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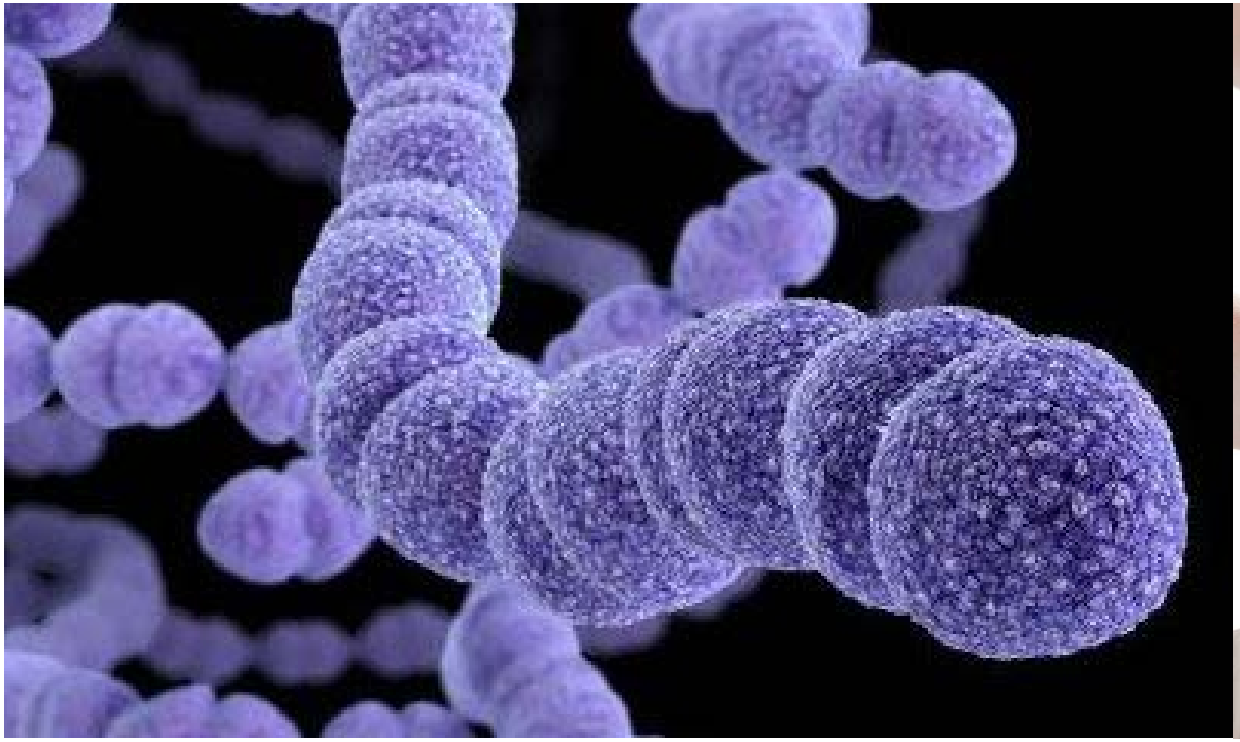
Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Center

USE OF PNEUMOCOCCAL VACCINES IN THE ELDERLY: AN ECONOMIC EVALUATION



KCE REPORT 274
HEALTH TECHNOLOGY ASSESSMENT

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
95%CI	95% confidence interval
BP	Bacteraemic pneumonia
BAL	Bronchoalveolar lavage
CAP	Community acquired pneumonia
CEA	Cost-effectiveness analysis
CEAF	Cost-effectiveness acceptability frontiers
CFR	Case fatality ratio
CSF	Cerebrospinal fluid
CUA	Cost-utility analysis
EMA	European Medicines Agency
EQ-5D	EuroQol 5 dimensions
HRQoL	Health-related quality of life
HUI	Health utilities index
ICER	Incremental cost-effectiveness ratio
INAMI/RIZIV	Rijksinstituut voor ziekte- en invaliditeitsverzekering /Institut national d'assurance maladie-invalidité
IP	In-patient
IPD	Invasive pneumococcal disease
non-IPD	Non-invasive pneumococcal disease
MZG/RHM	Minimale Ziekenhuis Gegevens / Résumés Hospitaliers Minimum
(m)ITT	Modified intention-to-treat analysis
NBP	Non-bacteraemic pneumonia
NRC	National Reference Centre
PCV10	10-valent Pneumococcal conjugate vaccine

PCV13	13-valent pneumococcal conjugate vaccine
PCV7	7-valent pneumococcal conjugate vaccine
PP	Per protocol
PPV23	23-valent polysaccharide pneumococcal vaccine
PSA	Probabilistic Sensitivity Analysis
QALY	Quality adjusted life years
QoL	Quality of life
SD	Standard deviation
SE	Standard error
SF-12	Short-form 12
SF-36	Short-form 36
SF-6D	Short-form 6 dimensions
SG	Standard gamble
TTO	Time trade-off
UAT	Urine antigen test
VAE	Vaccine adverse event
VAS	Visual analogue scale
VE	Vaccine efficacy or effectiveness
WTP	Willingness-to-pay

SCIENTIFIC REPORT

1 INTRODUCTION

1.1 Pneumococcal disease in the elderly

More than 90 serotypes of the bacterial pathogen *Streptococcus pneumoniae* (*S. pneumoniae or "pneumococcus")* are known, and are distinguished by their unique polysaccharide capsule.

S. pneumoniae causes the highest burden in elderly persons, in terms of morbidity and mortality. The most severe form of pneumococcal disease, invasive pneumococcal disease (IPD), is responsible for meningitis and septicaemia, as well as an important part of community-acquired pneumonia (CAP) cases, so-called invasive CAP. IPD incidence ranges 10-60 per 100 000 in persons aged ≥65 years in European countries.[1-4] Additionally, *S. pneumoniae* causes non-invasive CAP, which is three times more frequent than invasive CAP in adult patients hospitalised for pneumonia.[5] Altogether, *S. pneumoniae* is the most frequent cause of CAP in adults, with around 20% of all adult CAP cases caused by this pathogen in Europe.[5-8] The mortality due to *S. pneumoniae* is also substantial in this age group. Recent EU studies indicate that in elderly patients, IPD and pneumococcal pneumonia lead to death (during a period of 30 days post diagnosis) in around 20% and 10% of cases, respectively.[4, 9-13]

In Belgium, the incidence of IPD was estimated at 30 per 100 000 inhabitants among adults >50 years in a Belgian multicentre study in 2009-10, after correction by capture-recapture analysis.[14] The mean duration of hospitalization for IPD was 21 days, Intensive Care Unit admission was required for 31% of patients, 19% of patients died and 14% had sequelae.[4] In those aged ≥75 years, case fatality of IPD amounted to 30%.

1.2 Pneumococcal vaccination of the elderly

1.2.1 Pneumococcal vaccines

Two pneumococcal vaccines are now indicated for all elderly ≥65 years and for other adults with chronic conditions in Belgium (Table 1).

1. A 23-valent polysaccharide vaccine or **PPV23** (currently Pneumovax 23, Sanofi Pasteur MSD) is licensed in Belgium since 1995 for the

prevention of pneumococcal infections due to vaccine serotypes in persons ≥2 years of age presenting with an increased risk of mortality and severe morbidity due to pneumococcal infections. The current recommendation of the Superior Heath Council (CSS/HGR) includes the use of PPV23 for this risk group.[15] PPV23 covers a high proportion of pneumococcal serotypes causing IPD in the elderly ≥65 years of age (80% of all IPD in 2009-11),[4] and has shown a moderate efficacy against IPD (around 50-75%) but inconclusive efficacy against non-bacteraemic pneumococcal pneumonia and the protective efficacy is short lived (boosters are recommended every 5 years).[16-18] Despite being recommended by the CSS/HGR for all elderly ≥65 years of age in Belgium since the nineties, PPV23 uptake has always been low in this group and decreased from an estimated 16% in 2004 to 10% in 2013.[19] Possible explanations for this low uptake are that the vaccine is not reimbursed, the Flemish association of General Practitioners recommended it for elderly at higher risk only, and many clinicians do not believe in PPV23 due to its limited duration of efficacy, and its unclear efficacy against (non-bactaeremic) CAP.[20]

2. A pneumococcal conjugate 13-valent vaccine or **PCV13** (Prevenar 13, Pfizer) was approved in adults by the European Commission for the prevention of IPD in October 2011 and for the prevention of pneumococcal CAP in March 2015.[21] In the CAPITA trial, PCV13 showed a moderate vaccine efficacy against IPD and pneumococcal CAP due to any serotype in the elderly, at 49% (95%CI 21-67) and 22% (95%CI 2-39, mITT analysis), respectively.[22] The proportion of disease that is covered by the vaccine serotypes in those ≥65 years of age is lower compared to PPV23 (60% of all IPD in 2009-11),[4] and decreased over time due to an indirect effect of the infant PCV vaccination since 2007 on vaccine serotypes (see below).

None of these two vaccines are reimbursed in Belgium. However, Pfizer submitted recently a request for PCV13 reimbursement to the INAMI/RIZIV (see below).

There are no studies comparing the direct effect on clinical disease of both vaccines, but conjugate vaccines are considered to elicit a superior immune response when compared with PPV23.[22, 23] Indeed, the immune responses in terms of OPA (opsonophagocytic activity) geometric mean titres induced by PCV13 in subjects 60–64 year-old one month post-vaccination were statistically significantly higher than in the PPSV23 group for 8 of the 12 serotypes common to both vaccines.[24, 25] However, the clinical implication of this difference in immune response is unknown (see section 4.1);[23, 24] indeed, there is no established correlate of protection against pneumococcal disease after either PPV23 or PCV in adults.[21]

1.2.2 Belgian recommendations

Between 1993 and 2013, the CSS/HGR recommended to administer PPV23 to all elderly above 60 years of age, with or without underlying disease.[26] In 2013, it recommended to use either PPV23 or PCV13 followed by PPV23 (after 8 weeks minimum) in all elderly 65-75 years of age, with a unique PPV23 revaccination after 5 years; for persons above 75 years of age, either PCV13 or PPV23 was proposed according to the clinical profile of the subject. In 2014 shortly after the CAPITA study results emerged, the CSS/HGR adapted again its recommendations with a primary vaccination with PCV13 followed by PPV23 after 8 weeks minimum for all adults 65-85 years of age (Table 1).[27] The need for booster doses with both vaccines was not defined, in line with the PCV13 manufacturer posology.[a] Due to a lack of efficacy data in subjects above 85 years, pneumococcal vaccination in this group was proposed on an individual basis only. However, these recommendations were based on clinical information and a number of assumptions, and it is unclear whether and when re-vaccination is warranted, and with which vaccine.

[a] Prevenar 13 EPAR: the need for revaccination with a subsequent dose of Prevenar 13 has not been established.

Table 1 – 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
Pneumococcal serotype coverage in Belgium in ≥65 years of age, last estimates for 2015 (based on NRC, see Table 13)	66% of all IPD	25% of all IPD
Retail price in Belgium in 2016[28]	€31.93 per dose[b]	€74.55 per dose
Recommended schedule in Belgium (CSS, 2014)[27]	*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:* • There is currently limited data on the effect of pneumococcal vaccination above 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).	

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

1.2.3 Economic and ethical implications

The 2014 CSS/HGR recommendation to vaccinate all adults 65-85 years of age with PCV13 followed by PPV23, regardless of their health status, involves a total of 1 703 600 eligible Belgians of this age.[27] If 60% of this group would be vaccinated (value of influenza vaccination uptake in this group in 2013), their vaccination would cost more than 105 millions euros in terms of vaccine cost only, at the retail price.[28] If only a cohort of one year of age (e.g. all persons of 65 years of age) would be vaccinated at an uptake of 60%, this would still represent an annual cost of €7 790 700.

Pfizer, the PCV13 manufacturer, has submitted a request for PCV13 reimbursement to the INAMI/RIZIV at the end of 2015. The CSS/HGR recommendation and the INAMI/RIZIV decision on reimbursement may therefore have substantial economic implications for the health care budget and/or on the target group themselves.

The current situation without reimbursement, also raises inequity issues: part of the cost for the vaccine is paid for through complementary private insurance organised by the sickness funds (an amount of around €25). This covers most of the cost of PPV23 (€28.40 per dose), but PCV13 is around three times more expensive (€77.55, Table 1). The total cost of both vaccines would thus be €103 per person. In England and Wales, where PPV23 was introduced and funded from August 2003 to August 2005 in a step-wise manner, the uptake among those ≥65 years of age increased from about 30% to 75%.[29]

1.3 Indirect effect from infant vaccination

In the European Union (EU), pneumococcal conjugate vaccines covering the 7, 10 and 13 serotypes that most frequently cause IPD (PCV7, PCV10 and PCV13, respectively) in infants from industrialised countries were licensed in 2001 (PCV7) and in 2009 (PCV10 and PCV13), and were progressively introduced in the universal childhood vaccination schedule of most EU countries since 2004. Among 29 European countries included in a 2013 ECDC survey, 22 (76%) had replaced PCV7 by PCV13 and 16 (55%) had introduced PCV10. In Belgium, PCV7 was available in pharmacies in 2004, included in the infant vaccine schedule in 2007 and replaced by PCV13 in 2012. PCV13 is being replaced by PCV10 in the Flemish Community since July 2015 and in the Fédération Wallonie – Bruxelles since May 2016.[28]

Widespread PCV vaccination, implemented at high uptake, provides an indirect effect on non-vaccinated subjects, including the elderly, through a reduction of *S. pneumoniae* carriage and transmission. The indirect effect on the elderly has been well demonstrated for PCV7 vaccination,[30, 31] but the decline in pneumococcal infections due to PCV7 types has been partly countered by increases in infections due to non-PCV7 types, i.e. so-called "vaccine-induced serotype replacement". A few studies also documented the indirect effect of infant PCV10 or PCV13 on the elderly after more than two years of widespread vaccination (see 3. Indirect effect of infant PCV vaccination on adult disease).[32-35] This indirect effect is crucial when estimating the additional benefits of using and funding PCV13 in the elderly, as it may decrease the preventable fraction of IPD and CAP disease due to PCV13 serotypes.[23] In other words, decisions on which pneumococcal vaccine and which schedule should be preferred when vaccinating the elderly partly depends on the added value of its direct effect in the elderly compared to the ongoing indirect effects of the infant PCV10/13 vaccination on the elderly exposure to *S. pneumoniae.*

1.4 Research questions

The research presented in this report evolves around an economic evaluation of options for pneumococcal vaccination in different age groups >50 years.

The costs and benefits of different vaccination strategies are compared with the "current" (2013) strategy i.e. vaccinating a low proportion of the elderly with PPV23 only. These vaccination strategies involve the administration of PPV23 alone, PCV13 alone, as well as options combining the two vaccines at different uptake levels (ranging 20-60%), as described in Table 39. These comparisons also imply estimating the current disease burden.

The aims of the study are to help decision making at the INAMI/RIZIV on the PCV13 request for reimbursement (although introduced after we started this study), at the level of Community decision makers in charge of vaccine programmes, and for clinicians.

This report does not incorporate specific risk group vaccination strategies due to the lack of data in this group and the feasibility of vaccination in the Belgian context. First, there are no data on the PCV13 efficacy in persons with unstable co-morbidities or who are immunocompromised. Second, there are no data on the numbers of persons with higher risk for pneumococcal disease in Belgium. Third, 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 - that are similar for risk and non-risk groups of this age.

Three main research questions are included in this evaluation:

1. What is the clinical impact of the vaccination strategies in terms of:
    - Incremental number of hospitalizations, outpatient cases[c], fatalities and long term sequelae due to pneumococcal disease
    - Incremental number of cases and deaths from the clinical categories of pneumococcal disease, such as IPD and non-IPD cases, distinguishing where data availability allows between hospitalised and non-hospitalised patients.
2. What is the cost-effectiveness of the vaccination strategies compared incrementally to each other (using an efficiency frontier approach)
3. What is the budget impact of the vaccination strategies

The same research questions are addressed as well for an age category younger than the target age of the HGR/CSS (≥65 years), i.e. adults from 50 to 64 years of age. The three research questions are analysed separately per age group because of strong age dependency in main input parameters such as case fatality ratios, vaccine efficacy and remaining life expectancies.

In terms of clinical categories in the elderly, IPD refers mainly to meningitis, septicaemia and pneumonia with bacteraemia and non-IPD refers to pneumonia without bacteraemia. In contrast to childhood vaccination, sinusitis and otitis media are not considered, because they occur infrequently in adults and the severity they represent (with morbidity and mortality being quantified in this analysis through the loss of quality adjusted life years (QALY)) is very small. This makes them unlikely to contribute significantly in a cost-effectiveness analysis of adult pneumococcal vaccination.

A health care payer perspective will be applied. The way the vaccine is paid (i.e. partially reimbursed by RIZIV/INAMI, limited reimbursement by mutualities or not funded) has no impact on the cost-effectiveness results as the perspectives of all health care payers are combined. However, a higher vaccine uptake is expected in case of reimbursement, and therefore pragmatic scenarios with stepwise lower vaccine prices (e.g. through tenders) and higher uptake are also considered (scenarios with higher uptake will not change the incremental cost-effectiveness ratios but may change the impact on clinical and cost outcomes separately, and thus also the budget-impact analyses). Potential indirect effects exhibited by elderly vaccination are not considered in this study as carriage of *S. pneumoniae* in this group is considered negligible for the transmission dynamics of this pathogen, implying that a static model can be used.[36-38] However, indirect effects of infant PCV vaccination on disease in the elderly are considered.

[c] 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.

