 (12)	10 (10)	62 (62)
Hearing loss cases	3 (3)	1 (1)	1 (1)	1 (1)	6 (6)
Neurological sequelae cases	3 (3)	1 (1)	1(1)	1 (1)	6 (6)
Bacteraemia without focus and other IPD	27 (27)	23 (23)	23 (23)	20 (20)	92 (92)
Pneumococcal pneumonia hospitalisations	1706 (1691)	1393 (1381)	1416 (1403)	1235 (1224)	5750 (5699)
Outpatient pneumococcal pneumonia cases	1517 (1501)	778 (768)	822 (805)	489 (481)	3606 (3578)
Deaths meningitis	4 (4)	1 (1)	3 (3)	5 (5)	13 (13)
Deaths bacteraemia without focus and other IPD	4 (4)	4 (4)	4 (4)	5 (4)	17 (17)
Pneumonia deaths	74 (71)	77 (75)	109 (107)	138 (134)	398 (389)
Total deaths	82 (79)	82 (80)	116 (114)	147 (143)	428 (419)
Undiscounted quality adjusted life years lost	1816 (1759)	1078 (1057)	802 (800)	465 (456)	4161 (4109)
Discounted quality adjusted life years lost	1535 (1489)	978 (959)	761 (758)	454 (445)	3727 (3675)
Total medical cost undiscounted	13 336 267 (13 264 497)	9 339 376 (9 263 490)	7 039 081 (6 983 160)	3 991 872 (3 958 089)	33 706 596 (33 497 893)
Total medical cost discounted	12 328 033 (12 257 762)	9 137 858 (9 059 440)	6 940 564 (6 886 382)	3 954 000 (3 919 567)	32 360 455 (32 111 754)

6.2 Effectiveness and cost-effectiveness analyses

We first consider the assumption that both vaccines have efficacy against non-IPD (main base case).

In the 50-64 year olds, PPV23 vaccination would cost about €83 000 per QALY gained versus the current situation while PCV13 would cost about €201 000 per QALY gained, using 25% uptake for both vaccines. In this age group, introducing PPV23+PCV13 vaccination at 25% uptake would prevent 24 deaths and gain 478 QALYs versus the current situation. However, it would "only" prevent 10 deaths and gain 190 QALYs versus PPV23 25% uptake, while requiring an extra €48 million in vaccination costs. In terms of hospitalisations for pneumococcal pneumonia, the PPV23+PCV13 strategy versus PPV23 would prevent on average 194 hospitalisations in addition to the 217 prevented by PPV23 25% uptake program.

In the 65-74 year olds over the remaining lifetime of the vaccinated cohorts, substantially more deaths and hospitalisations can be avoided with both vaccines at 50% uptake. Slightly more QALYs can be gained with PPV23 than with PCV13, although more pneumococcal pneumonia (outpatients and hospitalised) are prevented by PCV13. For instance, about 45 deaths and 600 hospitalisations are averted and 500 QALYs are gained by a combined higher uptake PPV23 and PCV13 program versus the current situation. It is important to remember though, that these effects are obtained under the assumption of a vaccine uptake twice higher compared to these strategies in the 50-64 year olds. On average PPV23 and PCV13 vaccination cost about €60 000 and €170 000 per QALY gained, respectively, versus the current situation in this age group.

In the 75-84 year olds, the number of prevented outcomes further improves (but with 10% higher uptake than in the previous age group) and the balance tips further in favour of PPV23. The uncertainty on the pneumococcal pneumonia hospitalisations and outpatient cases averted becomes larger, moreover as the PCV13 efficacy has negative values in the lower bound of the uncertainty interval. The ICER becomes greater for PCV13 containing strategies and lower for PPV23 containing strategies, in comparison to the previous age groups.

Figure 3 presents the cost-effectiveness acceptability frontiers (CEAFs) when all vaccination strategies are compared against each other (according to the efficiency frontier approach). The CEAFs show for each willingness to pay (WTP) level per QALY, the probability that the strategy depicted at that WTP level is the one strategy (amongst all strategies being compared) that results in the highest "net benefit". The net benefit of a new strategy versus its comparator is calculated by the additional vaccination costs required by the new strategy above its comparator, minus the clinical treatment costs avoided by the new strategy, minus the number of QALYs gained by the new strategy multiplied by the WTP level considered. A common feature of all scenarios is that the current situation remains the "best" option when the WTP per QALY is relatively low, i.e. the current situation has the highest probability of yielding the highest net benefits at the lowest range of the WTP spectrum shown, see Figure 3. Note also that strategies targeted at those aged 85 and older are never selected as the most cost-effective, simply because we concluded from our reviews that neither vaccine has conclusive evidence on efficacy in that age group.

Assuming efficacy against non-IPD for both vaccines, the best options with increasing WTP for a QALY are to vaccinate the age group 75-84 years with PPV23 only (from about WTP €50 000 to €60 000 per QALY), which expands to the 65-84 years with PPV23 (from about €60 000 to €80 000 per QALY) and further to the 50-84 years with PPV23 (€80 000-€100 000), and adding revaccination with PPV23 for about €100 000 to €350 000 per QALY (see Figure 3, left panel). This implies that it is better, in terms of cost-effectiveness, to have high uptake PPV23 in the 75-84 year olds, before expanding this strategy to younger age groups.

If we assume that PPV23 has 0% efficacy against non-IPD, then the overall picture remains very similar (in favour of PPV23 only) up to a WTP of €200 000, albeit that the WTP now has to be higher to switch between options: the WTP should be at least €75 000 to switch from the current situation to PPV23 vaccination the other options, see Figure 3, right panel). Only when WTP exceeds €300 000 then a PCV13 containing strategy emerges as showing the highest net benefit (PPV23+PCV13 + revaccination with PPV23).

Figure 3 – Cost-effectiveness acceptability frontier for all strategies and age groups combined, assuming efficacy against non-invasive CAP for both vaccines (left panel) and assuming PPV23 has 0% efficacy against non-IPD (right panel)