2 BURDEN OF PNEUMOCOCCAL DISEASE IN THE ELDERLY

Pneumococcal disease can be divided into invasive pneumococcal disease (IPD) and non-invasive disease (non-IPD). IPD is the most severe form and is defined on laboratory grounds as the isolation or detection of *Streptococcus pneumoniae* from a normally sterile site.[39] In adults, IPD mostly present as invasive pneumococcal pneumonia, meningitis or septicaemia, and can lead to septic shock. Studies from other settings have shown that the majority of IPD are hospitalised. In this study, we assumed that all IPD cases are hospitalised in the Belgian health care system.

In the elderly, non-invasive diseases include community-acquired pneumonia (CAP), in which *S. pneumoniae* is not isolated nor detected in normally sterile fluids but detected or isolated in sputum, broncho-alveolar lavage or urine. As indicated above, other non-invasive diseases such as sinusitis and otitis media are not considered in this study.

Pneumococcal CAP may thus be invasive or not. We assumed that all invasive CAP will be hospitalised. Non-invasive CAP may be hospitalised or may be only seen in an outpatient visit, depending on severity, co-morbidities, age etc.

Pneumococcal serotypes are distinguished by their polysaccharide capsule. All the current pneumococcal vaccines target specific serotypes and the distribution of pneumococcal serotypes changed markedly after the introduction of universal infant vaccination.

This chapter describes the current epidemiology and evolution of pneumococcal disease and the distribution of pneumococcal serotypes. The next sections describe the estimates for hospitalisations, outpatient visits, deaths, sequelae, health utilities and costs for pneumococcal disease in Belgium. Data on pneumococcal burden are based on Belgian sources when available or on literature review from studies in similar settings when Belgian data were not found.

2.1 Incidence of pneumococcal disease

2.1.1 Hospitalised invasive pneumococcal disease

The incidence of IPD by age has been estimated based on the number of strains and samples sent to the Belgian National Reference Centre (NRC) in the latest available year (2015). These numbers have been corrected for the under-reporting of the NRC estimated by a capture-recapture analysis (2 sources) on 2009-11 data, and incidence have been calculated using age- and year-specific population data as denominator. The NRC receives isolates from a stable number of around 100 hospital laboratories distributed all over the country, and performs typing and antibiotic sensitivity testing. Table 2 describes the IPD incidence of IPD cases aged >18 years (i.e. sample taken from otherwise sterile fluid) in 2015. IPD incidence rates increased with age, from about 5 per 100 000 in young adults (18-49 years) to 80 per 100 000 in those ≥85 years of age.[14] The incidence of IPD clinical syndromes has been estimated based on the distribution of these syndromes by age group in a Belgian prospective study conducted in 2009-11 (Table 2).[4] Pneumonia, including empyema, and meningitis represented 75-81% and 3-9% of all IPD, respectively. In the Belgian setting, blood cultures and other invasive bacteriological examinations are mostly performed in hospitalised patents, and very rarely for outpatients. We thus assumed that all these IPD cases were hospitalised.

Note that a two-source capture-recapture analysis, based on dependent sources, tends to underestimate incidence; the dependence between the sources in that study was not assessed but we also applied a higher IPD incidence in the sensitivity analyses of this study.[14]

Table 2 – Incidence of invasive pneumococcal disease per 100 000 inhabitants in Belgium, 2015 NRC data corrected for underreporting

Age group / diagnosis	Meningitis	Invasive pneumonia	Others IPD*	Total IPD
18-49 years†	0.2	4.0	0.4	4.6
50-64 years	1.3	12.4	1.2	14.9
65-74 years	1.1	22.1	2.2	25.5
75-84 years	1.6	32.0	3.2	36.8
≥ 85 years	3.6	69.6	7.0	80.2

*NRC: National Reference Centre; IPD: Invasive pneumococcal disease. *: bacteraemia without focus, septicaemia, septic arthritis, peritonitis etc. †: data on the 18-49 years provided for information but not included in the model.*

Alternatively, the MZG/RHM database contains information on hospitalisations for which diagnostic codes refer to pneumococcal disease. The incidence of cases hospitalised with pneumococcal disease, by code, in the last available year (2013) is shown in Table 3 (for earlier years, see previous KCE reports).

Table 3 – Age-specific hospitalisations rate per 100 000 population for Pneumococcal Disease related ICD9 codes in MZG/RHM (Belgium 2013, first or secondary diagnostic field)

Age group / diagnosis	Pneumococcal meningitis ICD9 320.1	Pneumococcal pneumonia ICD9 481	Pneumococcal septicaemia ICD9 038.2
18-64 years	0.7	13.8	4.4
65-74 years	1.6	41.9	15.0
75-84 years	1.3	60.8	19.8
≥ 85 years	0.0	88.2	43.6

†: data on the 18-49 years provided for information but not included in the model.

By definition, pneumococcal meningitis and septicaemia are IPD. However, hospitalised pneumococcal pneumonia may be invasive or not. We expect that the hospitalisations coded as pneumococcal pneumonia (ICD9 481) contains a large proportion of invasive pneumococcal pneumonia, as the determination of the pneumococcal aetiology is mostly done by culture of blood or pleural sterile fluid in the Belgian setting. However, as this proportion is unknown and coding by hospitals is not done for surveillance purposes, we opted for this study to use the NRC data to derive the incidence of the different IPD syndromes, including invasive pneumococcal pneumonia.

2.1.2 Hospitalised non-invasive pneumococcal disease

As only scarce data are available on non-invasive CAP in Belgium, we searched for the proportion of all hospitalised pneumococcal CAP that are non-invasive in studies from similar settings (Europe or North America). Studies differed in their definition of pneumonia: a number of studies distinguish *invasive* (i.e. *S. pneumoniae* isolated or detected in a normally sterile fluid) and *non-invasive* pneumonia, while other studies distinguish *bacteraemic* (i.e. isolation from blood) and *non-bacteraemic* (no isolation from blood) pneumonia. A difference is that non-bacteraemic pneumonia may still be invasive pneumonia if *S. pneumoniae* is isolated from the pleural fluid. Some studies classified as non-bacteraemic pneumonia those cases in which no blood culture was performed, while they could still be invasive (based on other sterile fluid). Only some of these studies assessed the assumption that cases with and without missing blood cultures have the same baseline characteristics.

A meta-analysis estimated the proportion of pneumococcal pneumonia that is bacteraemic, based on studies from all countries published till June 2010.[5] Although the proportion of hospitalised cases is not provided, the review states that the majority of included studies were prospective studies among hospitalised cases. Similar search strings were used to update the literature search, using selection criteria described in Appendix 1.2, and additional references were found in the bibliography of screened papers.

The 2013 meta-analysis included 28 studies and reported a pooled estimate of 25% (range 2.2-50.9%) hospitalised CAP that were bacteraemic. This proportion varied by diagnostic test: the Binax urine test increased the

diagnostic yield over culture by an additional 11.4% or by 0.87 additional cases for every case detected by blood or sputum culture. Most studies did not conduct all tests on all cases, and some of them tested a low proportion of cases by Binax test. The proportion of bacteraemic pneumonia was higher in more severe disease.[5]

Six studies published after 2010 and involving a comprehensive recruitment of all CAP (not only based on positive laboratory results) were retrieved (Table 60).[40-45] Four studies involved adults of all ages and two were restricted to older adults (≥50 years) but the mean age was fairly similar at around 65 years. Five studies diagnosed non-invasive or non-bacteraemic CAP based on urine assay and/or culture of airway sample (sputum, broncho-alveolar lavage) and one was limited to culture of airway sample.[40]

The proportion of non-bacteraemic CAP ranged 59-88% in these studies, with a pooled estimate of 75% (similar using inverse variance-weighted proportion, fixed or random effect). The lowest proportion (59%) was found in the study not using urine assay for detecting non-invasive CAP,[40] which is in line with the higher diagnostic yield of the Binax urine assay (see above).[5] A multicentre European study also found a lower proportion of non-bacteraemic pneumonia, at 68%, but it involved more severe cases (requiring intravenous antimicrobials) and only 35% of CAP cases were tested by urine assay.[45] When studies performing urine assay/test in <80% of CAP cases were excluded,[40, 45] the pooled estimate based on four studies increased to 82.7% (95%CI 80-86) using inverse variance-weighted proportion assuming a fixed effect (or 81.5% (95%CI 73-90) using random effect).[41-44] No recent study provided data by age.

The difference in case characteristics between non-bacteraemic and non-invasive CAP is limited because only few pleural fluids were included in non-bacteraemic cases in these studies. One Dutch study recruited patients on the basis of laboratory results under clinical practice, i.e. all blood cultures growing S. pneumoniae and all positive pneumococcal UAT (BinaxNOW®), and was thus not included as the patient population of invasive and non-invasive could not be compared because it depended on test practices.[13] A number of other studies were too small to be included.

In conclusion, as no single study is more likely to represent the Belgian epidemiology better than others, the pooled estimate from four recent studies of higher quality, i.e. using urine assay/test to detect non-bacteraemic cases in >80% of CAP cases, is proposed. We thus assume that 82.7% of inpatient pneumococcal CAP are non-invasive. This estimate is used further to derive the incidence of non-invasive pneumococcal CAP from invasive pneumococcal CAP (see input parameter section).

Key points

- **Based on the pooled estimate of four studies of higher quality, the proportion of hospitalised adult pneumococcal CAP that is non-invasive in settings similar to Belgium is estimated at 82.7% (95%CI 80-86 fixed effect).**

2.1.3 Outpatient non-invasive pneumococcal disease

2.1.3.1 Estimates of all-cause outpatient pneumonia incidence

Outpatient pneumonia cases were identified in the Intego data using code R81 (pneumonia). We estimated the outpatient pneumonia incidence per age group by dividing numbers of cases in 2013 per age group by the total practice population of general practitioners included in the Intego-project. Outpatient pneumonia incidences increase with increasing age, from 6 per 1000 in 50-54 years to 15 per 1000 in those ≥85 years (Table 4). Comparing these incidences over time suggests that childhood pneumococcal vaccination did not translate so far into a decreasing trend in outpatient pneumonia incidence for patients above 50 years of age.

Table 4 – Incidence of outpatient all-cause pneumonia in 2013 per 1000 persons, Intego (R81 codes)

Age group	Cases (2013)	Denominator (Practice population 2013)	Incidence per 1000
50-64 years	159	26 555	6.0
65-74 years	75	11 157	6.7
75-84 years	84	8325	10.1
≥85 years	63	4187	15.0
Total	381	50 224	7.6

The estimated practice population is used as denominator.

Since classified bronchitis cases (code R78: bronchitis and bronchiolitis) in the Intego-database might contain a proportion of misclassified pneumonia cases, we investigate data on bronchitis incidence. When compared to the GRACE study (personal communication, Oppong),[46] the ratio pneumonia/bronchitis was similar, at around 12%, suggesting no major misclassification of pneumonia cases.

2.1.3.2 Proportion of outpatient CAP due to pneumococcal disease

The majority of outpatient CAP in Belgium have no etiological diagnosis, and no data are therefore available from the NRC on this outcome. We searched the literature for original studies and reviews on the proportion of outpatient CAP attributable to pneumococcus. We focused our search on high income (mostly European, excluding the US) country settings, published after 1999 and containing data on (elderly) adults. Details of this review can be found in Appendix 1.

A 2013 systematic review estimated the proportion of CAP attributable to pneumococcus at 27.3% (95% CI: 23.9%, 31.1%), mostly in high income countries, but the majority of included studies involved hospitalized cases.[5] A 2012 systematic review included European studies published in 1990-2007 and involved subjects ≥18 years of age.[7] The pooled proportion of pneumococcal pneumonia among all outpatient CAP with aetiology determined was calculated at 38% (compared to 27% in hospitalized cases), based on the "percentage mean" (not weighted) from the included studies. However, the inclusion criteria and calculation method in Welte et al were unclear and most of these studies were published before 2000. Among the included studies in both meta-analyses, we selected those published from 2000 onwards and updated the literature search (Appendix 1) to retrieve five studies for closer inspection (see Table 6).[11, 47 48-50]

Four studies were conducted in Spain and one in Denmark (Table 5). Two studies recruited outpatient CAP at primary health care centres (PHC) only, two studies recruited patients at PHC and emergency wards, and one study included patients initially examined at a hospital emergency ward. Four studies involved adults from all ages (mean age ranging 47-61 years) and one only involved elderly ≥65 years. The studies used different denominators to calculate the proportion of pneumococcal outpatient CAP : all outpatient CAP cases, only tested outpatient CAP cases or only outpatient CAP cases with aetiology determined (thus excluding cases in which no pathogen was identified). Not all studies included viral aetiologies and atypical bacteria (mycoplasma and chlamydia). In order to account for aetiologies that are more difficult to detect, we defined here the proportion of pneumococcal CAP as the proportion of all *tested* CAP that were diagnosed with *S. pneumoniae*.

These studies involved together 1146 tested outpatient CAP and found a range of 10-21% of pneumococcal CAP among tested adult outpatient CAP (Table 5). No study provided these data by age. The unweighted average percentage of pneumococcal aetiology among adult outpatient CAP amounts to 16% (i.e. unweighted as in Welte) and the weighted pooled proportion is 12.3% to 13.7% (using inverse variance-weighted proportion and fixed or random effect, respectively). The proportion of pneumococcal CAP was higher, at 21%, in the two studies in which only a minority of cases were tested (24-35%) compared to 10-15% in the three studies that tested most cases (≥93%). This could be explained by a propensity to test more severe CAP cases in routine practice. After exclusion of the three studies with a low proportion of tested CAP (<40%) and/or involving only the most severe cases seen at emergency wards,[11, 49, 50] the pooled estimate based on the two remaining studies (Denmark and Basque region of Spain) amounts to 10.5% (95%CI 7.7-13.2) using inverse variance-weighted proportion.[47, 48]

A Belgian study among 38 GPs was not included because it was based on "tentative diagnoses" (GP diagnosis) of pneumonia and bronchopneumonia.[51] Most cases (97%) were tested by urine assay/test, and 10.8% (17/157) of these cases had a pneumococcal aetiology. This suggests that the above pooled estimate from the two selected studies is plausible as a Belgian parameter.

An additional review provided no specific estimate for outpatient CAP but confirmed that the proportion of outpatient CAP due to *S. pneumoniae* is lower than the proportion of *S. pneumoniae* in hospitalised CAP. In the meta-analyses, the odds of *S. pneumoniae* being the cause of a CAP was 1.45 (95%CI: 1.19-1.77) times higher in studies with episodes treated in the hospital and 2.33 (95%CI: 1.80-3.02) times higher in the ICU, compared to studies with CAP episodes managed in primary care.[8]

Table 5 – Findings of studies reporting the proportion of outpatient CAP due to *S. pneumoniae*

Study	Setting and study design	Characteristics of outpatient CAP	Outcome definition	Number of cases	% pneumococcal CAP on tested CAP
Holm 2007[47]	Denmark, 2002-2003. Prospective study in GP offices	≥18 years Median 61 years, range 22-88. LRTI, based on symptoms and signs.	CAP: X-Ray (+) pneumonia Pnc: Culture or PCR (93%)	48 outpatient CAP, all tested	15% (7/48) but 6/7 later hospitalised, including 4 IPD pneumonia
Vila Corcoles 2009[11]	Spain, Tarragona region, 2002-05. Prospective cohort study in 8 PHC	≥65 years 42% 65-74 years 36% 75-84 years 21% ≥85 years	CAP: ICD-9 pneumonia codes confirmed by X-Ray and review of clinical records Pnc: culture, serology or urinary antigen test	118 outpatient CAP, 24% (28/118) tested (calculated from paper)	21% (6/28) calculated from the paper, including 1 IPD pneumonia
Capelastegui 2012[48]	Spain, Basque country, 2006-07. Prospective study in 1 hospital and 150 GP.	≥18 years, excluding immunosuppressed. No age distribution for outpatient.	CAP: new X Ray (+) Pnc: culture or urinary antigen test	424 outpatient CAP, all tested	10% (43/424) of all tested (recalculated)*
Cilloniz 2012[49]	Spain, Barcelona, 2000-10. Prospective study in emergency ward of a large hospital.	≥16 years, excluding immunosuppressed and tuberculosis, discharged for outpatient treatment. Mean 47 years, 19% ≥65 years.	CAP: new X Ray (+) Pnc: culture or urinary antigen test	568 outpatient CAP, 93% tested (527/568)	12.5% (66/527) of all tested (recalculated),** including 16 bacteraemic pneumonia
Sicras-Mainar 2012[50]	Spain, Badalona, 2008-09. Retrospective multicentre study in 6 PHC and 2 hospitals.	≥16 years, excluding tuberculosis and lung cancer. Mean 51 years, 26% ≥65 years.	CAP: ICD-9 and X Ray (+) Pnc: no details provided, current practice (retrospective study).	340 outpatient CAP, 35% tested (119/340)	21% (25/119) of all tested (recalculated)*

**: % of study is on all CAP with aetiology identified. **: % of study is on all CAP, including those not tested for aetiology. PHC: Primary Health Care Centres.*

Key points

- **Based on the pooled estimates from two studies (Denmark and Spain), selected for their quality and representativeness, the proportion of outpatient CAP attributable to pneumococcal infections is estimated at 10.5% (95%CI 7.7-13.2).**

2.2 Mortality due to pneumococcal disease

2.2.1 Mortality due to invasive pneumococcal disease

2.2.1.1 IPD mortality in Belgian databases

The case fatality ratio (CFR) of IPD in Belgium was calculated based on hospital deaths in IPD cases matched between the NRC and the Hospital database (MZG/RHM), per clinical syndrome (see Appendix 1.Matching of the MZG-RHM and NRC databases). Hospitalisations were matched with those of the NRC over the period 2007-2012, using the following ICD codes in the primary diagnostic field:

- Pneumococcal meningitis (ICD9 code 320.1), see Table 6
- Pneumococcal septicemia (ICD9 code 038.2), see Table 7
- Pneumococcal pneumonia (ICD9 code 481), see Table 8

Case fatality ratio (CFR) of IPD was 12.2% overall in all ≥18 years, increased with age up 23% in in ≥85 years, and was generally higher in meningitis (16% overall, up to 50% in ≥85 years) and septicemia (16% overall) compared to invasive pneumonia (9% overall). It should be noted that hospital deaths due to pneumonia may underestimate the CFR as they do not cover pneumonia patients in long term facilities (such as nursing homes) that are are higher risk of pneumonia with fatal outcome, and are rarely hospitalised.