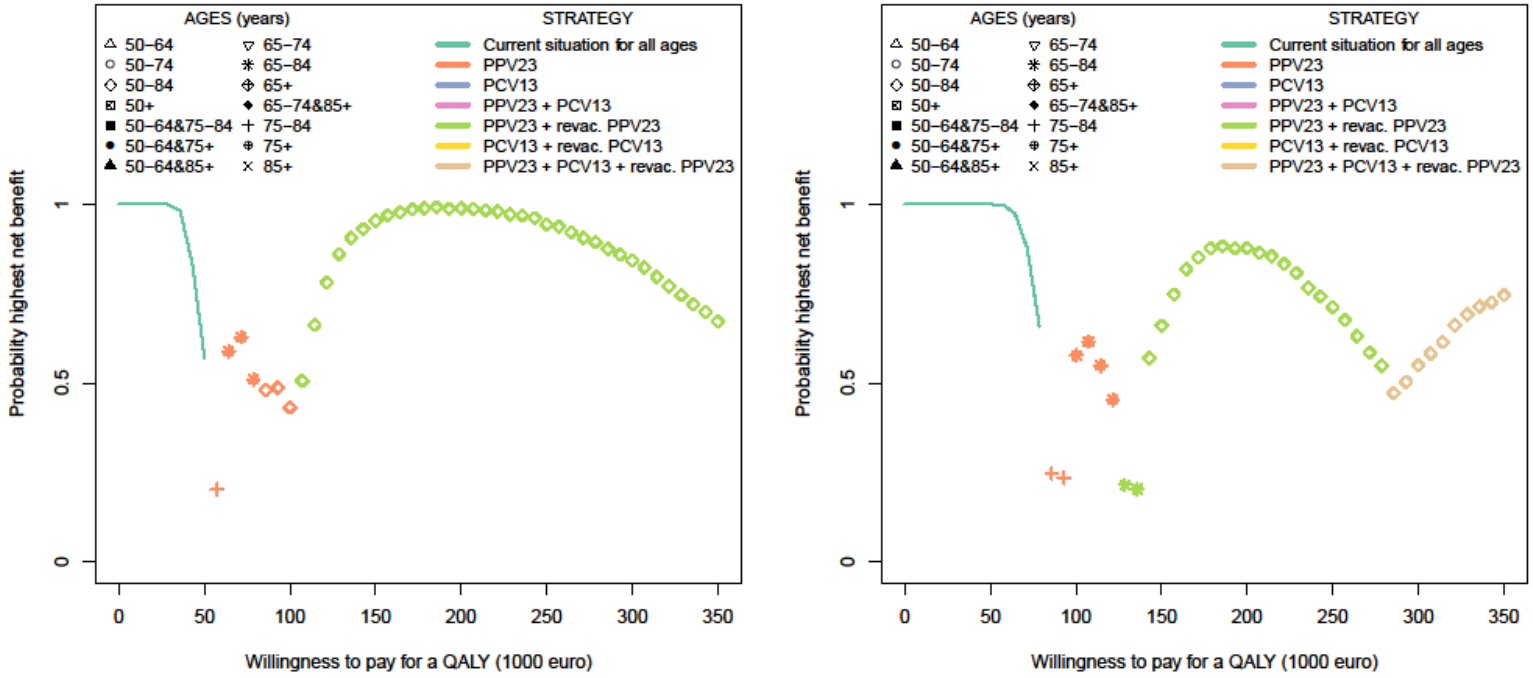
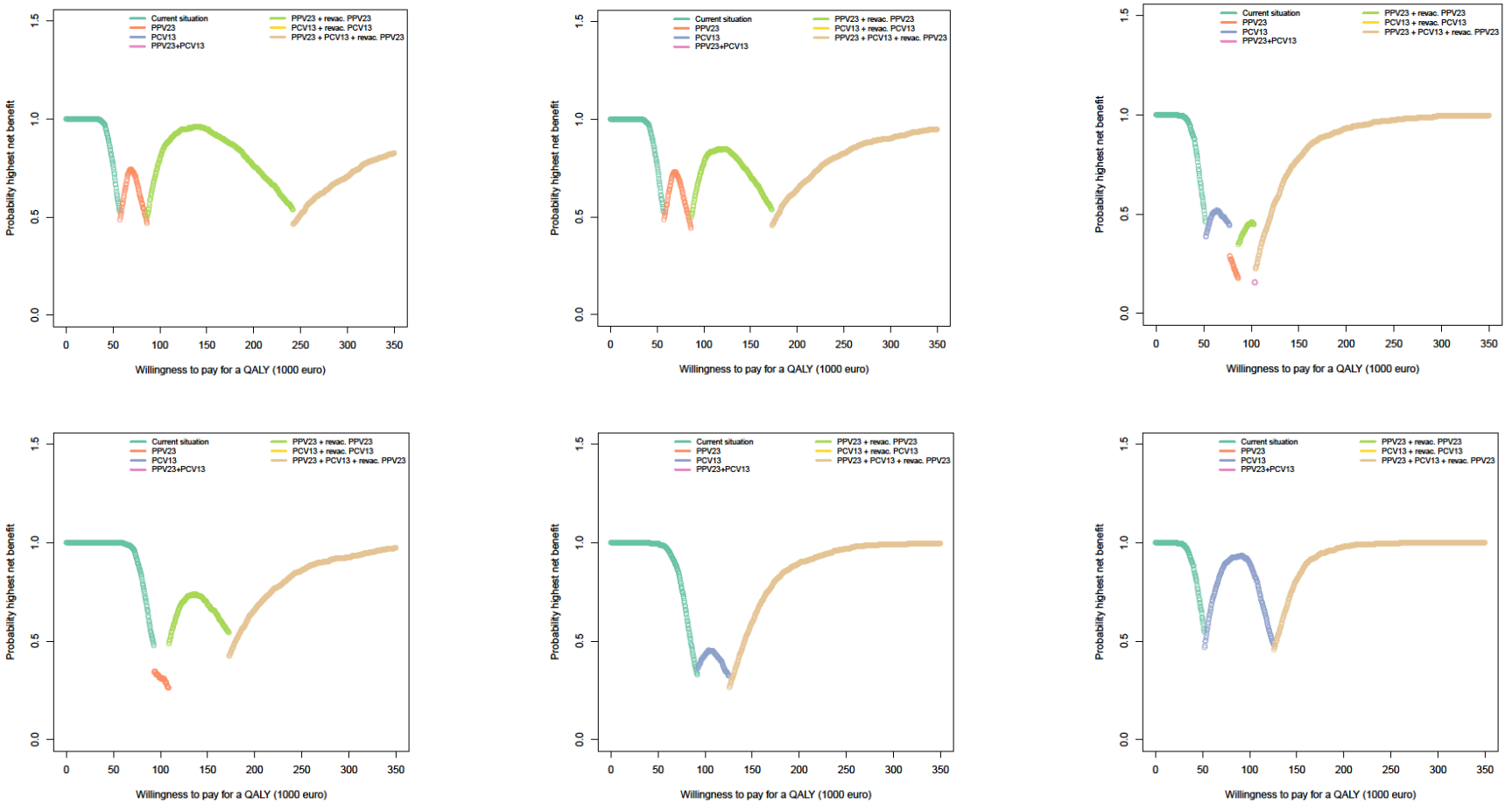


Figure 4 – Cost-effectiveness acceptability frontiers for the 65-74 year with increasing PCV13 price reductions (left to right, using 75%, 50% and 25% of the baseline price), assuming efficacy against non-invasive CAP for both vaccines (top row) or assuming PPV23 has 0% efficacy against non-invasive CAP while PCV13 has baseline efficacy (bottom row)



Our probabilistic sensitivity analysis showed that the uncertainty in the results stems mainly from uncertainty on the QALYs gained, i.e. the effectiveness of the vaccines and the disease burden estimates. The parameters related to vaccine effectiveness, especially against non-invasive CAP, and the degree of age dependence imposed, are of major importance. Those related to IPD become more important if baseline protection against non-IPD is no longer assumed. The other influential parameters are mainly those related to death rates and those that determine the estimation of non-invasive incidence.

The multivariate sensitivity analyses highlight that PCV13 price reductions and a relapse in PCV13 serotypes that are not covered by the PCV10 vaccine, currently used in the childhood vaccination programme in Belgium, could change the prioritisation of PPV23 over PCV13 for the ages 50-74 years. This finding is illustrated by a bivariate analysis shown in Figure 4, showing the impact of increasing PCV13 price reductions (from left to right) for the age group 65-74 year olds (detailed multivariate sensitivity analyses available in the Scientific report). It indicates that from a 50% to 75% price cut, single dose PCV13 emerges as the most beneficial option for WTP values around €50 000-100 000 per QALY; this is particularly the case when PPV23 is assumed to have 0% efficacy against non-IPD. This change in the most beneficial option occurs earlier, i.e. for lower WTP values, if we simultaneously assume a relapse of PCV13 types in adults. However in our many additional analyses, PCV13 price reductions were consistently more influential than other parameter changes for the comparison between both vaccines.

Furthermore, the assumption of substantially higher (i.e. doubling or tripling) pneumonia incidence or death rates would improve the cost-effectiveness of PPV23 substantially, but would only marginally improve the relative cost-effectiveness of PCV13 versus PPV23. Since modeling risk group vaccination was beyond the scope of this report, such higher burden scenarios may mimic to some extent the burden of risk groups; however, the results would likely differ due to lower or non-existing vaccine efficacy in these groups. Under those scenarios, the cost-effectiveness of both vaccines substantially improved, but it still only affected the choice of PPV23 over PCV13 if we simultaneously assumed PCV13 price cuts and a relapse in PCV13 serotype incidence.

The cost-effectiveness of PPV23 would further considerably improve if the retail price of PPV23 (€28.46 per dose in 2015) was reduced to be more in line with prices observed in other EU countries (€12.46 per dose in France). With such price reductions, our initial conclusions remain similar as single dose PPV23 vaccination remains most cost-effective in 75-84 year olds, whereas revaccination with PPV23 over single dose PPV23 remains most cost-effective for 65-74 year olds. With a 75% reduction in PPV23 price, the mean ICERs for these strategies become €20 000-€37 000 and €37 000-€48 000 per QALY gained, respectively, depending on the inclusion of an effect on non-invasive pneumonia.

The impact of simultaneous changes in PPV23 price (25%, 50% and 75% price reductions), PPV23 efficacy against IPD (82% (69-90) instead of 56% (40 to 68) in 50-84 year olds) and in the incidence of hospitalised cases (200% of the baseline value) was also explored. It showed that under the assumption that PPV23 offers a protection against non-IPD, either a strong price reduction alone (at least 75%) or a two by two combination of (lower) price reductions with either a higher hospitalisation incidence or a higher vaccine efficacy is sufficient for PPV23 vaccination to be cost-effective at a €35 000 per QALY threshold. However when we assume that PPV23 has no protection against non-IPD, price reductions alone are no longer sufficient and need to be combined with a higher hospitalisation incidence for PPV23 to be cost-effective. The impact of an increased vaccine efficacy on the results is indeed modest compared to the impact of an increased incidence in pneumococcal hospitalisation. Note that the €35 000 WTP threshold was taken from the upper limit of the UK NICE threshold range (£20 000 - £30 000 or €23 000 - €34 800, £1 = €1.16, September the 22nd 2016), as no such value exists in Belgium.

6.3 Budget-impact analyses

The budget-impact of PPV23 and PCV13 vaccination over a 10 year horizon is shown in The budget-impact of PCV13 is more sensitive to price than to

Table **11**, with the assumption that both vaccines have efficacy against non-IPD (main base case). It shows that the avoided treatment costs, benefiting mainly the national health insurer INAMI/RIZIV and patients, are much lower than the required vaccination costs incurred by the funder of preventive vaccination – which are mainly regional governments (Flanders, Wallonia, Brussels) and patients. PPV23 vaccination results in a low (< 10%) return on investment, and net costs (or negative direct net benefits) in excess of €90 million for e.g. the 50-84 year olds.

The budget-impact of introducing PCV13 versus the current situation, using the baseline (retail) price and uptake levels (see Table 9 above) for single dose PCV13 vaccination, shows a worse pattern than for PPV23: avoided treatment costs are much lower than the required vaccination costs, resulting in a worse (< 3%) return on investment, and net costs in excess of €220 million for 50-84 year olds. A shorter 5 year time horizon is also modelled (see Scientific report). There is little difference between the 5 or 10 year time spans because the change in uptake is modelled as having the largest impact in the first year of the new vaccination program.

uptake changes. 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. Naturally, the highest net costs occur for the highest uptake levels.