Table 6 – Case fatality ratio of pneumococcal meningitis as primary diagnosis, cases matched in MKG (ICD9) and NRC, 2007-12

Age groups	Total admissions	N fatal	CFR (%)
18-49 years†	46	7	15.2
50-64 years	68	9	13.2
65-74 years	43	5	11.6
75-84 years	18	4	22.2
≥85 years	8	4	50.0

†: data on the 18-49 years provided for information but not included in the model.

Table 7 – Case fatality ratio of pneumococcal septicaemia as primary diagnosis, cases matched in MKG (ICD9) and NRC, 2007-12

Age groups	Total admissions	N fatal	CFR (%)
18-49 years†	281	15	5.3
50-64 years	368	61	16.6
65-74 years	298	49	16.4
75-84 years	348	64	18.4
≥85 years	223	50	22.4

†: data on the 18-49 years provided for information but not included in the model.

Table 8 – Case fatality ratio of invasive pneumococcal pneumonia as primary diagnosis, cases matched in MKG (ICD9) and NRC

Age groups	Total admissions	N fatal	CFR (%)
18-49 years†	505	7	1.4
50-64 years	509	31	6.1
65-74 years	404	40	9.9
75-84 years	404	58	14.4
≥85 years	255	57	22.4

†: data on the 18-49 years provided for information but not included in the model.

2.2.1.2 IPD mortality in the literature

Mortality due to pneumococcal meningitis in all adults was 26% (19/73) at discharge in the Belgian IPD study.[4] This was similar to the 27% (38/142) within 100 days mortality in ≥16 year-olds in a study on notified cases in Denmark.[52] In the Netherlands, 14-day mortality in adults ≥16 years of age was 187/709 (25%) episodes in 697 patients included in 1998-2002 and in 2006-2009,[53] and 85/352 (24%) episodes in 343 patients included in 1998-2002.[54] Total meningitis-related mortality over the follow-up period in the latter cohort was 30%. Increasing mortality with age was reported by Ostergaard and Weisfelt, and also in UK.[52, 54-56]

Key points

- **In Belgium, the CFR of IPD was estimated at 12% overall in all ≥18 years and increased with age up to 23% in the ≥85 years. Hospital deaths due to pneumonia may underestimate the CFR as they do not cover pneumonia patients in long term facilities.**

2.2.2 Mortality due to hospitalised non-invasive pneumococcal disease

In the absence of Belgian mortality data on non-invasive disease we performed a literature review. We only covered non-invasive (or non bacteraemic) pneumonia, as it represents the majority of non-invasive disease and other diseases are not considered in this study. The methods for literature search are described in Appendix 1. In short, the review selected studies from non-US Western countries (mostly Europe), published in 2000 or later, with data on adults including elderly ≥65 years of age. Available studies mostly report on IPD overall or on all-cause CAP. In order to identify cases, microbiological examination for CAP-aetiology has to be performed, which is not standard practice in all settings and situations, suffers sensitivity and specificity problems, and is performed using different strategies. As a consequence, “diagnostic bias” cannot be excluded from any of the published reports since aetiological testing is mainly performed in the more severe pneumonia cases.

The CAPITA study used an elaborate testing protocol combining blood culture and specific urine antigen test (UAT) in all participants presenting with suspected CAP, but did not separately report on CAP and IPD mortality as this was not foreseen in the protocol.[22] Another study from The Netherlands selected its population on the use of UAT for pneumococcal infection at admission, which was found related to patient characteristics (more often immunocompromised, prior antibiotherapy).[13] In this specific population, case fatality ratio was higher in IPD (13%) than non-IPD (9%) pneumonia but in multivariable regression adjusting for age and severity at presentation (ICU admission) the association was not significant (adjusted OR 2.21; 95%CI 0.94-5.21); mortality and use of UAT were not found to be related.

A study in Spain looking at prognostic significance of bacteraemia in hospitalized pneumococcal pneumonia cases was limited to patients in whom blood cultures were requested, which were not always taken if UAT was positive.[57] In this study, the 30 day mortality was significantly higher in bacteraemic than in non-bacteraemic cases of pneumococcal pneumonia (adj OR 2.7; 95%CI 1.5-4.8 and adj HR 2.8; 95%CI 1.6-5.1, adjusted for patient characteristics and severity of illness at admission), Table 9. In a prospective emergency ward study in Spain,[49] 16/66 outpatient pneumococcal CAP cases were bacteraemic, but none of them died. An older Spanish hospital-based prospective study recruited all CAP patients (N=2457 of whom 718 pneumococcal) except immunosuppressed ones and looked for risk factors for early as compared to late CAP mortality.[58] All patients were blood cultured but not all underwent UAT. According to the authors, bacteraemic pneumococcal pneumonia was significantly more frequent in both early and late CAP deaths but all presented analyses were for all cause CAP (the values in Table 9 refer to pneumococcal CAP cases only).

A Danish study reported on hospitalized pneumococcal lower respiratory tract infection (LRTI) recognised from lab surveillance, which were completed with chart review (retrospectively; N=705, ≥16 years, median age 68).[59] Cases with prior hospitalisation in the same year were excluded, comorbidity was documented and treated as confounder. This study was not included in Table 9 because the scope was LRTI and not CAP, but the report contains information on cases with infiltrate on X-ray (i.e. fulfilling definition of CAP), in whom mortality was 11% in non-bacteraemic and 18% in bacteraemic pneumococcal pneumonia (unadjusted). Mortality was highest (28%) in bacteraemia without infiltrate.

Key points

- **All retrieved studies suggest a higher mortality for bacteraemic pneumococcal CAP cases than for non-bacteraemic ones. Since Capelastegui 2014 is the only prospective study focusing on pneumococcal CAP and has the highest number of cases, it is proposed as best reference to derive parameters, although subjects were included based on culture used for diagnostic work-up, which possibly selects the more severe cases. This study suggests an adjusted mortality HR of 2.8 for bacteraemic versus non-bacteraemic hospitalised pneumococcal pneumonia.**

Table 9 – Thirty day mortality in bacteraemic versus non-bacteraemic pneumococcal CAP in adults

	Van Mens 2015	Capelastegui 2014	Garcia-Vidal 2008
Country	The Netherlands	**Spain**	Spain
Design	Pneumococcal CAP only Retrospective laboratory surveillance completed with hospital records Selected on UAT-use Hospitalised <3 days before testing Mortality within 30 days after testing	**Pneumococcal CAP only** **Prospective hospital surveillance;** **excluded if immunodepressed or recently (<14d) hospitalised** **Mortality within 30 days after admission**	all CAP; Pneumococcal etiology reported Prospective hospital survey Excluded if immunodepressed Mortality within 30 days after admission
Study period	2008-2010	**2001-2009**	1995-2005
Age (mean ± SD)	≥18 years	**≥18 years (63.6±18.5 in BP; 65.2 ± 17 in NBP)**	≥18 years
Bacteraemic/non-bacteraemic cases (N studied population)	206/168 (not specified)	**399/492** **(not specified)**	244/474 (2457 CAP hospitalisations of whom 718 pneumococcal)
Deaths in bacteraemic/non-bacteraemic	No numbers given; 13% vs 9%	**37 (9.3%)/18 (3.7%)** **(adj HR 2.8; 1.6-5.1)**	34 (13.9%)/21 (4.4%)
Length of stay (mean ± SD) in bacteraemic/non-bacteraemic	10 days/ 8 days (p=0.05)	**10 (13.7) days/ 7 (5.5) days** **OR 1.2 (1.04-1.3); adj OR 1.1 (1-1.2)**	Not given for pneumococcal cases

BP: bacteraemic pneumonia; NBP: non bacteraemic pneumonia; CAP: community acquired pneumonia; HR: hazard ratio.

2.2.3 Mortality due to outpatient pneumococcal pneumonia

In the absence of Belgian mortality data on outpatient pneumonia we performed a literature review. We searched the literature for original studies and reviews on mortality due to outpatient pneumonia. We focused our search on high income (mostly European, excluding the US in view of different health care system characteristics) country settings, published after 1999 and containing data on (elderly ≥65 years) adults. Details of this review can be found in Appendix 1. Only studies in which CAP is clearly defined as a typical clinical picture with radiological confirmation of a new infiltrate were included. Mortality of outpatient CAP is usually reported as a post-hospitalisation follow-up of inpatient CAP, and is usually counted within 30 days from diagnosis ("30 day mortality"), or – more rarely - within 7 days. Post-30 day mortality is only very exceptionally studied.

In Belgium such data are unavailable since in adult outpatient management for lower respiratory tract infections (LRTI), X-rays are rarely (9.1%) performed.[51] Flamaing reports on an aetiological study in a cohort of 549 adults (of whom 340 ≥50 years of age) with a primary care clinical diagnosis of LRTI, that 40/50 X rays taken showed radiological signs of pneumonia. There were no deaths reported, but only 85 participants had a follow-up visit at 4-5 weeks.

Very few European studies give separate results for in- and outpatients, most of them showing very low (1-2%) mortality rates in outpatient CAP.[2] Specific assessment protocols are being used in primary care as well as hospitals to discriminate severe, care-demanding CAP from lower-risk CAP that can be treated outside hospital. Outpatient treated pneumonia patients are generally younger and have fewer comorbidities than hospitalized patients. Three out of four studies reporting on outpatient CAP mortality for such patients were from Spain (see Table 10). Note that Spain had a high rate of multiple antibiotic-resistant pneumococci at the time of those studies. These studies are described in the rest of this section.

Villa Corcolez et al prospectively followed a study cohort that included all (including comorbid and immunocompromised) community-dwelling >65 year-olds assigned to eight participating primary health care centers (PHCC) in the region of Tarragona, Catalonia, for 3 years and registered all first CAP events (through hospital discharge data or PHCC records) within that period.[11] The cohort was created for a PPV vaccine effectiveness study: 4986/11240 (44.4%) subjects were vaccinated before the study started and another 1449 (12.9%) during the 40-month study period.[60] Incidences of CAP were 11.6 per 1000 among immunocompetent subjects and 30.9 per 1000 among immunocompromised patients. Diagnostic and therapeutic management of CAP events were left to the treating physician. Aetiological diagnosis was performed in 75.7% and 25% of cases were treated outpatient; aetiology of the outpatient deaths (2/118) is not given (see Table 1). Overall 30-day case-fatality rate was 12.7% (2% in cases managed as outpatient and 15% in hospitalised patients).

Cilloniz reports on the outcome of 568 CAP cases that were admitted to the emergency ward of a third-level hospital but not hospitalized.[49] Aetiological diagnoses (including urinary antigen testing) were established in 188 (33.1%) of 527 patients in whom any testing was performed, but it is not clear from the report which testing algorithm had been used. Of those 188, 66 (35.1%) had a pneumococcal infection, and another 14 had a mixed infection including *S. pneumoniae*. None of the 3 patients (CFR 0.5%) who died within 30 days was infected with *S. pneumoniae*.

An older study in Switzerland recruited 170 adult (median age 43.1, range 15-96 years) ambulatory CAP patients through 11 GPs, with at least 4 weeks follow-up, and thorough aetiological work-up but no UAT.[61] Immunodepressed or comorbid (30%) patients were not excluded, and 14 (8.2%) patients were hospitalized within the follow-up period. Two patients died, both were old (83 and 86 years) and severely comorbid (liver cirrhosis and end-stage heart failure, respectively), both had pneumonia of indeterminate origin. One patient died in hospital and the other at home (outpatient CFR 1/156; 0.6%) a few days after start of the pneumonia.

Table 10 – Case fatality ratio (CFR) in outpatient X-ray confirmed all-cause CAP

	Vila Corcoles 2009[11]	Sicras-Mainar 2012[50]	Cilloniz 2012[49]	Bochud 2001[61]
Country	**Spain**	Spain	Spain	Switzerland
Design	**Prospective cohort from primary care centers;**	Retrospective; primary care + hospital;	Prospective; emergency ward, discharged for outpatient treatment	Prospective cohort from family physicians
	30 day mortality	30 day mortality	30 day mortality	Mortality within 4 weeks or later
Study period	**2002-2005**	2008-2009	2000-2010	4 years, before 2001
Mean age in years ±SD (min age)	**74.6 ±7.5 (65)**	57.5 ±19.1 (18)	47.2 ±17.6 (16) (outpatients)	43.1 (range 15-96)
	(overall)	(overall)	(110 outpatients ≥65)	(overall)
Outpatient/inpatient cases	**118/355**	340/241	568/2655	156/14
(N studied population)	**(11 240 followed)**	(90 315)		
Deaths/outpatient CAP cases	**2/118 (1.7%)**	0/340	3/568 (0.5%)	1/156 (0.6%)

No specific data about mortality of outpatient pneumococcal pneumonia in Europe have been reported. A general CFR of 0.8% for outpatient CAP (without further details) was reported from CAPNETZ (Germany), with most of the patients reported to die of other causes.[62] CAPNETZ is a competence network for CAP detection consisting of 12 clinical centres, both with private practitioners and hospitals, spread over Germany. Pletz compared CAPNETZ cases of non-pneumococcal and pneumococcal CAP (diagnosis including BINAX) in both outpatients and inpatients (69%) aged ≥18 years (mean 60 ±18 years).[63] The study found no difference in 30-day mortality between patients with pneumococcal (CFR 4.9%) and non-pneumococcal (CFR 4.0%) pneumonia, although the first were more frequently hospitalized. Interestingly, 5.6% of pneumococcal and 9.9% of non-pneumococcal deaths occurred at home, and another 7.4% and 10.1%, respectively, at a nursing home; however CFR for outpatient cases was not separately reported.

The best reference to derive parameters on outpatient CAP mortality is the study of Vila Corcolez 2009, since it is a primary care and not a hospital based cohort study using a prospective design, limited to the age group of interest, in a setting that is similar to Belgium (urban area with easy access to hospital).[11] The main difference with Belgium is the higher PPV23 vaccination coverage within this cohort. CFR of outpatient CAP was 2/118 (1.7%) in this study.

Key points

- **No specific data about mortality of outpatient pneumococcal pneumonia in Europe have been reported. Studies on outpatient all-cause CAP mortality were used as a proxy. Among the three retrieved Spanish and one Swiss studies, the cohort study published by Vila-Corcoles was selected to inform our model parameters since it was a primary care based and prospective study. CFR of outpatient CAP was 1.7% in this study.**

2.3 Long term consequences following meningitis and empyema

Since Belgian data on long term sequelae and complications due to pneumococcal disease are scarce, a literature search was performed. The methods for literature search are described in Appendix 1. In short, the review selected studies from non-US Western countries (mostly Europe), published in 2000 or later, with data on adults including elderly ≥65 years of age.

2.3.1 Pneumococcal meningitis

Pneumococcal Meningitis accounts for 50% of community acquired acute bacterial meningitis in adults in Europe, with 21% mortality.[64] In Belgium, pneumococcal meningitis represented 5.8% (65/1112) of IPD cases in ≥50 year-olds in the IPD study (Table 12).[4]

Prevalence of sequelae following pneumococcal meningitis in adults was estimated at 25.7% (14.0-37.3) in a meta-analysis based on six adult studies in high-income countries (Table 12).[65] Studies published after 2000 included in this review reported overall proportions of sequelae ranging from 4.5% to 55.6%, depending on their sampling frame and testing procedures.

A more specific review focused on the frequency of hearing loss (defined by audiometry) and other neurological sequelae in recent EU studies. Four studies were retrieved but used different criteria for the severity of hearing loss.[52, 54, 66, 67] Overall the four studies found a range of 20-26% of survivors with hearing loss >30dB, including one third unilateral and two third bilateral. Among hearing loss patients, 68-82% have hearing loss at 30-90 dB and the remaining 18-42% (5-7% of all cases) presented hearing loss >90 dB (Table 11).[54, 66] Among other neurological sequelae, spasticity/paresis was reported in 8.6% (one study), and cranial nerve palsy in 27.6-34.2%.[65] Heckenberg et al reported 116/531 (22%) hearing loss (defined as >10 dB) in adult survivors of pneumococcal meningitis followed prospectively in the Netherlands.[53]

An older Dutch study reported 30% sequelae in meningitis survivors (neurological lesions and/or hearing impairment at discharge) in a hospital-based prospective follow-up of 352 adult cases of pneumococcal meningitis (positive CSF culture) with mean age 58 (SD17) years.[54] Partial recovery of neurological lesions after discharge has been described.[68] Delayed cerebral thrombosis was reported in another prospective Dutch study as a rare (1.3%; 10 on 741 cases) but severe complication of pneumococcal meningitis that may occur in adults after initial good recovery and discharge.[69] In the Belgian IPD study, 22% of adult meningitis patients were discharged with persisting symptoms.[4]

2.3.2 Pneumococcal empyema

The occurrence of **empyema** is one of the main factors associated with poor outcome in CAP, and is a frequent cause of prolonged treatment (medical and surgical) and hospital stay, and even of treatment failure. Empyema is a purulent (third stage) pleural effusion diagnosed through a thoracocentesis, showing pus or a pathogen recognized within the pleural fluid with Gram stain. Complicated parapneumonic effusion is the preceding second stage, in which pleural fluid shows low glucose or pH, high LDH and high white blood cell content. Not all studies discriminate between second and third stage, since both require drainage. Poor outcomes could result from any or all of the following: prolonged hospitalization, prolonged evidence of systemic toxicity, increased morbidity from any drainage procedure, increased risk for residual ventilatory impairment, and increased mortality.[70] Empyema complicating pneumococcal CAP may involve both invasive and non-invasive CAP, since *S pneumoniae* cannot always be cultured from the pleural fluid in empyema cases, even if pneumococcal aetiology of the CAP is established.