The budget-impact of PCV13 is more sensitive to price than to uptake changes. 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. Naturally, the highest net costs occur for the highest uptake levels.

Table 11 – Mean vaccination costs, treatment costs avoided, return on investment and direct net benefits over a 10 year periods for improved uptake of PPV23 and PCV13 vaccination versus the current situation

Age group	PPV23				PCV13			
	Avoided treatment costs over 10 years (disc)	Vaccination costs over 10 years (disc)	Return on Investment over 10 years (%)	Direct net benefits over 10 years	Avoided treatment costs over 10 years (disc)	Vaccination costs over 10 years (disc)	Return on Investment over 10 years (%)	Direct net benefits over 10 years
50-64 years	2 635 906	34 767 582	7.6	-32 131 676	2 169 300	75 680 673	2.9	-73 511 373
65-74 years	3 738 451	38 348 749	9.7	-34 610 298	2 876 329	84 319 197	3.4	-81 442 868
75-84 years	3 222 201	31 608 894	10.2	-28 386 693	1 170 738	69 871 409	1.7	-68 700 671
85-105 years	0	10 120 288	0	-10 120 288	0	22 514 983	0	-22 514 983
50-84 years	9 596 559	104 725 226	9.2	-95 128 667	6 216 367	229 871 279	2.7	-223 654 912
50-105 years	9 596 559	114 845,514	8.4	-105 248 955	6 216 367	252 386 261	2.5	-246 169 894

7 DISCUSSION

The analyses presented in this report were complicated due to different levels of uncertainties. There is uncertainty on all aspects that have a major influence on cost-effectiveness: the effectiveness of both PPV23 and PCV13, the price of PCV13, the preventable burden of disease under the influence of the changing infant vaccination programme, and the willingness to pay for a QALY in Belgium. Yet through elaborate literature reviews and uncertainty analyses, we can draw some clear conclusions from these analyses.

The current annual disease burden of pneumococcal disease in adults over 50 years is important, with about 5800 hospitalisations and 3600 additional patients treated in ambulatory care, as well as at about 430 deaths, and 4150 QALYs lost. The associated health care costs for treatment amount to about €33 million.

7.1 Based on cost-effectiveness, if we are to use pneumococcal vaccines, how should we do this?

We found a strong preference for using PPV23 over PCV13 in all age groups at WTP levels below €300 000 per QALY.

On average versus the current situation, high uptake PPV23 vaccination would be about 2 to 6 times more efficient at gaining QALYs than PCV13 vaccination, depending on the age group. 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 €201 000, €171 000 and €338 000, respectively.

The strong preference for PPV23 over PCV13 would only revert when joint changes would occur in variables, i.e. several variables as a single variable change is not sufficient. This would require changes in PCV13 vaccine price, with large, up to 75%, reductions required, in disease burden preventable by PCV13 (e.g. an incidence relapse in serotypes included in PCV13 but not in PCV10), and a longer duration of PCV13 protection than currently estimated from empirical medical evidence. Although a combination of such changes from our baseline assumptions (as yet unproven, and therefore completely hypothetical) could make PCV13 more attractive in age groups under 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-IPD or has some (uncertain) efficacy against it, as measured in observational studies.

Our analyses focused on the average person, running average risks of acquiring symptomatic infection and of experiencing severe disease. If it can be shown that PCV13 protects better in people at medium or high risk of severe pneumococcal disease than PPV23, then a more focused strategy may turn out to be more cost-effective than we could show here for the average person. Additionally, our literature reviews revealed that neither of these vaccines has proven effectiveness for the average person over 84 years.

In view of the above, if we are to use 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 this may be an argument to use PPV23 in this group selectively. If surveillance indicates a rise in serotypes included in PCV13 but not in PCV10, then the choice between PPV23 and PCV13 could be reconsidered for each of the age groups, if at the same time large PCV13 price reductions are feasible.

Combination strategies were generally found to be less attractive than single dose PPV23 vaccination, requiring much greater WTP levels. Revaccination with PPV23 should only be considered if the Belgian policy makers are willing to pay more than at least €100 000 per QALY gained.

7.2 Based on cost-effectiveness, should we use pneumococcal vaccines in all adults ≥50 years at all?

This question 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 assumption of efficacy against non-IPD for both vaccines 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 greater, and the certainty by which PPV23 is cost-effective at a given WTP level, is also more sensitive to the uncertainties we observed throughout our results.

High uptake PPV23 vaccination could even be more cost-effective if its price was reduced to be in line with the prices observed in other countries. With a 75% price reduction of its initial value (€28.46 per dose in 2015), the cost per QALY would drop to €20 000 in the 75-84 year olds.