Fletcher's review of European data included two eligible studies describing the frequency of empyema complicating adult pneumococcal CAP.[71] This frequency was reported at 6.4% (8/125) among hospitalized adults in a Barcelona study.[72] In a third-level hospital study in Barcelona, 626 hospitalized patients (mean age 63.6 ± 18.9 years) with pneumococcal CAP were prospectively followed between 2001 and 2009; 18 (8%) of them developed empyema from unspecified aetiology.[12] The proportion of cases with pleural effusion was 15.2-19.5% in the same two studies. Pneumococcal empyema occurred in 3/66 (4.5%) adult CAP outpatients that had been admitted at the emergency department in another Spanish study,[49] and these empyema cases all had to be readmitted for treatment in hospital. A similar figure was reported in an older prospective multi-center study in adults (16-97 years, mean age 61.5) in Spain, with empyema in 8.3% of 638

cases with pneumococcal CAP;[73] pneumococcal aetiology included positive BAS or BAL in the latter studies and immunocompromised patients were not excluded, in contrast to Cilloniz 2012.

The frequency of pneumococcal empyema among IPD cases in ≥50 year-olds in Belgium was recently reported at 6.6% (73/1112) from a prospective study in 50 hospitals in 2009-2011 (Table 12).[4] Among 1875 adults hospitalised with IPD, 1332 were included in the analysis, of whom 1112 were 50 years of age or more. Screening failures (no informed consent) and possible nosocomial IPD (diagnosed ≥5 days after admission) were excluded, thus some empyema cases may have been missed. Frequency of empyema was higher in 50-64 year-olds (9%) than in IPD-cases ≥65 years of age (6%).

Mortality following pneumococcal empyema was reported in the same study from Belgium at 11% among all adults (during hospital stay), whereas another 37% were discharged with persisting symptoms (dyspnoea, pain, fatigue, pleural infiltrate).[4] This was similar to the 11% (2/18) mortality reported by Cilloniz, the only study specifying CFR of empyema complicating pneumococcal CAP.[12] Lower mortality rates were reported from a recent retrospective study on all-cause empyema in Switzerland that registered 4 deaths in 78 (5.1%) empyema (defined as all-cause parapneumonic) patients and 3 (3.8%) still suffered from thoracic pain 12 months after diagnosis; no other sequelae were reported.[74] In that study, 48/78 cases had a positive culture of whom only 8 were pneumococcal.

Table 11 – Frequency of sequelae in pneumococcal meningitis, per type

	Ostergaard 2005[52]	Kastenbauer 2003[66]	Weisfelt 2006[54]	Worsoe 2010[67]	Aubertin 2006[75]
Country	Denmark	Germany	The Netherlands	Denmark	France
Study period	1999-2000	1984-2002	1998-2002	1999-2003	2001-2003
Age group (mean)	>16 years (61 years)	>16 years (50 years)	Adults (58 years)	>18 years	>18 years (56 years)
Number adult survivors	96	66	243	144	105 (ICU)
Any neurological sequelae*			30%		34.3%
Hearing loss >30dB	No definition	25.8%	21.8%	20.0%	No definition
- unilateral	NA	9.1%	6.8%	NA	NA
- bilateral	NA	16.7%	15.0%		NA
Hearing loss 30-70 dB	NA	16.7%	11.3%	12.5%	NA
Hearing loss 70-90db	NA	4.5%	3.7%	>70 dB: 10.4%	NA
Hearing loss >90db	NA	4.5%	6.8%		NA
Other neurological	22.0%	unclear	unclear (multiple sequelae)	NA	NA
- cranial nerve palsies	NA	4.6%	28%	NA	NA
- hemiparesis	NA	NA	7%	NA	8.6%
- focal cerebral deficit	NA	NA	11%	NA	NA

*The proportion of survivors with each type of hearing loss is calculated by applying the proportion on all cases with audiometry to the total cases with hearing loss. *: Including hearing loss.*

An Italian retrospective long-term (19-180 months, median 62) follow-up study in adults (16-91 years; mean 59) who were surgically treated for all-cause parapneumonic empyema (any pathogen) found 44/104 (40%) patients with some degree of remaining dyspnoea, which was not impairing daily activities; 46/104 (44%) had abnormal spirometric evaluation.[76] Older age was associated with poorer functional outcomes, but prior respiratory condition was unknown in this study which limits the conclusions. Moreover the study was limited to patients requiring surgery, and those are the most severe cases of empyema.

Table 12 – Frequency and mortality due to sequelae or complications of pneumococcal empyema and meningitis in adults ≥50 years of age

Clinical syndrome	Frequency	Case fatality ratio	Sequelae (% of cases)
Pneumococcal empyema	6.6% of IPD (73/1112)[4] - 8.6% in 50-64 years - 5.5% in ≥65 years	11% in ≥18 years (10/94)[4]	Too few data
Pneumococcal meningitis	5.8% of IPD (65/1112)[4] - 8.6% in 50-64 years - 4.4% in ≥65 years	26% in ≥18 years (19/73)[4]	25.7% (95%CI 14.0-37.3)[65]

2.3.3 Conclusions

Pneumococcal meningitis prevalence among IPD cases in Belgium was 5.8% in ≥50 year-olds with a CFR of 26% among all adults, which is similar to other European data. Sequelae were described in an estimated 26% of the survivors, but this estimate is sensitive to the length of follow-up. No study described the prevalence of each complication among cases with sequelae, but partial data suggest that an equal share of hearing loss and other neurological sequelae is expected (e.g. 20-26% hearing loss in Table 12 and 22% of other neurological sequelae in Ostergaard at al).[52, 54] However, the proportion of cases with more than one sequelae is not described.

In Belgium, the prevalence of pneumococcal empyema among IPD cases was estimated at 6.6% in ≥50 year-olds. Overall CFR of invasive empyema in adults was 11%. Empyema complicating CAP is a larger entity that covers non-IPD cases as well. The prevalence in other European studies ranged from 4.5% to 8% in adults (≥18 years) with a mortality of 11% in empyema complicating pneumococcal CAP. Sequelae of pneumococcal empyema may reduce quality of life in survivors, due to thoracic pain and dyspnoea, but there are insufficient data describing this and they are biased towards the most severe cases, which hampers adequate quantification of this rare event.

Key points

- **For pneumococcal meningitis, the prevalence among IPD cases in Belgium was estimated at 5.8% in ≥50 year-olds and the CFR at 26% in all adults. Sequelae were described in an estimated 25.7% of the survivors, 20-26% presented hearing loss (one third unilateral and two third bilateral) and 22% other neurological sequelae. Among hearing loss patients, 68-82% have hearing loss at 30-90 dB and the remaining 18-42% (5-7% of all cases) presented hearing loss >90 dB.**
- **For pneumococcal empyema, the 2009-11 Belgian IPD study estimates for invasive empyema can be used as estimates for all pneumococcal empyema. The prevalence of empyema was estimated at 6.5% of pneumococcal cases, and the CFR at 11% in adults ≥50 years of age. No sufficient data are available to quantify the proportion of sequelae following empyema, but available studies suggest it involves mostly thoracic pain and mild dyspnoea in most severe cases.**

2.4 Serotype distribution

2.4.1 In invasive pneumococcal disease

The distribution of pneumococcal serotypes in Belgium is only available on IPD cases during 2009-11 from a prospective multicentre study.[4] However, the distribution of serotypes within a serogroup changed over recent years under the influence of pressures exerted from the infant PCV vaccination program, as some serotypes of a given serogroup could be vaccine serotypes, while vaccine-related serotypes (i.e. from a vaccine serogroup) were non-vaccine serotypes (if no cross protection occurred within the serogroup).[d] Serogroup data are available from the NRC for many other years and counts and proportions of serogroups in adults ≥18 years of age in 2015 are presented in Table 13.

To estimate the serotype distribution of IPD cases in Belgium, we applied the proportion of vaccine serotypes within specific serogroups from a recent German study in adults to the counts of each vaccine serogroup in Belgium in 2015 (Table 13).[77] Van der Linden et al was selected because PCV history is similar in Germany and Belgium, the data are recent (2010-14), and the study is very large, containing sufficient details on specific serotypes. Table 13 indicates that PCV13 serotypes are estimated to account for about 25% of IPD cases, and PPV23 serotypes for 66%. About 42% of the serotypes found in IPD in this age group are exclusively covered by PPV23 (and thus not by PCV13), whereas a third is not covered by either of the vaccines.

Table 13 – Vaccine serogroups and serotypes in IPD (2015) among adults above 50 years of age, Belgium NRC and Van der Linden et al

Vaccines	Proportion of serogroups (counts)*	Proportion of all cases not in vaccine serogroups†	Proportion of vaccine serotypes (estimated counts)
PCV13 and PPV23 (12 serotypes)§	37.4% (371)	13%	24.4%(288)
PPV23 only (11 serotypes)**	45.3% (450)	3.5%	41.8% (415.2)
PCV13 only (6A)	3.4% (34)	28% of serogroup 6 is 6A	1.0% (9.5)
Serotype 3	9.2% (91)	NR	9.2% (91)
Serotype 19A	9.2% (91)	86% of serogroup 19 is 19A	7.9% (78.3)
All PCV13	40.8% (405)	NA	25.3% (251.4)
All PPV23	82.7% (821)	NA	66.2% (657.2)
No vaccine	13.9% (138)	NA	32.9% (326.3)
Total	100% (993)		100% (993)

*NA: non applicable; NR: non relevant; NRC: National Reference Centre; IPD: Invasive pneumococcal disease; *: serogroups from which at least one serotype is included in the vaccine; **: serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F; §: serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F; †: estimated according to van der Linden et al.[77]*

[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.

2.4.2 In non-invasive pneumococcal disease

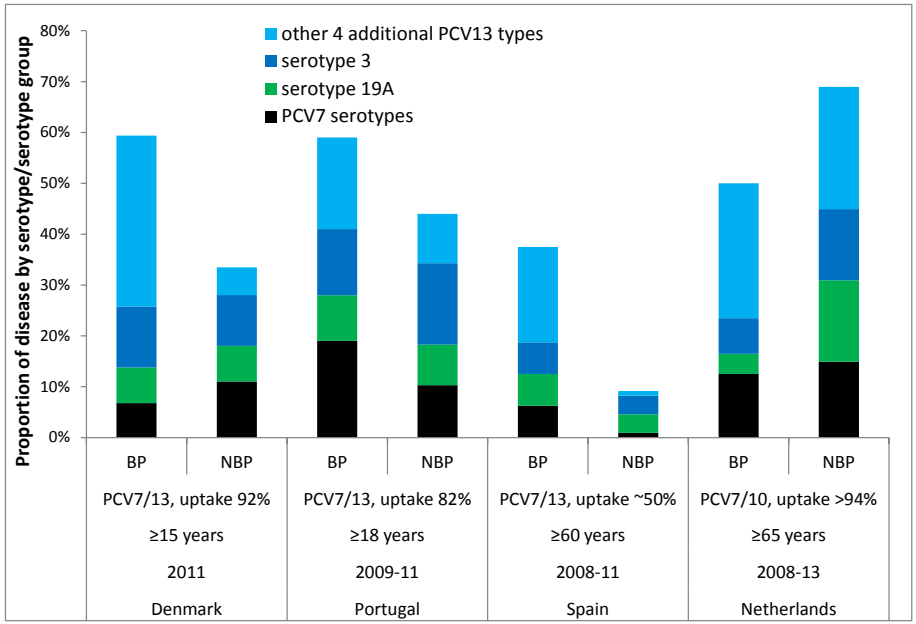
No Belgian data are available on the serotype distribution of non-invasive disease, as the determination of serotypes at the NRC is performed on isolated strains only, and few samples from non-invasive sites are sent. A few research studies from other countries used urinary assays to determine the causative serotype for non-invasive CAP. The main question here is to which extent the serotype distribution of IPD can be used for non-invasive CAP.

A literature review was performed to address this question. The methods for literature search are described in Appendix 1. In short, the review selected studies published after introduction of PCV10 or PCV13 in the infant vaccination schedule and comparing the serotype distribution between invasive and non-invasive pneumococcal pneumonia in adults including elderly ≥65 years of age, in settings similar to Belgium. Because serotype distribution and trends (including serotype replacement) vary across the different regions of the world, inclusion was limited to studies from other EU countries,

2.4.2.1 Results of the literature review

Four studies were included: three observational studies from Denmark, Spain and Portugal (two papers for one study) and the placebo arm of the CAPITA randomised controlled trial in the Netherlands (Table 14). Two studies involved adults of all ages,[40, 78, 79] one prospective cohort in Spain included only elderly (≥60 years) and the placebo arm of the CAPITA trial involved elderly 65 years of age and older (Table 14).[22, 42] In the infant populations of the study sites, PCV vaccine choice over time (PCV7, PCV10 and PCV13) and uptake differed. Three studies limited the detection of non-bacteraemic pneumonia to pneumonia with a positive culture of airway respiratory samples such as sputum or broncho-alveolar fluid; the two other studies (in the elderly) also used a urinary assay.[22, 42] The CAPITA trial involved a smaller number of subjects and restricted recruitment to immunocompetent subjects, and there was a number of selection biases in the recruitment of this trial.[22, 80] One UK study was excluded because it mixed bacteraemic and non-bacteraemic cases.[41]

Figure 1 – Proportion of serotype categories in bacteraemic/invasive pneumonia (BP) and non-bacteraemic/non-invasive pneumonia (NBP) in Denmark,[40] Portugal,[78, 79] Spain,[42] and the Netherlands[22]



BP: bacteraemic pneumonia; NBP: non-bacteraemic pneumonia; PCV7, PCV10 and PCV13: 7-valent, 10-valent and 13-valent pneumococcal conjugate vaccine, respectively, represent the PCV vaccine used in the study population since PCV introduction; uptake for 2 doses and is the most recent estimate in the study period.

All studies concluded that the serotype distribution of bacteraemic and non-bacteraemic pneumococcal pneumonia differed substantially in terms of vaccine serotype coverage. In the three observational studies in which infant PCV7 was followed by PCV13, the six PCV13 serotypes that are additional to PCV7 were more frequent in bacteraemic/invasive cases (31-53%) compared to non-bacteraemic/non-invasive cases (8-34%), as were the totals of PCV13 serotypes (Figure 1). In Denmark, the association between bacteraemic CAP and PCV13 serotypes was also found after adjusting for age, sex, comorbidity and other clinical confounding factors in multivariate analysis (OR 1.88, p=0.02).[40] The proportion of PCV7 serotypes widely varied across studies (Figure 1), likely attributable to variations in infant PCV uptake across the respective countries and periods. In Denmark (2011) where PCV7 infant vaccination was followed by one year of high (about 90%) uptake PCV13,[40, 81] the proportion of PCV7 serotypes in CAP was below 10%. In contrast in Barcelona (2001-08) where non universal infant PCV7 uptake was reportedly at around 50%.[82] PCV7 represented 20% and 32% of IPD in bacteraemic and non-bacteraemic CAP, respectively.[83]

Table 14 – Serotype distribution in bacteraemic/invasive and non-bacteraemic/non-invasive pneumococcal CAP in adults

Study, country, period, design	Age of cases	Numbers of cases, disease definitions, case characteristics	Infant PCV programme	Serotype	% in bacteraemic / invasive CAP	% serotypes in non-bacteraemic / non-invasive CAP
Benfield, Denmark 2011 Prospective study in 15 hospitals[40]	≥15 years Mean 68 years (both) 60% ≥65 years	- 272 non-bacteraemic CAP (NBP), 20% COPD - 192 bacteraemic CAP (BP), 44% COPD 98.5% hospitalized Culture only, from: - BP: blood - NBP: airway sample and negative blood culture. No blood culture in 27% NBP. Unknown for pleural fluid.	Universal PCV7: 2007-10 PCV13: 2010-11 Uptake 92% for 2 doses in 2011 [81]	PCV7 serotypes	6.8% (13/192)	11.8% (30/272)
				6 add. PCV13	52.6% (101/192)	22.4% (61/272)
				5 add. PCV13 in PPV23*	51.5% (99/192)	22.0% (60/272)
				PCV13 overall	59%	34%
				11 PPV23 additional	~ 28%	~ 23%
				PPV23 overall	87%	57%
				Non covered by PPV23	13%	43%
Ochoa-Gondar, Tarragona, Spain 2008-11 Prospective cohort[42]	≥60 years Mean of cohort 71.7 years	- 109 non-invasive CAP - 16 invasive CAP Culture and/or urine assay: - Invasive CAP: any sterile site (+) - Non-invasive CAP: sputum or urine assay (+) with blood culture (done in 68%) (-)	Non-universal PCV7: 2001-09 PCV13: 2010 Uptake 45-51% in 2008-11[84]	PCV7 serotypes	6% (1/16)	1% (1/109)
				6 add. PCV13	31% (5/16)	8% (9/109)
				5 add. PCV13 in PPV23*	31% (5/16)	7% (8/109)
				PCV13 overall	38% (6/16)	9% (10/109)
Horacio, Portugal 2009-2011 Prospective study in 30 laboratories[78, 79]	≥18 years, 40% ≥65 years	- 1300 non-invasive CAP - 1265 IPD: any, not only pneumonia Culture only, from: - IPD: any sterile fluid	Non-universal PCV7: 2001-09	PCV7 serotypes	19%; 14.2% in 65+ (2010)	10.3%; 8.4% in 65+ (2010)
				6 add. PCV13	41.0%	33.4%
				5 add. PCV13 in PPV23*	40.5%	30.7%

Study, country, period, design	Age of cases	Numbers of cases, disease definitions, case characteristics	Infant PCV programme	Serotype	% in bacteraemic / invasive CAP	% serotypes in non-bacteraemic / non-invasive CAP
		- non-invasive pneumonia: sputum, bronchial secretions or BAL (8% of all) (+), with sterile fluid (-) NBP without blood culture performed: unknown	PCV13: 2010-11 Uptake: 82% 2 doses[85]	PCV13 overall	59%	43.7%; 40.6% in 65+
				11 PPV23 additional	20.5%	22.3%
				PPV23 overall	80%	66%; 67% in 65+
				Non covered by PPV23	20%	34%
CAPITA (Bonten), Netherlands, 2008-13, not immune-compromised **Placebo arm of RCT[22, 86]**	≥65 years	- 56 invasive disease - 87 non-invasive CAP Culture or urine detection: - IPD: any sterile fluid (+) - non-invasive CAP: urine test (+) and sterile fluid (-) First episode, **per protocol** subjects Analysis of all pneumococcal CAP/IPD in PP	Universal PCV7: 2006-2010 PCV10: 2011-13 Uptake >94%[87]	PCV7 serotypes	13% (7/56)	15% (13/87)
				6 PCV13 additional	38% (21/56)	55% (47/87)
				5 add. PCV13 in PPV23*	34% (19/56)	52% (45/87)
				PCV13 overall	50% (28/56) mITT: 61%	70% (60/87) mITT: 67%

**: Major serotypes are limited to those included in PCV13 because non-vaccine types have not been typed. BP: bacteraemic pneumonia; NBP: non-bacteraemic pneumonia; CAP: community acquired pneumonia; COPD: Chronic obstructive pulmonary disease; BAL: bronchoalveolar lavage.*

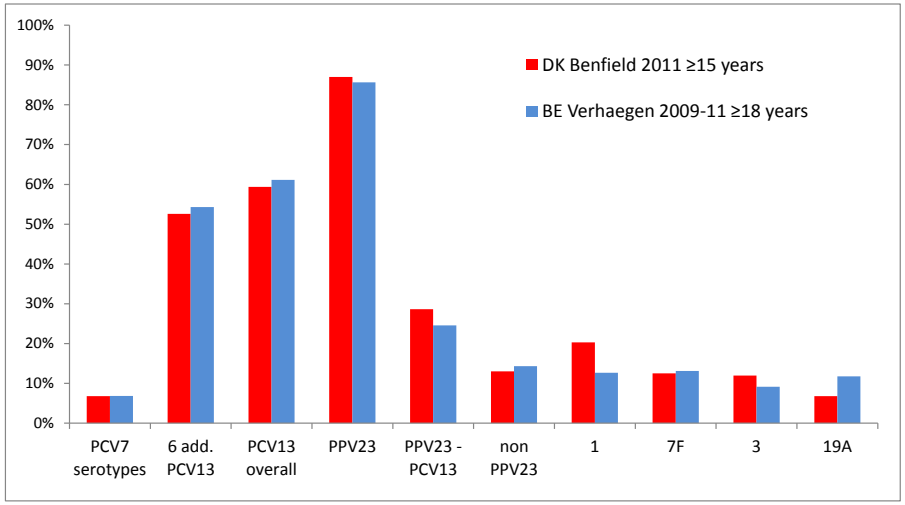
In the Netherlands, infant PCV7 was followed by PCV10 at high uptake (>90%) and the serotype distribution in the placebo arm of the (Dutch) CAPITA trial showed major differences with other recent EU studies.[22] The proportion of PCV13 serotypes in non-invasive pneumonia was higher than observed in other studies from Figure 1 and Table 14 (69% vs. 9-44%) and was mostly due to a predominance of the 6 additional PCV13 serotypes (55% compared to 8-34% in other countries, Table 14).[22, 40, 42, 78, 79] This proportion was as high as in Spain (70%) before PCV13 childhood use and under low PCV7 uptake (50%),[22, 83] the leading serotype in non-invasive pneumonia of the CAPITA study was 19A (16%),[22] contrasting with a low prevalence in invasive CAP (4%) in the same study or in invasive and non-invasive pneumonia in the three other studies (≤9%, Table 59 in appendix and Figure 1).[40, 42, 78, 79] This high prevalence of 19A can probably be explained by differences in recent PCV use: PCV10 replaced PCV7 in 2010 in infants and does not include serotypes 19A, as opposed to other studies where PCV13 predominated. Although PCV10 is considered to provide some level of cross protection against 19A IPD in PCV10 vaccinees, it does not protect against 19A carriage and does not show evidence of indirect effect (in unvaccinated subjects) against 19A.[88, 89] This difference could also be due to the different design, i.e. different recruitment, subjects (immunocompetent elderly) or laboratory methods (use of the highly accurate urine antigen tests) but it is unclear how this can influence serotype coverage. The Denmark study also reports that the CAPITA trial is showing a higher PCV13 serotype coverage than observed in Denmark and that the CAPITA findings may need to be adjusted by country-specific coverage rates.[90]

The results of the three observational studies were corroborated by two non-included studies on non-bacteraemic/non-invasive CAP, that also concluded that the distribution of serotypes causing non-invasive disease in adults differs significantly from those causing invasive disease, based on other analyses.[41, 43]

A limitation of this review is that two observational studies involved adults of all ages, and it is unclear to which extent these distributions apply to elderly (the only observational study including subjects ≥60 years of age had a comparatively small sample size).[42] However, two of these studies reported that the serotype distribution was not different between adult age groups.[40, 79] Other limitations are that some level of misclassification is possible since blood culture was not performed in all cases labelled as “non-bacteraemic”, and that the three studies that limited detection methods to culture (Table 14) probably have a lower sensitivity for pneumococcal detection. However, there is no indication that these limitations could bias the serotype distribution.

Despite the differences in setting, childhood PCV exposure, age group and methods of detection, all studies showed that the serotype distribution of invasive pneumonia does not represent the serotype distribution of non-invasive pneumonia. The four observational studies conducted in countries starting to use PCV13 (2008-11) showed that PCV13 coverage is lower in non-bacteraemic/non-invasive pneumonia compared to bacteraemic/invasive pneumonia. The Dutch CAPITA trial showed diverging trends but was characterised by a higher proportion of PCV13 serotypes that are not included in PCV10, likely due to the early use of PCV10 in the childhood PCV programme of the Netherlands.

Figure 2 – Serotype distribution in bacteraemic / invasive pneumococcal disease in adults in Denmark and Belgium[4, 40]



Only one study was conducted in a vaccination setting similar to Belgium, with high uptake universal PCV7 followed by PCV13, i.e. Benfield et al in

Denmark.[40] We compared the adult serotype distribution between the subjects of the Benfield study and the cases reported to the Belgian NRC in 2009-11.[4, 40] Figure 2 shows that the baseline serotype distribution around 2011 was very similar in the two settings. In this study the proportion of PCV13 serotypes was 59% and 34% for invasive and non-invasive CAP, respectively. The proportion of PPV23 serotypes is 87% and 57% for invasive and non-invasive CAP, respectively.

2.4.3 Conclusions for parameters

The Danish study by Benfield et al. is the most recent and most comparable to Belgium in terms of (a) past vaccine history and uptake i.e. PCV7 followed by PCV13 at high uptake, and (b) IPD serotype distribution in adults (Figure 2).[4, 40] The serotype distribution of non-bacteraemic CAP described in that study seems thus the most relevant for Belgian parameters on non-invasive CAP, but needs to be updated to the 2015 situation to account for the effect of more infant PCV13 years. Further details about methods and final parameters used in the model are given in Table 47 with an additional overview in Table 40.

This study however cannot inform future serotype distribution in adults due to the recent change from PCV13 to PCV10 for the Belgian infant vaccination programmes (2015-16), as this change in vaccine policy is expected to modify the indirect effects of infant vaccination on the serotype distribution of pneumococcal disease in adults >50 years.

Key points

- **A 2013 Danish study (Benfield et al) is the most suitable to inform serotype distribution among non-invasive adult pneumonia in Belgium, but would need to be extrapollated to the 2015 year (see Table 47).**
- **Future serotype distribution in adults is however unknown in Belgium, due to the change of PCV13 to PCV10 in infants (2015-16), as this switch is expected to generate a different indirect effect on adult serotype distribution.**

2.5 Health utilities

As no Belgian data was available on the health-related quality of life (HRQoL) impact of pneumococcal disease states in adults, a literature review was undertaken with the objective to summarize the published evidence (see Appendix 4 for details). An initial review focused on pneumococcal infections in adults, and a subsequent search also included other pathogens (e.g. Meningococcus).

2.5.1 Results of the literature review

The initial review identified 9 primary studies of reporting utility weights relevant for adult pneumococcal diseases and 23 cost-utility analyses of adult pneumococcal vaccination. The updated review (March 2016) identified 2 additional primary QoL studies[91, 92] and 1 additional cost-utility analysis.[92] The results are presented in Table 15, and further details are in Appendix 4.

Table 15 – Quality of life studies relevant to pneumococcal diseases in adults: summary of results

Studies	Method	Disease	Dimension / Health state		Score / Utility
Mangen, 2015, The Netherlands[92]	EQ-5D	Pneumococcal community acquired pneumonia	*Mean (SE) QALY loss for:*		*EQ-5D*
			- Hospitalised community acquired pneumonia and IPD		0.0709 (0.02)
Honselmann, 2015, Germany[91]	EQ-5D	Severe sepsis or septic shock	*Median (IQR) score/utility for:*	*VAS*	*EQ-5D*
			- Survivor of severe sepsis or septic shock at 1 year	50 (25 – 75)	0.8 (0.3 – 0.9)
			- Reference population	70 (50 – 90)	1 (0.9 – 1)
Orwelius, 2013, Portugal[93]	EQ-5D VAS	Community-acquired sepsis, severe sepsis, septic shock	*Median (IQR) score/utility for:*	*VAS*	*EQ-5D*
			- Survivor of sepsis, severe sepsis or septic shock at 6 months	70 (50 – 80)	0.68 (0.50 – 0.91)
Galante, 2011, Argentina/UK[94]	EQ-5D VAS	Pneumococcal diseases	*Mean (95% CI) score/utility for:*	*VAS*	*EQ-5D*
			- Ambulatory pneumonia (acute disease)	58.4 (55.1 – 61.7)	0.508 (0.442 – 0.575)
			- Hospitalised pneumonia (acute disease)	46.4 (42.6 – 50.1)	0.035 (-0.048 to 0.118)
			- Meningitis (acute disease)	34.2 (30.5 – 37.9)	-0.330 (-0.394 to -0.265)
			- Sepsis (acute disease)	31.7 (27.8 – 35.6)	-0.295 (-0.359 to -0.231)
			- Long-term hearing loss sequelae	60.1 (56.7 – 63.5)	0.635 (0.578 – 0.691)
			- Long-term neurologic sequelae	43.4 (40 – 46.8)	0.319 (0.252 – 0.386)
			Median (IQR) score/utility for:	*VAS*	*EQ-5D*
			- Ambulatory pneumonia (acute disease)	60 (50 – 70)	0.673 (0.3746 – 0.708)
			- Hospitalised pneumonia (acute disease)	45 (39.5 – 60)	-0.056 (-0.239 to 0.258)
			- Meningitis (acute disease)	30 (25.5 – 50)	-0.429 (-0.484 to -0.221)
			- Sepsis (acute disease)	30 (20 – 40)	-0.331 (-0.484 to -0.166)
			- Long-term hearing loss sequelae	60.5 (52 – 70)	0.725 (0.378 – 0.812)
			- Long-term neurologic sequelae	40 (30.5 – 51)	0.205 (0.082 – 0.603)
Karlsson, 2009, Finland[95]	EQ-5D VAS	Severe sepsis or septic shock	*Median (IQR) score/utility for:*	*VAS*	*EQ-5D*
			Survivor of severe sepsis or septic shock		
			- Before disease onset	65 (40 – 80)	0.81 (0.62 – 0.90)
			- At follow-up (at 17 months on average)	68 (51 – 80)	0.75 (0.56 – 0.94)

Studies	Method	Disease	Dimension / Health state		Score / Utility
			Reference population		
			- Before disease onset	70 (68 – 77)	0.86 (0.81 – 0.88)
			- At follow-up (at 17 months on average)	70 (68 – 77)	0.86 (0.83 – 0.88)
Korosec Jagodic, 2006,Slovenia[96]	EQ-5D	Severe sepsis or septic shock	*Mean utility (SD) for:*		*EQ-5D*
			- Survivor of severe sepsis or septic shock at 2 years		0.72 (0.24)
Granja, 2004, Portugal[97]	EQ-5D VAS	Severe sepsis or septic shock	*Median (IQR) score/utility for:*	*VAS*	*EQ-5D*
			- Survivor of severe sepsis or septic shock at 6 months	75 (50 – 80)	0.84 (0.58 – 1)
Sisk, 2003, USA[98]	HALex	Unspecified septicaemia	Mean (range) score for:		HALex
			- Unspecified septicaemia (acute disease)		0.2 (0.15 – 0.25)
De Wals, 2002, Canada[99]	EQ-5D	Sequelae following serogroup C meningococcal disease	Mean utility decrement for survivor with sequelae (mainly skin scar and amputations)		0.282
Drabinsky, 2001, USA[100]	EQ-5D VAS	Severe sepsis of infectious origin	*Mean score/utility for:*	*VAS*	*EQ-5D*
			- Survivor of severe sepsis at day 30	61	0.53
			- Survivor of severe sepsis at day 60	68	0.62
			- Survivor of severe sepsis at day 90	71	0.68
			- Survivor of severe sepsis at day 180	72	0.69
Stouthard, 1997, The Netherlands[101]	PTO	All-cause pneumonia, sequelae following bacterial meningitis	*Mean (95% CI) utility for:*		*PTO*
			- Pneumonia (during 2 weeks followed by complete recovery in the remaining year)		0.90 (0.809 – 0.984)
			- Bacterial meningitis sequelae: permanent locomotor impairment		0.83 (0.702 – 0.964)
			- Bacterial meningitis sequelae: permanent cognitive impairment		0.75 (0.616 – 0.881)
			- Bacterial meningitis sequelae: permanent locomotor and cognitive impairment		0.24 (0.139 – 0.348)

EQ-5D: EuroQol 5 dimensions; VAS: visual analogue scale; PTO: person trade-off; IQR: interquartile range; SD: standard deviation; SE: standard error; CI: confidence interval.

2.5.2 Selection of utility values for the Belgian economic evaluation

2.5.2.1 Selection criteria

Utility weights used for quality-adjusted life-year (QALY) computations in our cost-effectiveness analysis should comply with the following four criteria, see Cleemput et al for details:[102]

- Health states should be described with a generic descriptive instrument (preferentially the EQ-5D).
- QALYs should preferably be based on original Belgian empirical data. If original Belgian empirical data are not available, generic health state descriptions and valuations from "culturally-equivalent" countries in the same patient population can be used.
- Health state values from different studies should be treated with utmost caution. Consistency in methodology for the valuation of utilities of different health states in the economic evaluation should be pursued.
- QoL values should preferably relate to pneumococcal infections, rather than to any bacterial infection.

2.5.2.2 Selection of a primary QoL study

None of the 11 published primary QoL studies identified in the literature review fulfilled the four selection criteria defined above (see Appendix 4 for details).

In Galante et al[94] the generic EQ-5D instrument was used to derive the QALYs for 6 different health states related to pneumococcal infections in adults (i.e. ambulatory pneumonia, hospitalized pneumonia, meningitis, septicaemia, neurologic sequelae following meningitis and hearing loss sequelae following meningitis). Three out of the four selection criteria defined above are thus fulfilled.

In this study, the health state descriptions were valued using preference values from the UK general population (the UK 'tariffs'), which can be assumed comparable to Belgium. However, the classification (description) of health states with the EQ-5D instrument was made by Argentinians. Due to cultural differences, it is thus possible that the classification of the same health states by other (European) countries would have been interpreted differently and would have produced different results. It is also possible that the presentation of the symptoms of a disease would be different between countries (e.g. a typical pneumonia could be more severe in another setting) and would have required locally specified health states descriptions. For example, the description of hospitalised pneumonia was perceived as pertaining to uncomplicated pneumonia cases, which indeed constitute the majority of hospitalised pneumonia in Belgium. However, complicated pneumonia cases (i.e. empyema, lung abscess and necrotizing pneumonia) are more severe and would likely require longer hospitalisation times. Due to those problems of transferability, the QoL weights derived in Galante et al were only selected as the primary source of input data when no more appropriate alternative was available to us.[94] Therefore Galante et al data were used for the QoL weights of outpatient pneumonia cases and sequelae of pneumococcal meningitis. For hospitalised pneumococcal pneumonia patients, we had the opportunity to analyse an unpublished dataset from France (see next section).

2.5.2.3 Conclusions for QoL input data used

The ESSEC Chair of Health Systems (France) conducted a study, named PNEUMOCOST, aimed at deriving the treatment costs of an hospitalised pneumococcal pneumonia and its consequences in terms of quality of life and mortality. This study was sponsored by Pfizer. Though this study was not published yet at the time of writing this report, access to those data was granted through a confidentiality agreement with ESSEC.