In addition to cost-effectiveness analyses, our budget-impact analyses also showed that PPV23 requires a much lower investment upfront, and yields a superior return on investment for the health care system compared to PCV13. Still, the return on investment yielded by higher uptake PPV23 use remains modest, at less than 11%, and the additional vaccination costs required to achieve this are high, at over €100 million over a 10 year period.

7.3 Limitations

The main conceptual limitations are that we did not investigate risk group vaccination, for the reasons outlined in the introduction, and that an explicit WTP threshold does not exist in Belgium.[75] A WTP threshold would allow to focus the analyses more and perform threshold analyses on price differentials between PCV13 and PPV23, uncertain elements defining the disease burden, and decision uncertainty for policy makers.

A model limitation is that we ignore herd immunity from vaccinating 25% to 60% of members of age groups >50 years; however we model the herd immunity impact of childhood vaccination on adults. These levels of vaccine uptake, in elderly adults which are not core transmitters of the pathogen, likely lead to only a small underestimation of the benefits of adult PCV13 vaccination versus PPV23 vaccination, and not to the extent that it would change our findings. A dynamic transmission model of both the childhood and adult pneumococcal vaccination programmes would substantially increase the complexity of the analyses as well as the uncertainty of the estimates, since many aspects of pneumococcal transmission and carriage are unquantified.

Also in ambulatory care, only pneumococcal pneumonia is considered (partially) preventable by these vaccines, because we considered the direct vaccine impact on acute otitis media (AOM) negligible in adults. Finally, the analyses are mainly limited by the limitations of the data. The incidence of pneumococcal pneumonia and other aspects of disease burden remain difficult to quantify, and the effectiveness of the vaccines by age and over time against each outcome is highly uncertain. Nonetheless through our extensive sensitivity analyses, we believe that we have made the most of the available data to address the research questions put before us.

7.4 Findings from other economic evaluations

Four published economic analyses on pneumococcal vaccination in other countries used the results of the CAPITA study (search up to March 2016), from England, the Netherlands, Germany and the US.[76-79] The two first ones did not consider PPV23 as a competitor for PCV13, i.e. they only assessed PCV13, as PPV23 was either not an option to prevent pneumococcal disease in the elderly (the Netherlands), or is already implemented (England). Van Hoek et al found that the introduction of PCV13 in the elderly would cost as much as £257 771 per QALY gained, from a health care payer perspective.[79] Relying on the upper limit of the explicit WTP threshold (£35 000 per QALY) set by NICE, this intervention would thus not be considered cost-effective in England. This study has a number of assumptions and methodological choices in common with our study, i.e. waning of vaccine immunity, indirect effect of infant vaccination programme on elderly disease (though no replacement modelled), the use of a health care payer perspective, and it did not consider a target vaccination of risk groups neither.

The Dutch study by Mangen et al, which was sponsored by Pfizer, concluded that PCV13 vaccination (single dose, 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 the group ≥65 years under a societal perspective.[77] The main difference with our study is that Mangen et al focuses 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. 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 so far in the infant programme 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. When Mangen et al focused on vaccinating low risk elderly 65-74 years of age, they found that PCV13 would cost €50 184 per QALY gained versus no vaccination. A major difference with our study is that Mangen costs for hospitalised cases (IPD and CAP) are at least twice higher than the Belgian costs we estimated: costs in Mangen ranged €11 000-€18 000 for IPD versus €1700-€9000 in our study (depending on age group and clinical syndrome) and €6500-€10 500 versus €1700-€5900 for inpatient CAP (depending on age group).

A German economic evaluation found that PPV23 dominates PCV13 vaccination, i.e. one time vaccination with PPV23 prevents more hospitalisations and deaths at lower costs than one-time vaccination with PCV13.[76] The cost per QALY of PPV23 vaccination was much lower than in our study, ranging €14 400 – 15 700 depending on age at vaccination. Based on that, the German Standing Committee on Vaccination recommends routine vaccination with PPV23 for all adults from the age of 60 years.

The difference with all previous analyses, is that we use a multi-cohort approach informed by demographic data, with full age dependence and waning over time of vaccine efficacy according to age in years, include the possibility of a relapse of PCV13 serotypes, compare more strategies and explore many more aspects of the uncertainty. In comparison with the Blommaert et al explorative analysis for Belgium,[80] we use the most up to date Belgian and international data after careful literature review, a different approach to estimating the incidence of hospitalisations, made more aspects of the analysis age dependent and perform many more scenario and uncertainty analyses.

8 CONCLUSIONS

Our analyses show that vaccination with both vaccines can decrease the number of outpatient episodes, hospital admissions and deaths due to pneumococcal disease in the elderly. PPV23 vaccination of 50% of the 65-74 year-olds and 60% of the 75-84 year-olds could prevent, over their remaining lifetime, 812 hospitalisations and 80 deaths compared to the current situation, while PCV13 vaccination with the same uptake would prevent 524 hospitalisations and 43 deaths. PCV13 would however prevent more hospitalisations and deaths than PPV23 if we assume that the latter does not protect against non-invasive pneumonia. There is currently too much uncertainty as to the level of protection against non-invasive pneumonia by PPV23 to state that the protection of one vaccine is superior to the other.