The PNEUMOCOST database contains 523 hospitalised pneumococcal pneumonia patients (mostly 50+ aged patients), in which we distinguish between bacteraemic and non-bacteraemic pneumonia cases by whether or not pneumococcus was isolated from blood or from pleural fluid only. EQ-5D descriptive scores and utilities (using French tariffs)[103] were obtained at different time intervals: 1 month, 3 months, 6 months and 12 months after diagnosis. Due to a lack of clinical information to distinguish meningitis and bacteraemia without focus cases from the database, the QALY estimates derived for bacteraemic pneumoniae were applied to all invasive pneumococcal diseases (i.e. meningitis, bacteraemia without focus, other invasive pneumonia).

Post-hospitalisation observations were collected for a subset of 323 patients at different time interval and were used to derive QALY estimates after hospital discharge. For each patient, we estimated the average monthly quality of life measurement by interpolating measurements with a natural spline function.

To calculate the total QALY loss of a disease episode for a patient, we took the difference between the estimated quality of life measurement at each month and the French population norm (see below). QALY estimates per patient are calculated by summing the observed QoL weight differences at each month, and dividing this sum by 12 (to adjust the scale appropriately from months to years), Table 16. Age-specific baseline quality of life data for susceptible low risk individuals and survivors of pneumococcal disease without sequelae were taken from the French population norms.[104] Data on low risk patients were selected instead data of all patients (Table 16), in view of the strategies evaluated in the current report, which target in the first place healthy adults using vaccines with unproven or limited evidence of effectiveness in high and medium risk groups, while a high proportion of high and medium risk patients are represented in the PNEUMOCOST database (41% and 66% <65y and ≥65y, respectively). Furthermore, the French population norms would have to be adjusted for risk group-specific norms, using proportions of these risk groups in the Belgian general population to estimate the deviation from the norm of the average observed in PNEUMOCOST. In univariate sensitivity analysis we include a scenario using the average estimates, based on the proportions of these risk groups in France. This is in line with the recent Belgian guidelines that recommend that (1) in the absence of Belgian data, population norms from another country should be used and (2) when quality of life data from another country are used, baseline population norm data should also originate from that country.

Uncertainty around QALY estimates derived from the PNEUMOCOST database and for the population norms are included by bootstrapping directly from PNEUMOCOST and the population norm data (both these datasets were kindly made available through a personal communication of Gerard de Pouvourville, ESSEC, 2016). This method does not require assuming a distribution.

Table 16 – QALY loss estimates of surviving hospitalised pneumococcal pneumonia patients (PNEUMOCOST-survey), up to 12 months, by age group and disease type

Age group	Disease	Average QALY loss (over 1 year)	Minimum QALY loss (over 1 year)	Maximum QALY loss (over 1 year)	Number of patients
0-64 years	Non-invasive	0.0491	-0.3283	0.9692	69
	Invasive	0.0203	-0.3288	0.5244	36
≥65 years	Non-invasive	0.0679	-0.2713	0.8336	21
	Invasive	0.1741	-0.2768	0.6710	28

Utility weights for the states ambulatory pneumonia, hearing loss and neurological sequelae were obtained from the Galante et al study.[94] Weights for hearing loss and neurological sequelae following meningitis were 0.635 (95%CI 0.578–0.691) and 0.319 (95%CI 0.252–0.386) and were assumed to last lifelong. The utility weight for ambulatory pneumonia was 0.508 (95%CI 0.442–0.575) and was applied during 8.5 days.[94] Around both these mean estimates a normal distribution was defined based on the confidence intervals reported in Galante et al.[94] Quality of life losses for vaccine-related adverse reactions were not included. As per the Belgian guidelines on economic evaluations,[102] QoL losses for caregivers (e.g. next of kin) were not included in the base case.

2.6 Costs of pneumococcal disease

2.6.1 Cost of hospitalised episodes of pneumococcal disease

Costs for hospitalised episodes of pneumococcal disease were based on anonymised data obtained after using pneumococcal disease diagnostics based on ICD9 codes in the MZG-MFG database in the period 2007-12, and selecting only patients who had a matching laboratory confirmation in the NRC database (see details on matching in Appendix 1). The MZG-MFG database contains information on the length of stay and costs. The methodology of costing is in accordance with KCE guidelines and is summarised in Table 17. The same ICD9 codes were used as described under mortality (which was part of the same linkage). Cost estimates were based on all available years, and were scaled to 2015 using Belgian consumer price index, see Table 18.

Table 17 – Cost categories, and methodology cost estimation

Cost category	Description	Methodology
HOSP	Hospitalization cost, cost of staying at the hospital	Length of stay multiplied by weighted average daily hospitalization costs for acute hospitalization in last available year 2012.
BPMR	Blood Plasma, Mother's milk, radio-isotopes	Sum of patient share and RIZIV/INAMI share.
DELIVER	Medical deliveries	To the RIZIV share €6.20 per admission was added, after correction for inflation, to account for the patients' share for medical imaging acts. No patient share was included for other costs than medical imaging (a limitation of the database).
PHARMA	Pharmaceutical products	Pharmaceutical cost are calculated as the sum of the RIZIV's and patients' share. The RIZIV's share includes the extrapolated fee for service cost of what KCE termed "forfaitized" drugs (Extrapolation factor see Table 5 KCE guidelines) and the recorded total cost for "non-forfaitized" drugs. The patients' share includes the recorded cost of all products in the non-reimbursement category and a lump-sum of €0.62 per day of hospital stay.
IMPL	Implantations	RIZIV shares were summed (this is an underestimation, but a drawback of the database used).
CM&NM	Clinical microbiology and nuclear medicine	To the sum of all RIZIV costs €7.44 per admission was added after correction for inflation to account for the patients' share.

Table 18 – Mean costs of pneumococcal disease, per clinical syndrome (ICD9 primary diagnosis) in cases matched in MZG/RHM and NRC, 2007-12

Age groups	Meningitis	Septicemia	Pneumonia
18-49 years	€ 5564	€ 3745	€ 3466
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: Résumés Hospitaliers Minimum/Minimale Ziekenhuis Gegeven; SHA/AZV: Séjour Hospitalier Anonyme/Anoniem Ziekenhuis Verblijf; NRC: National reference centre.

2.6.2 Cost of outpatient pneumococcal CAP

Observations to base outpatient pneumonia cost estimates on were sourced from the GRACE project's work package 9.[46] This work package involved observational studies of adults with lower respiratory infections with the aim of developing models to; (i) differentiate viral from bacterial infections; (ii) detect patients with pneumonia; and (iii) identify patients at risk of adverse outcomes including severe and prolonged illness.

By a text string search on the diagnostic field, 8 Belgian outpatient pneumonia cases were identified. We cost the patient medications recorded based on official Belgian tariffs (http://beta.bcfi.be), see Appendix 7 for details. The aggregated cost per patient ranges from €35 to €163 per pneumonia episode (see Table 67 in Appendix 7), with a mean of €80.9.

3 INDIRECT EFFECT OF INFANT PCV VACCINATION ON ADULT DISEASE

3.1 Indirect effect of PCV13 vaccination

Twelve eligible studies were retrieved: ten studies described the indirect effect of PCV13 vaccination on adult IPD over 2-5 years of vaccination,[9, 32, 33, 35, 90, 105-109] and two studies on adult CAP (Table 5).[110, 111] Studies based on ICD codes only, without medical validation of diagnostic codes or without stratification by adult age group were excluded.[112-114]

3.1.1 PCV13 indirect effect on IPD

The ten studies from EU and US describe an indirect effect on IPD in the elderly after two to five years of widespread PCV13 vaccination, with infant vaccine uptake ranging 76-97% (Table 5 and Figure 3). All studies found a mild reduction in overall IPD ranging -9 to -25%, due to a decline in PCV7 serotypes (-44% to -89%) and in the six additional PCV13 serotypes (-18% to -64%), Table 19. Non-PCV13 types showed modest non-significant increases after two to three years of vaccination (≤22%),[32, 90, 105] except in Norway,[107] but higher and significant rises after four years of universal infant PCV13 with high uptake (three studies), up to +53% in a EU multicentre study.[33, 108] In this multicentre study, non-PCV13 serotypes systematically rose in each country. The rises in non-PCV13 types explain the mild decrease in overall IPD in most studies despite the high indirect effect on vaccine types.

Three studies provided yearly incidence or incidence decline.[32, 33, 35] The decreases in PCV7 serotypes tended to stabilize but the decreases in the six additional PCV13 serotypes and the increases in non-PCV13 types gradually intensified in each PCV13 year. Based on the five PCV13 year period in the multicentre EU study Spidnet (2010-2014), we estimated that the PCV13 serotypes declined by an average of 16% by year and the non-PCV13 types rose by an average of 4% per year.[35]

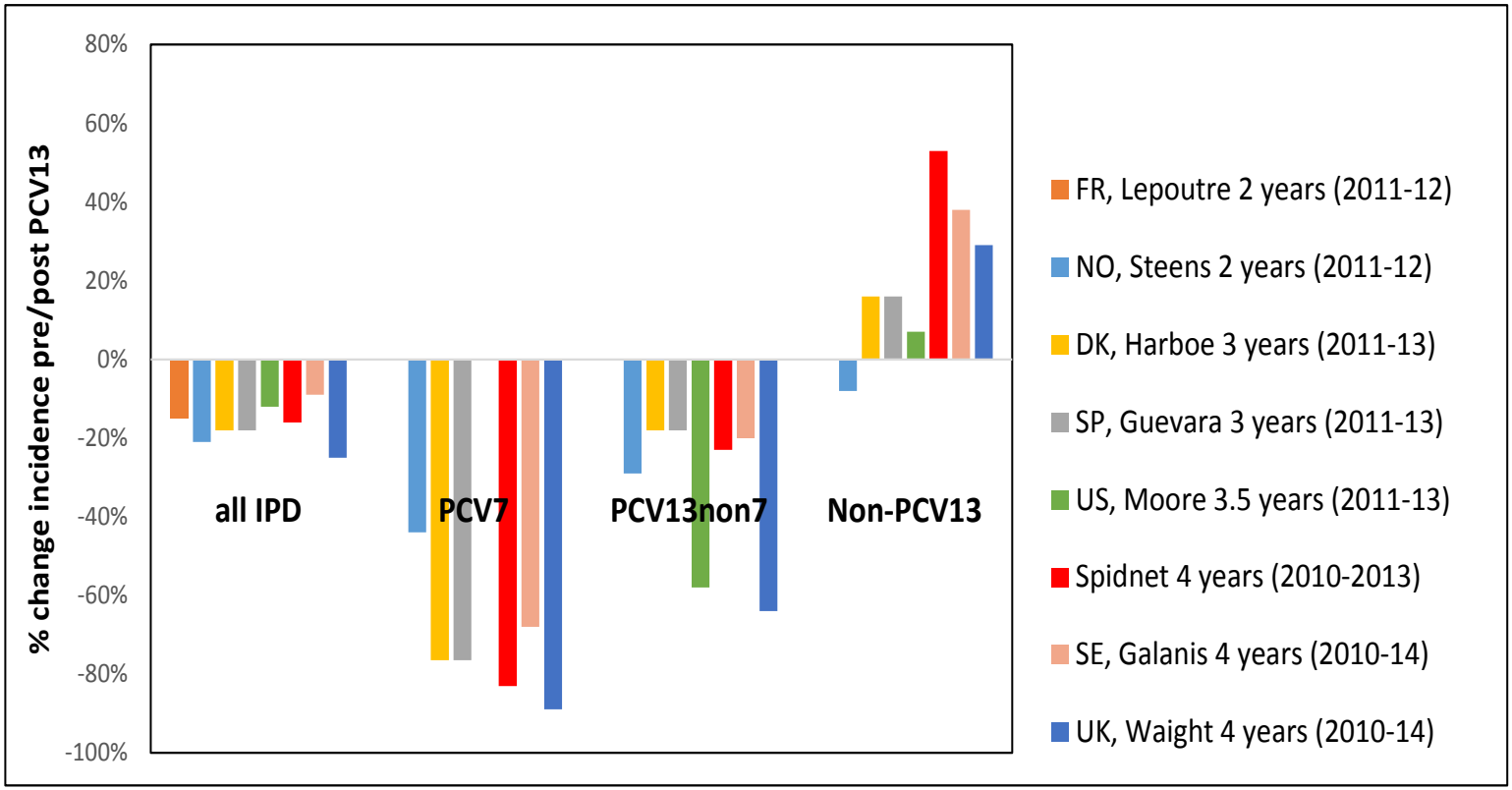
One Spanish study also compared mortality rates in elderly before and after infant PCV13 and found no change (-16%, -41 to 20).[9] One study provided data on serotypes unique to PPV23. In Denmark, the proportion of serotypes unique to PPV23 increased from 15.2% in the pre-PCV period to 18.2% in the PCV7 period and 18.9% in the first two PCV13 years (+24% over 13 years).[90] All non-PCV13 serotypes increased by 49% over the same 13 year period.

Table 19 – Changes in IPD incidence rates in ≥ 65 years after PCV13 universal infant vaccination compared to PCV7 period, by serotype group

Study, country	PCV13 study period	N years PCV13 use, uptake	All IPD	PCV13 types	PCV7 types	Six additional PCV13 types	Non-PCV13 types
Steens, Norway[107]	2011-12	2 years, 92%*	-21% (-30 to -8)	NA	-44% (-65 to -12)	-29% (-45 to -8)	-8% (-25 to 13)
Lepoutre, France[106]	2011-12	2 years, 94%**	-15% (-19 to -11)	NA	NA	NA	NA
Guevara, Navarra Spain[105]	2011-13	3 years, 78%***	-23% (SS)	NA	-62% (SS)	-35% (SS)	22% (NS)
Harboe, Denmark[90]	2011-13	3 years, 90%†	-18% (-24 to -12)	NA	-76%	-18%	16%
Moore, US[32]	2011-13	3 years, 76%§	-12% (-22 to 1)	NA	NA	-58% (-64 to -52)	7% (-4 to 20)
Grau, Spain[9]	2010-13	3 years, >60%	-23% (-35 to -8)	NA	-50% (-66 to -25)	-27% (-45 to -3)	1% (-22 to 32)
Waight, UK[33]	2010-14	4 years, 94%^	-25% (-31 to -19)	NA	-89% (-92 to -82)	-64% (-70 to 57)	29% (17 to 42)
Galanis, Stockholm[108]	2010-14	4 years, 97%	-9% (-22 to 4)	NA	-68% (-78 to -52)	-20% (-40 to 6)	38% (9 to 75)
Slotved, Denmark[109]	2011-14	4 years, >80%	NA	-48% (-72, 0)	NE	NA	NA
SpIDnet, 4 countries‡[115]	2010-13	4 years, 93-97%	-16% (SS)	NA	-83% (SS)	-23% (SS)	53% (SS)

: Immunization (not specified) in children born from 2009 onwards; **: primary immunization in children born 2008 and after; *: at least one dose among <2 years in 2013; †: 2+1 dose; ^: 2 doses at 12 months, https://www.gov.uk/government/statistics/cover-of-vaccination-evaluated-rapidly-cover-programme-2013-to-2014-quarterly-figures; §: ≥3 doses before 12 months; ‡: restricted to SpIDnet countries with universal PCV13 vaccination: France, Ireland, Scotland and Norway. NA: non available; NE: non evaluable (no case); SS: statistically significant: NS: non-statistically significant.*

Figure 3 – Changes in IPD incidence in ≥65 years in EU and US studies after PCV13 infant vaccination programme compared to PCV7 period, by serotype group



** France, Ireland, Scotland and Norway (with universal PCV13 vaccination); IPD: invasive pneumococcal disease; PCV13non7: the six additional serotypes that are in PCV13 and not in PCV7.*

3.1.2 PCV13 indirect effect on pneumococcal pneumonia

One UK prospective cohort study described the indirect effect of infant PCV13 on hospitalised adult pneumococcal CAP (≥16 years of age) after three years of PCV13 vaccination.[110] Adult pneumococcal pneumonia, bacteraemic and non-bacteraemic, defined as suggestive clinical picture and X-Ray with positive urine assay (BinaxNOW), decreased by 37% between the last PCV7 year and the third PCV13 year (Table 20). The effect was higher in the oldest ages. PCV7 serotypes declined markedly under PCV7 vaccination and tended to remain stable or to increase under PCV13, but involved small number of cases with year-to-year variations. The six additional PCV13 types decreased in each age group, with an average decline of 13% (95%CI 5-20) by year, which is comparable to the decreases in IPD (Table 19). No consistent rise of non-PCV13 types was observed.

Table 20 – Changes in pneumococcal pneumonia in adults (≥16 years) after PCV13 infant vaccination programme compared to PCV7 period

PCV13 use, uptake	Age group	Periods	Pneumococcal CAP	PCV7 types	Additional PCV13 types	Non-PCV13 types
Rodrigo, UK[110] (Period 2008-13)						
2010-13, 94%	All ≥16 years	2012-13 vs 2009-10 (three years PCV13)	-37%	+44%	-45%	-7%
	65-74 years		-18%	+294%	-36%	+25%
	75-84 years		-27%	+100%	-27%	-50%
	≥85 years		-41%	0%	-45%	0%

One US study compared the serotype distribution in samples from non-invasive respiratory disease (culture based only) under two years of PCV7 followed by two years of PCV13.[111] The proportion of PCV7 serotypes also remained stable over the four years and were more commonly isolated from patients ≥65 years of age compared to younger adults. The proportion of PCV13 serotypes declined over time in those ≥65 years of age.