Vaccination with PPV23 was found to be more cost-effective than PCV13 in all age groups at WTP levels below €300 000 per QALY. The higher attractiveness of PPV23 over PCV13 would only revert under a combination of a large reduction of PCV13 vaccine price (up to 75%), an increase in disease burden preventable by PCV13 (but not by PCV10 e.g. if the PCV10 infant vaccination would cause a rise in non-vaccine serotypes by serotype replacement), and a longer duration of PCV13 protection than currently estimated. These changes would however be highly hypothetical.

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. These values lie usually above those of (mostly childhood) vaccine interventions that have been funded or reimbursed in the past, but also below those of a range of curative interventions in the adults >50 years that have been funded, and below other interventions that have not been funded, such as hepatitis A vaccination in adults.[81] Note further that decisions on the reimbursement (or not) of a new intervention do not solely rely on its cost-effectiveness and that many other aspects are considered (such as ethical, clinical, budget-impact etc). However there is no willingness-to-pay threshold defined in Belgium for the cost-effectiveness criteria to decide on the introduction of health interventions.[75] Only NICE (National Institute for Health and Clinical Excellence) has explicitly mentioned threshold values of £20 000 and £30 000 per QALY for their decision making (this corresponds to roughly €23 000 and €34 800, £1 = €1.16, September the 22nd 2016). If NICE's threshold values were applied to the results of our analyses, PPV23 vaccination would not be cost-effective in the base case described above. Lower costs per QALY, i.e. <€30 000 per QALY for PPV23 vaccination of the 65-84 years, were obtained if the incidence of pneumococcal pneumonia hospitalisations would double and/or the PPV23 price would decrease to reach the prices in force in other countries.

PCV13 options would present a significantly higher cost per QALY gained at about €201 000, €171 000 and €338 000, respectively, in the same age groups. Combination strategies of PPV23 and PCV13 vaccines were generally less cost-effective than the administration of a single vaccine, by preventing a modest number of hospitalisations and deaths with higher costs per QALY gained: for instance, adding PCV13 to PPV23 would prevent 89 hospitalisations and 12 deaths in the 75-84 years of age for a cost of €688 500 per QALY gained.

The budget-impact of both vaccines is high (even more for PCV13) as the avoided treatment costs are much lower than the vaccination costs. In the 75-84 year olds, the net costs (i.e. the avoided treatment costs minus the vaccination costs) rise up to €28 and €68 million for PPV23 and PCV13, respectively, over a 10-year period. Net costs for other age groups are even higher.

The decision to increase PPV23 use (e.g. through reimbursement) and/or to combine PCV13 and PPV23 would thus depend on the willingness-to-pay of decision makers and on potential price reductions in Belgium. In any case, it is essential to monitor the incidence and pneumococcal serotypes over time to detect any change in the epidemiology that would put into question the conclusions from the present study. Currently the serotype is not determined in pneumococcal cases in Belgium (only the serogroup is determined), though this is crucial information.

Clinicians should be aware that the spectrum covered by PCV13 serotypes in adults is much smaller than for PPV23, and continues to decline under the influence of infant PCV vaccination. If PCV13 is administered (although this does not appear to be the most cost-effective option), a better clinical protection is offered if it is followed by PPV23 as it would protect against the additional serotypes (representing today 42% of all invasive disease).

RECOMMENDATIONS

In adults 50-84 years of age, both PPV23 and PCV13 vaccines decrease the number of outpatient episodes, hospital admissions and deaths due to pneumococcal disease caused by the serotypes they cover. Since PPV23 covers more serotypes, but exerts more uncertain protection against non-invasive pneumococcal pneumonia, neither vaccine is superior to the other.

To the federal (INAMI/RIZIV) and federated authorities competent in the field of vaccination:

- **Under most assumptions and hypotheses tested in this study, PPV23 is more cost-effective than PCV13. This is also valid when we assume no PPV23 protection against non-invasive pneumonia.**
- **An increase of PPV23 uptake in the 75-84 year-olds would be the most cost-effective intervention, whether or not we assume that PPV23 protects against non-invasive pneumonia. At the current PPV23 price, the incremental cost per QALY gained (ICER) would be €52 000 with or €85 000 without assuming PPV23 protection against non-invasive pneumonia. At a PPV23 price reduced by 75%, the cost per QALY would drop to €20 000 with or €37 000 without assuming PPV23 protection against non-invasive pneumonia.**
- **A combination of PPV23 and PCV13 vaccines is less cost-effective than the administration of a single vaccine. In particular, compared to PPV23 alone, the addition of PCV13 would only prevent a modest number of additional hospitalisations and deaths, at a cost per QALY exceeding €200 000.**
- **PCV13 would only be more cost-effective than PPV23 under the assumptions of:**
  - **a drastic price reduction (≧75%), and**
  - **a markedly longer duration of PCV13 protection than currently established , and**
  - **an increase in the proportion of pneumococcal cases caused by PCV13 serotypes.**
- **The incidence and serotypes of pneumococcal disease in the elderly should be determined and monitored, to detect any change in the epidemiology that would put into question the conclusions from the present study.**