3.2 Indirect effect of PCV10 vaccination

3.2.1 PCV10 indirect effect on IPD

Reporting of PCV10 indirect effects vary by country and over time. In similar settings, four studies assessed changes in adult IPD under PCV10 vaccination, in Finland and the Netherlands.[34, 116-118] Two EU countries that used exclusively PCV10 (Finland and the Netherlands) did not observe a decline in overall IPD incidence of the elderly in the first 2-4 years after introduction.[116, 117] PCV10 serotypes declined in the studies comparing incidence rates, mostly due to a large decline in PCV7 serotypes, but this was compensated by non-PCV10 serotypes increases in all studies, partly due to serotype 19A rises (Table 21). Changes in PCV10 types and non-PCV10 types also showed a gradual year-to-year gradient over the PCV10 years. An 2016 updated analysis in Finland showed a continued increase in non-PCV10 serotypes in elderly, with a late net increase in overall IPD incidence: incidence in the 65 years increased from 32 in 2009-10 (pre-PCV10) to 38 per 100 000 in 2015.[118] However, other factors may have contributed such as a prolonged influenza season in 2014–2015.

No study was conducted in a country that used the same PCV sequence as in Belgium: PCV7 followed by PCV13 followed by PCV10: Finland did not use PCV7 and the Netherlands directly switched from PCV7 to PCV10.

Table 21 – Changes in IPD incidence rates in adults ≥ 65 years after PCV10 infant vaccination compared to PCV7 period, by serotype group

Study, country	PCV10 period	PCV13 use, uptake	All IPD	PCV7 serotypes	Additional PCV10 (1, 5 and 7F)	Additional PCV13 (3, 6A and 19A)	Serotype 19A	Non-PCV10 types
NIDR, Finland,[117] 2014 vs 2010*	2011-14	4 years, 95%[89] *	+1%	-55%	-43%	NA	+245%	+74%
Knol, the Netherlands,[116] 2011-13 vs 2009-11	2011-13°	2 years, 95% (2013)	+6% (-5 to 18)	-55% (-67 to 38)	-2% (-34 to 26)	NA	+40% (2 to 92)	+25% (10 to 43)

** No PCV7 has been used in Finland.*

3.2.2 PCV10 indirect effect on non-invasive pneumococcal pneumonia

Only one study from the Netherlands described the indirect effect of the first 2 years of infant PCV10 vaccination on non-invasive pneumococcal CAP in the elderly, based on a post-hoc analyses of two Dutch studies, including the placebo arm of the CAPITA study (42 256 subjects).[119] It did not measure incidence but compared the trends over time in the proportions of vaccine serotype groups between IPD and non-invasive CAP. The authors concluded that the time trends of vaccine and non-vaccine serotypes in non-invasive CAP closely resembled those seen in IPD surveillance data and they suggested that national IPD data can be used to extrapolate absolute changes seen in the IPD data to non-invasive CAP, using the relative changes observed in the serotypes causing IPD over time. However, the proportion of PCV10 serotypes causing non-invasive disease showed no change over time, albeit that this observation is limited by the low numbers of cases.

Key points

- **In all studies describing the indirect effect of infant PCV13 vaccination, overall IPD decreased mildly (-9 to -25%) due to a decline in PCV7 serotypes (-44% to -89%) and in the six additional PCV13 serotypes (-18% to -64%). Non-PCV13 types rose significantly after four to five years of universal infant PCV13, up to +50% after five years.**
- **A multicentre study pooling IPD data from five EU countries with high PCV13 uptake (France, Norway, Ireland, Denmark and Scotland) can be used to inform parameters for PCV13 indirect effect of our study (see Table 48). In that study, the PCV7 decline tended to stabilize after four PCV13 years. Over the five years, the six additional PCV13 serotypes declined by an average 16% by year and the non-PCV13 types rose by an average of 4% per year.**
- **One UK study measuring the PCV13 impact on pneumococcal pneumonia showed comparable indirect effect than observed on IPD, with a stabilization of PCV7 incidence and an average decline of 13% per year of the six additional PCV13 types.**
- **In the two countries using infant PCV10, overall IPD did not decline and even tended to increase in Finland after five PCV10 years. PCV10 serotypes declined in all studies but non-PCV10 types increased rapidly, driven by a 19A rise. However, no study could be found from a country with the same infant PCV history than Belgium (PCV7 followed by PCV13 and then PCV10) to inform parameters on PCV10 indirect effect for our study (see details on parameters in 3.2.1. PCV10 indirect effect on IPD).**
- **Early changes in non-invasive CAP following two years of infant PCV10 were described in one Dutch study, and authors suggested that the relative changes observed in IPD data can be used to extrapolate the absolute changes seen in non-invasive CAP.**

4 PNEUMOCOCCAL VACCINES IN ADULTS

4.1 Efficacy and effectiveness of the 13-valent conjugate vaccine

A literature search was performed, and the methods are described in Appendix 1. In short, the review selected studies on efficacy and effectiveness from non-US Western countries (mostly Europe), covering cases from 2000 or later, and presenting efficacy or effectiveness data on all adults (no sub-group with risk factor), including elderly ≥65 years of age. Up to March 2015, only few studies on PCV13 efficacy or effectiveness in adults were retrieved. No efficacy estimations were available at the time of the first PCV13 European authorisation as it was solely based on immunological correlates of protection, i.e. Ig and OPA.[21] PCV13 has only been authorized in adults for all pneumococcal disease in 2015: it was authorized in Europe in 2011 against IPD only and in 2015 against pneumonia; in the US, it is recommended in all elderly since 2014 (≥65 years of age).[21, 120] One large trial measuring efficacy against community acquired pneumonia (CAP) and IPD in the elderly, the CAPITA study, was completed in 2013 and the results were published in 2015. We found five articles and one conference communication reporting on the efficacy part of the CAPITA trial,[22, 80, 86, 121-123] and two posters reporting on an Italian study measuring the PCV13 effectiveness on adult IPD.[124, 125]

The CAPITA trial recruited subjects ≥65 years of age in the Netherlands over 2008-10. Only 19% of initial respondents were finally included in the CAPITA trial. The trial followed 84 496 subjects ≥65 years of age during 3.97 years (2008-13).[22, 121] Included subjects were younger - the response rate decreased markedly with increasing age - and less likely to be female (OR 0.59) compared to the general population, thus not totally representative.[80] The majority (58%) of recruited subjects were healthy, i.e. without comorbidities, and the remainder (42%) had “stable comorbidities” but were immunocompetent at the time of recruitment. Patients with unstable comorbidities or immunocompromised were excluded. The modified intention-to-treat analyses (mITT) involved all confirmed CAP/IPD with onset at least 14 days after vaccination, including 82 subjects who became immune-deficient or suppressed before disease onset; these were excluded from the per protocol (PP) analyses. Sixty-nine percent of subjects were aged 65-74 years of age, 28% were 75-84 years of age and only 3.5% were aged 85 years or older.[22] Vaccinated and placebo subjects had similar baseline characteristics. A study evaluating the number of missed pneumonia episodes estimated that 37% of suspected pneumonia episodes were missed by the screening system.[122]

4.1.1 Invasive pneumococcal disease

In the CAPITA trial, efficacy against IPD was based on a passive surveillance of trial subjects by sentinel laboratory centres.[22] In mITT analysis, 100 first episode of IPD were reported and PCV13 vaccine efficacy (VE) against a first occurrence of IPD was significant at 48.5% (95%CI 20.9 to 67.0), Table 22. VE against vaccine type IPD was significant at 75.8% (95%CI 46.5 to 90.3) but this analysis was based on low numbers of cases, i.e. 8 in vaccine group vs. 33 in placebo group. VE against vaccine type invasive pneumonia was slightly lower than VE against non-pneumonia IPD (73.9% vs. 80.0%, respectively) but 95%CI (not available) are likely to be wide due to small numbers (personal communication van Werkhoven).

4.1.2 Pneumococcal community acquired pneumonia

In the mITT analysis, 309 pneumococcal community acquired pneumonia (CAP) were reported. PCV13 efficacy was significant at 22.4% (95% CI 2.3 to 38.5) against a first occurrence of any (type) pneumococcal CAP and at 37.7% (95%CI 21.8 to 62.5) against a first occurrence of vaccine-type CAP (which was the primary endpoint) (Table 22).[22] Efficacy against all episodes of vaccine type CAP and against the first episode showed similar estimates (37.5% vs. 37.7%, respectively in mITT) and was not calculated for other endpoints. In Italy, a test negative and a Broome design was used to measure VE against any pneumococcal CAP and vaccine serotype CAP, respectively.[124, 125] It involved 59 pneumococcal CAP cases and 127 non-pneumococcal CAP controls and analyses were not adjusted to potential confounding factors. Efficacy estimates were non-significant and amounted to 24.3% (95%CI -104.6 to 72) for pneumococcal CAP and 37.2% (95%CI -290.8 to 89.9) for vaccine type pneumococcal CAP (Table 22) and numbers of cases were small. Analyses were not stratified for invasive and non-invasive CAP.

Table 22 – PCV13 efficacy/effectiveness against pneumococcal disease in the elderly, by outcome

	CAPITA,[22] VE (95%CI)	Martinelli,[125] VE (95%CI)
Region, country	The Netherlands	Apulia, Italy
Design	RCT	Observational, test negative and indirect cohort designs
Study period	2008-13	2013-2015
Age	≥65 years, mean age 72.8 ±5.7 years	≥65 years
N vaccinated/non vaccinated cases	PP: 27/56 for IPD and 7/28 for PCV13 IPD; 100/144 for pnc CAP and 49/90 for PCV13 Pnc CAP mITT: 34/66 for IPD and 8/33 for PCV13 IPD; 135/174 for pnc CAP and 66/106 for PCV13 Pnc CAP	4/59 for pnc CAP and 4/39 for PCV13 CAP
For a first episode of disease		
Any IPD	PP: 51.8% (22.4 to 70.7) mITT: 48.5% (20.9 to 67.0)	NA
- PCV13 IPD	PP: 75.0% (41.4 to 90.8) mITT: 75.8% (46.5 to 90.3)	NA
VE against all-cause CAP	mITT: 5.1% (-5.1 to 14.2)	NA
VE against Pnc CAP	PP: 30.6% (9.8 to 46.7) mITT: 22.4% (2.3 to 38.5)	NA
- PCV13 type Pnc CAP	PP: 45.6% (21.8 to 62.5) mITT: 37.7% (14.3 to 55.1)	NA
VE against NI CAP	PP: 24.1% (-5.7 to 45.8) mITT: 17.4% (-10.2 to 38.2)	NA
- PCV13 type NI CAP	PP: 45.0% (14.2 to 65.3) mITT: 41.1% (12.7 to 60.7)	NA
For any episode of disease		
VE against any episode Pnc CAP	NA	24.3% (-104.6 to 72) by test negative design
- any episode PCV13 type CAP	PP: 42.4% (18.4 to 59.7) mITT: 37.5% (15.0 to 54.3)	37.2% (-290.8 to 89.9) by indirect cohort

CAP: community acquired pneumonia; IPD: Invasive pneumococcal disease; 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.; NI: non-invasive; Pnc: pneumococcal; PP: per protocol analysis; VE: vaccine efficacy/effectiveness; VT: vaccine types.

4.1.2.1 Non-invasive CAP

In the CAPITA trial, PCV13 efficacy was lower against non-invasive CAP as compared to IPD (including invasive CAP): efficacy against a first occurrence of vaccine type pneumococcal non-invasive CAP and against IPD was 41.1% (95%CI: 12.7 to 60.7) and 75.8% (95%CI: 46.5 to 90.3) respectively, and for all types 17.4% (non-significant) and 48.5%, respectively, Table 22. However, non-invasive CAP cases contained a higher proportion of PCV13 serotypes (67%) compared to IPD cases (50%).

4.1.3 Effect of age on efficacy

VE by age group is only available from the CAPITA trial on large age groups against the primary endpoint, i.e. a first episode of PCV13 type CAP (PP), and in a post-hoc mITT analysis on vaccine type IPD and CAP (together).[22, 123] In both PP and mITT analyses, VE is (non-significantly) higher in the 65-74 years compared to those aged 75-84 years (Table 23).[22, 123] VE in those ≥85 years of age is negative but CIs are very large due to small numbers. The post-hoc analysis of CAPITA data modelled the interaction between VE against vaccine type IPD/CAP and age, and showed a significant decline in efficacy with increasing age (Hazard Ratio 1.057, 95%CI 1.008–1.109, Figure 4 and Table 23).[123] The model also suggests that no protection is afforded after 85 years of age.

Table 23 – Observed and modelled PCV13 efficacy against pneumococcal disease in the elderly by age group,* CAPITA study[22, 123]

Age	<75 years	75-84 years	85+ years
N vaccinated/non vaccinated cases	28/59	15/28	6/3
Observed VE against PCV13 CAP, PP[22]	52.5% (24.1 to 71.0)	46.4% (-4.3 to 73.6)	-100% (-1156 to 57.8)
Observed VE against PCV13 CAP/IPD, mITT[123]	49.3% (26.2 to 67.1)	40.5% (3.3 to 65.9)	-100% (-1000 to 28.6)
Modelled VE against PCV13 CAP/IPD, mITT[123]	65% in 65 years	40% in 75 years	Around 0%

**as defined at disease onset. CAP: community acquired pneumonia; mITT: modified intention-to-treat; PP: per protocol; VE: vaccine efficacy.*

Figure 4 – Vaccine efficacy against PCV13 type CAP and IPD by age in the CAPITA trial[123]

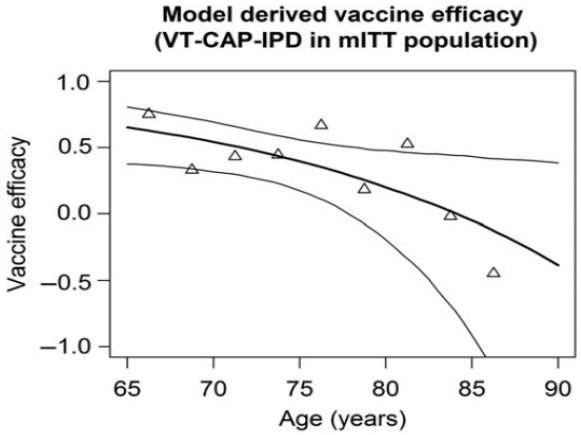


Figure 1. Model derived vaccine efficacy by age for first episode of vaccine-type community-acquired pneumonia (VT-CAP) or vaccine-type invasive pneumococcal disease (IPD) in modified intention-to-treat (mITT) population using a Cox proportional hazards model. Triangles represent crude estimates of age groups of 2.5 years each. The solid bold line represents the model derived vaccine efficacy. The 95% confidence interval (thin lines) was derived using 2000 bootstrap samples.

4.1.4 Effect of comorbidities on efficacy

The CAPITA trial excluded immunocompromised subjects at entry, but a secondary analysis (mITT analysis) computed efficacy against vaccine type disease in subjects in whom immunosuppression developed between study entry and onset of CAP (82 subjects, Table 24).[22] Efficacy was systematically higher and significant in immunocompetent subjects compared to participants who became immune-supressed after study entry, and in whom no significant efficacy could be demonstrated against any outcome. But caution should be taken in using these estimates because numbers of immune-supressed are very small in this trial and these recent immune-supressed patients may not be representative of the overall immune-supressed group of the same age.

Table 24 – CAPITA PCV13 efficacy against pneumococcal disease in the elderly, by risk group, in mITT analysis[22]

Risk group	Immuno-competent		Recently immuno-deficient/suppressed	
	VE	Vaccinated/non vac. cases	VE	Vaccinated/non vac. cases
VE PCV13 type Pnc CAP	45.2% (21.8 to 61.9)	51/93	-27.3% (-212.1 to 46.7)	14/11
VE PCV13 type IPD	75.0% (41.4 to 90.8)	7/28	66.7% (-315 to 99.4)	1/3
VE PCV13 non invasive CAP	44.4% (14.4 to 64.5)	35/63	30.0% (-105.5 to 77.6)	7/10

CAP: community acquired pneumonia; IPD: Invasive pneumococcal disease; mITT: modified intention-to-treat; Pnc: pneumococcal; VE: vaccine efficacy / effectiveness.

4.2 Efficacy and effectiveness of the 23-valent polysaccharide vaccine

The methods of the literature search are described in Appendix 1. In short, the review selected studies on efficacy and effectiveness from Western countries (mostly Europe), covering cases detected from 2000 or later, and presenting efficacy or effectiveness data against pneumococcal specific outcomes on all adults (no sub-group with risk factor), including elderly ≥65 years of age. We also included observational (effectiveness) studies because they are more representative of the total population, as clinical trials tend to exclude patients with severe comorbidities and immunodeficiencies. We opted for the restriction to recent studies due to changes in serotype distribution and detection methods in recent decades.

Clinical trials and observational studies adjusting for the main confounding factors and including a minimum of 100 pneumococcal cases were selected. IPD studies based on ICD discharge diagnoses and without laboratory confirmation, or mixing outcomes, were excluded. As studies using the screening method lack adjustment for the main confounding factors, these were excluded.

Four recent systematic reviews on PPV23 efficacy and effectiveness were retrieved.[16-18, 126] Those published before 2016, a 2013 Cochrane systematic review and one commissioned by the WHO, mixed valences of vaccines (from 2-valent to 23-valent), age, and outcomes for IPD (e.g. all IPD vs. only invasive pneumonia) and included studies of all periods. In particular, the 2013 Cochrane meta-analysis included an old but very large 1947 study (with a 2-valent vaccine) having a weight of 54% in the main IPD analysis of the most recent meta-analysis.[17, 127] Only one review provided specific VE estimates in the elderly but included only RCTs.[18] Primary studies included in these reviews and that fitted the selection criteria were retrieved and the literature search was updated and completed up to March 2016.