To the clinicians:

The current spectrum of pneumococcal serotypes covered in adults is much smaller for PCV13 than for PPV23, and continues to decline under the influence of infant PCV vaccination. The 11 serotypes that are covered by PPV23 but not by PCV13 represent today 42% of invasive disease and 24% of non-invasive pneumonia. If PCV13 is administered, it should be followed by PPV23 (after at least 8 weeks) to protect against these additional serotypes.

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COLOPHON

Title:	Use of pneumococcal vaccines in the elderly: an economic evaluation – Short report
Authors:	Adriaan Blommaert (UA), Germaine Hanquet (KCE), Lander Willem (UA), Heidi Theeten (UA), Nancy Thiry (KCE), Joke Bilcke (UA), Jan Verhaegen (UZ KULeuven), Philippe Beutels (UA)
Project coordinator:	Marijke Eyssen (KCE)
Reviewers:	Hans Van Brabandt (KCE), Erik Hendrickx (KCE)
External experts:	Nele Berthels (FAGG – AFMPS), Toon Braeye (WIV – ISP), Daniel Brasseur (Hopital Universitaire des Enfants Reine Fabiola), Joel Daems (RIZIV – INAMI), Barbara Michiels (Universiteit Antwerpen), Beatrice Swennen (ULB), Geert Top (VAZG), Nathalie Van de Vyver (Domus Medica), Koen Van Herck (Ugent), Yves Van Laethem (ULB)
External validators:	Pierre Chevalier (ex-INAMI – RIZIV), Alain Van Meerhaeghe (CHU - Charleroi), Philippe De Wals (Département de médecine sociale et préventive, Université de Laval, Canada)
Acknowledgements:	We thank Carl Devos (KCE), Stephan Devriese (KCE), Erik Hendrickx (KCE), Marijke Eyssen (KCE), Cécile Dubois (KCE), Karin Rondia (KCE) and Gudrun Briat (KCE) for their contribution to data collection, analysis or report revision. 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 Dr Raymond Oppong, Prof Joanna Coast (University of Birmingham) and Prof Herman Goossens (Laboratory of Medical Microbiology, Vaccine & Infectious Disease Institute, University of Antwerp) 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 Prof Gérard de Pouvourville (ESSEC) for giving access to unpublished data on Quality of Life in pneumococcal patients in France. We 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. Dr Lander Willem is supported by the FWO, project G043815N. Prof Joke Bilcke is supported by a postdoctoral grant from the FWO.
Other reported interests:	A university chair in Philippe Beutels’ centre 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 report. Heidi Theeten conducts a research study on carriership of pneumococcus in Belgium (2016-2019), a study which is 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. Yves Van Laethem is president of the Groupe Vaccination of the Conseil Supérieur de la Santé. Philippe De Wals is a member of the « Comité sur l’Immunisation du Québec » and of the National Advisory Committee on Immunization from Canada. He has been principal investigator of an economic evaluation on anti-pneumococcal vaccines funded by the Public Health Agency of Canada, and he further is affiliated to research centres that received grants from pharmaceutical compagnies to perform studies on anti-pneumococcal vaccines (Pfizer and GSK).

Coverpicture:	Left: Centers for Disease Control and Prevention (CDC), Atlanta, USA : http://www.cdc.gov/media/dpk/2013/dpk-untreatable.html
Layout:	Ine Verhulst
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Publication date:	27 October 2016
Domain:	Health Technology Assessment (HTA)
MeSH:	Pneumococcal Infections; Pneumococcal vaccines; Cost-Benefit analysis;
NLM Classification:	WC 204
Language:	English
Format:	Adobe® PDF™ (A4)
Legal depot:	D/2016/10.273/78
ISSN:	2466-6459
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How to refer to this document?	Blommaert A, Hanquet G, Willem L, Theeten H, Thiry N, Bilcke J, Verhaegen J, Beutels P. Use of pneumococcal vaccines in the elderly: an economic evaluation – Synthesis. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2016. KCE Reports 274Cs. D/2016/10.273/78. This document is available on the website of the Belgian Health Care Knowledge Centre.