In total 13 primary studies were retrieved, including one RCT in at risk patients and 12 eligible observational studies.[29, 42, 128-138]

4.2.1 *Invasive pneumococcal disease*

Among studies meeting the selection criteria, six studies estimated the VE against IPD, three from Spain, two from England and one from Canada (Table 25).[29, 129, 130, 132, 133, 135] Two studies used a case-control design,[129, 133] while four studies used the indirect cohort (Broome) design to measure VE against vaccine types and specific serotypes.[29, 130, 132, 135]

VE against any IPD was estimated by the two Spanish case control studies, at >70%, and involved lower numbers of subjects.[129, 133] VE against vaccine serotype IPD cases was significant in all studies except in one,[135] and ranged 24-45% in the indirect cohort studies and as high as 72-77% in the two case control studies. The much higher VE found by the two (classical) case-control studies compared to the four indirect cohort studies are unlikely to be related to the specific setting: in Tarragona region, an additional cohort study conducted in the same population than the case-control study during an overlapping period (2002-05) found a lower (adjusted) VE, at 39% (95%CI -176 to 87) against vaccine-type IPD and 40% (95%CI -65 to 78) against all type IPD, as opposed to 77% and 72% respectively in the case control study.[60, 133]

These cohort estimates were very similar to those of the indirect cohort design but this study was not included because it had <100 cases (22 IPD cases).

Effectiveness against serotypes that are unique to PPV23 was significant (39-64%) and close to the estimates for other PPV23 serotypes including PCV13 types in the two indirect cohort studies measuring it.[130, 132] The effectiveness by vaccine serotype showed two main trends: effectiveness against serotype 7F was systematically higher (>50%) than the overall effectiveness against the 23 serotypes and significant in all studies except in one (Wright et al). Effectiveness against serotype 3 was never significant and point estimates were negative in two studies. Importantly, this serotype was one of the two most frequent serotypes among IPD cases in each study and was more frequent than serotype 7F (except in Wright et al), suggesting that its low and non-significant effectiveness cannot be attributed only to a low statistical power.

Separate estimates were not available for pneumonia and non-pneumonia IPD cases. Four studies did not describe the clinical features of the IPD cases, i.e. whether these cases included non-respiratory IPD. Two Spanish studies reported that pneumonia and/or empyema was the main clinical presentation in 62.2% and 86.4% of the cases.[130, 133]

Table 25 – Study characteristics and PPV23 effectiveness/efficacy against IPD in all ≥65 years of age, by serotype group

	Andrews[29] #	Wright[135]	Guttierez[130]	Rudnick[132]	Vila-Corcoles[133] **	Dominguez[129]
Region, country	England & Wales	North East England	Madrid, Spain	Ontario, Canada	Tarragona, Spain	Catalonia, Spain
Design	Indirect cohort	Indirect cohort	Indirect cohort	Indirect cohort	Matched case control	Matched case control
Study period	2003-10	2006-12	2008-11	1995-2011	2002-07	2001-02
Age	≥65 years	≥65 years	≥60 years	≥65 years	≥60 years, mean 73.2	≥65 years, mean 76.7
N cases/controls	1270/1272	555/106	588/211	1311/313	88/176	131/393
Patients recruitment	IPD surveillance	IPD surveillance	IPD surveillance	IPD from RC	IPD/community	IPD surveillance
VE against all IPD	NA	NA	NA	NA	72% (46 to 85)	70% (48 to 82)^
VE against PPV23 types	24% (10 to 36)	28.5% (-17 to 57)	44.5% (24 to 60)	38.9% (20 to 53)	77% (40 to 92)	72% (50 to 85)
VE against PCV7 types	38% (23 to 50)	NA	NA	40.6% (24 to 54)§	NA	NA
VE against 5 PCV13 nonPCV7 types*	8% (-17 to 28)	NA	NA	43.1% (26 to 56) §	NA	NA
VE against PPV23 nonPCV13 types	NA	NA	64.4% (45 to 77)	39.2% (20 to 54) §	NA	NA

*#: crudes estimates (matching was by age and year of illness) because adjusted estimates were similar; *: 1, 3, 5, 7F, 19A **: by case-control using community controls §: on all adults ≥15 years of age, including 75% ≥65 years of age; ^: using all controls. RC: Reference Centre for S. pneumoniae; IPD: Invasive pneumococcal disease; VE: vaccine efficacy/effectiveness; VT: vaccine types; Pnc: pneumococcal.*

4.2.1.1 Effect of age and comorbidities

The three IPD studies that stratified VE by age suggest a (non-significant) VE decline against PPV23 types with increasing age (Table 32). VE estimates in ≥85 years of age were systematically lower (<26%) than the estimates in the other age groups and were not significant. Wright et al also reported similar VE point estimates against all IPD in the 60-79 years of age (68%, 95%CI 26 to 86) compared to those aged 80 years and above (71%, 95%CI 9 to 91) but only 37 cases were found in subjects ≥80 years of age, explaining the large confidence intervals.[135] The largest study included 378 cases and 405 non-vaccine controls in subjects ≥85 years of age.[29]

All six effectiveness IPD studies stratified VE by risk group, using similar definitions of risk. In the two studies comparing VE against all IPD across risk groups, estimates in healthy adults were (non-significantly) higher in one study and lower in the other compared to adults with risk groups (Table 27).[129, 133] In four of the five studies evaluating VE against PPV23 type IPD, VE in healthy adults were (non-significantly) higher than the estimates among immunocompetent high risk subjects, with a difference in point estimates ranging 6-22% (Table 26). In immunocompromised patients, VE against PPV23 serotypes was only measured in the indirect cohort studies, was never significant and had large CI (Table 26), even in the largest study involving 439 cases and 486 controls in immunocompromised subjects.[29] This contrasts again with the high VE in immunocompromised found against all type IPD in the two case-control studies (Table 27), which involve small numbers of cases in immunocompromised (29 and 39); it was even high (88%) and significant in the smallest case-control study.[133]

Table 26 – PPV23 effectiveness against PPV23 type IPD in subjects ≥65 years of age, by age and by risk group

Risk group	Andrews[29] #	Wright[135]	Rudnick[132]	Guttierez[130]	Dominguez[129]
Region, country	England & Wales	North East England	Ontario, Canada	Madrid, Spain	Catalonia, Spain
Design	Indirect cohort	Indirect cohort	Indirect cohort	Indirect cohort	Matched case control
Study period	2003-2010	2006-12	1995-2011	2008-11	2001-02
N cases/controls	1270/1272	534/101	1311/313	588/211	118/118
65-74 years	28% (1 to 47)	43.6% (-27 to 75)	Analyses for all subjects ≥65 years of age	54.2% (15 to 75)**	Analyses for all subjects ≥65 years of age
75-84 years	25% (3 to 43)	21.1% (-75 to 65)		54.1% (19 to 74)***	
85+ years	18% (-11 to 39)	7.5% (-159 to 67)		25.5% (-23 to 55)*	
No risk	34% (12 to 50)	-16.7% (-188 to 53)	68.6% (33 to 85)	59.9% (33 to 76)	83% (-62 to 98)
HR immunocompetent	20% (-9 to 41)	32.4% (-36 to 66)	46.7% (23 to 63)	31.7% (-2 to 54)	77% (45 to 90)
HR immunocompromised	22% (-5 to 42)	33% (-65 to 73)	-6.5% (-67.4 to 32.2)		46% (-54 to 81)

*#: crude estimates (matching was by age and year of illness) because adjusted estimates were similar; HR: high risk. *: 80+; **: 60-69 years; ***: 70-79 years.*

Table 27 – PPV23 effectiveness against all type IPD in subjects ≥65 years of age, by risk group

Risk group	Vila-Corcoles[133]	Dominguez[129]
Region, country	Tarragona, Spain	Catalonia, Spain
Design	Matched case control	Matched case control
Study period	2002-07	2001-02
N cases/controls	88/176	134/134
No risk	60% (-89 to 91)	83% (-62 to 98)
HR immuno-competent	71% (21 to 89)	75% (47 to 86)
Immuno-compromised	88% (47 to 97)	50% (-44 to 82)

HR: high risk.

The two UK indirect cohort studies stratified VE by age and risk group (Table 28). Andrews et al, the largest included study, shows a gradient of effectiveness by age and risk group, with a 56% VE point estimate among 65-74 years of age with no risk.[29] However, VE is quite variable across strata and has wide 95%CI due to small numbers. Wright estimates have very wide 95%CI and show diverging trends by risk group compared to other studies, such as a much higher VE among people 65-74 years with high risk compared to those of the same age with no risk factor (in which VE is negative, -237%, 95%CI -1820 to 40).[135] This is likely due to the low number of (non-vaccine type) controls in this study, with very low numbers in each strata (e.g. 24 controls for subjects with no risk factor, all ages confounded).

Table 28 – PPV23 effectiveness against PPV23 type IPD by age at diagnosis and risk group

Risk group / age group (age at diagnosis)	Andrews#[29]			Wright[135]		
	65-74 years	75-84 years	≥85 years	65-74 years	75-84 years	≥85 years
N cases/controls	369/343	523/524	378/405	200/39	228/44	127/23
No risk	56% (24 to 75)	27% (-16 to 52)	14% (-40 to 47)	-237.5% (-1820 to 41)	32.5% (-305 to 89)	36.0% (-178 to 85)
HR immuno-competent	21% (-46 to 57)	23% (-23 to 52)	11% (-51 to 48)	70.3% (-6 to 92)	-18.8% (-220 to 56)	5.0% (-395 to 82)
Immuno-compromised	-17% (-96 to 31)	38% (3 to 43)	35% (-15 to 64)	40.8% (-110 to 83)	33.3% (-234 to 87)	28.6% (-616 to 93)

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

4.2.2 Community acquired pneumonia

One small clinical trial was conducted among 596 patients with a risk factor (chronic obstructive pulmonary disease or COPD) in Spain and is described in Table 31 under VE by risk group.[128] Four observational studies involved bacteraemic and non-bacteraemic pneumococcal CAP adult patients, two used a cohort design and the two others a classical case-control design (Table 29).[42, 131, 134, 137] Another case-control study measured PPV23 effectiveness in patients with chronic pulmonary disease but was excluded because it had duplicate cases with an included study.[137, 138]

Effectiveness against pneumococcal CAP in subjects ≥65 years of age was estimated in three studies (Table 29),[42, 134, 137] two case control studies (significant at 53% and 37%) and one cohort study (non-significant at 32%). VE against bacteraemic pneumococcal CAP was estimated in three studies, at 44-66%, and was found significant in two of these. VE against non bacteraemic pneumococcal CAP was measured in the two Spanish studies conducted in the same hospitals in consecutive periods; it was significant at 42% in the case-control study and non-significant at 29% in the cohort study.[42, 137] In three analyses of these two studies, VE of non-bacteraemic CAP was lower compared to VE against bacteraemic CAP, with a ratio ranging 0.55-0.77, but 95%CI overlap.

Again for the CAP outcome, higher VE estimates were observed in case-control studies compared to cohort studies. This can be evidenced by comparing two studies conducted in the same population of the Tarragona region by the same research group: the case-control study found a higher VE against pneumococcal CAP (+21%) in similar age groups compared to the subsequent cohort study, but 95%CI also overlap.[42, 137]

Table 29 – PPV23 effectiveness against community acquired pneumonia (CAP) in adults

PPV23 effectiveness against	Vila-Corcoles[137]	Ochoa-Gondar[42] *		Wiemken[134]	Jackson[131]
Country, design	Tarragona, Spain, matched case-control	Tarragona, Spain, cohort		International, case-control	US, cohort
		Vaccinated anytime vs. non-vaccinated	Vaccinated in 5 years before study start vs. non-vaccinated		
Period	2002-07	2008-11		2001-12	1998-2001
Definition	Hospitalized + outpatient (5%)	Hospitalized CAP		Hospitalized CAP	Hospitalized CAP
Age	≥50 years, 74% ≥65 years	≥60 years, 21% ≥80 years		≥65 years	≥65 years
Number cases	304 pnc cases	515 (113 pnc)	84 pnc cases	2688 (279 pnc)	1428 (61 pnc)
all-cause CAP	NA	8% (-20 to 29)	25% (2 to 42)	NA	-7% (-14 to 1)
all Pnc CAP	53% (33 to 68) in ≥65 years	32% (-18 to 61)	51% (16 to 71)	37% (16 to 60)	NA
Pnc BP	66% (34 to 83) in ≥50 years	53% (-145 to 91) N=12	62% (-68 to 91)	NA	44% (7 to 67)
PPV23 Pnc BP	76% (34 to 91) in ≥50 years	NA	NA	NA	NA
Pnc NBP	42% (14 to 61) in ≥50 years	29% (-27 to 61)	48% (8 to 71)	NA	NA

*CAP: community acquired pneumonia; VT: vaccine types; Pnc: pneumococcal; BP: bacteraemic (community acquired) pneumonia; NBP: non bacteraemic pneumonia. *: the main analyses of this study compared vaccinated in the 5 years before the study to those never vaccinated and vaccinated >5 years before study start (considered as "unvaccinated"). The second analysis compared vaccinated any time to never vaccinated.*

4.2.2.1 *Effect of age and comorbidities on CAP*

Two studies on pneumococcal CAP estimated VE by age, one case-control study against all pneumococcal CAP and one cohort study against bacteraemic pneumococcal CAP (Table 30).[131, 137] The case-control study suggests an increasing VE with increasing age, with no effectiveness in those 50-64 years of age but a significant VE among subjects ≥85 years of age.[137] The cohort study suggests a (non-significant) decline with increasing age, and a low and non-significant VE in those ≥85 years of age, as observed in IPD effectiveness studies.[131]

Three studies evaluated PPV23 VE against pneumococcal CAP in risk groups, two in Spain and one in the US (Table 31). One trial included only subjects with high risk (COPD) and could not estimate VE against pneumococcal CAP as it only involved five cases in placebo subjects and no case in vaccinees.[128] Two studies estimated VE against all pneumococcal CAP, but only one compared the three risk groups; this case-control study found a significant VE against pneumococcal CAP in immuno-compromised subjects at 71%, involving 64 cases.[137] The US cohort study compared VE against bacteraemic CAP in immuno-competent and immuno-compromised subjects: VE was higher in immuno-competent subjects (54% vs. 22%, respectively) but the difference was not significant and this small study involved 61 cases in total.[131]

Table 30 – PPV23 effectiveness against pneumococcal community acquired pneumonia by age group

Outcome Age group/studies	Pneumococcal CAP Vila-Corcoles[137]	Bacteraemic pnc CAP Jackson[131]
Country	Tarragona, Spain	US
Design	Matched case-control	Cohort
Period	2002-07	1998-2001
Definition	Hospitalized and outpatient CAP (5%), ≥50 years	Hospitalized CAP
Total Pnc CAP cases	304 (226 ≥65 years)	61 (bacteraemic)
VE in 50-64 years	6% (-151 to 65)	NA
VE in 65-74 years	48% (19 to 67)*	54% (13 to 76)
VE in 75-84 years	NA	
VE in 85+ years	56% (16 to 77)**	22% (-87 to 68)

*CAP: community acquired pneumonia; NA: non available; pnc: pneumococcal. *: 65-79 years **: 80+ years.*

Table 31 – PPV23 effectiveness against pneumococcal community acquired pneumonia in adults by risk group

Risk group/studies	All pneumococcal CAP Alfageme[128]	 Vila-Corcoles[137]	Bacteraemic pnc CAP Jackson[131]
Country	Sevilla, Spain	Tarragona, Spain	US
Design	RCT	Matched case control	Cohort
Period	1999-2004	2002-07	1998-2001
Definition	COPD no immune-compromised	Hospitalized and outpatient CAP (5%)	Hospitalized CAP
Age	Adults, 69% ≥65 years	≥50 years, 74% ≥65 years	≥65
Total CAP cases	58 (5 pnc)	304 pnc cases	1428 (61 pnc)
VE in no risk	No subject	61% (-2 to 85)	54% (13 to 76)
VE in HR immuno-competent	NA (5 vs 0 case)	41% (10 to 61)	
VE in HR immuno-compromised	NA	71% (34 to 89)	22% (-87 to 68)

COPD: chronic obstructive pulmonary disease; CAP: community acquired pneumonia; HR: high risk; NA: non available; pnc: pneumococcal; RCT: randomised clinical trial.

4.2.2.2 *All-cause CAP*

No significant VE was found against all cause CAP in the two studies estimating it, at 8% and -7% (Table 29).[42, 131] However, VE against all cause CAP was significant at 25% in subjects vaccinated in the five years before study start in Ochoa-Gondar (see 57. PPV23 duration of protection). Only one US study was retrieved with specific estimates of PPV23 VE against outpatient (all cause) pneumonia. No effectiveness could be demonstrated, in any risk group, despite large numbers of cases (Table 32), and the point estimates were negative.[131]

Table 32 – PPV23 effectiveness against outpatient all-cause community acquired pneumonia in adults ≥65 years of age

Effectiveness against	Jackson[131]
Country	US, 1998-2001
Design	Cohort
Total CAP cases	3061
Overall	-4% (-13 to 4)
No risk	-2% (-11 to 7)
HR immunocompetent	
Immunocompromised	-18% (-31 to 5)

CAP: community acquired pneumonia; HR: high risk.

4.3 Duration of vaccine protection

4.3.1 *PCV13 duration of protection*

The CAPITA trial did not publish efficacy estimates by time after vaccination. However, based on post-hoc analyses of cumulative number of episodes plotted against the time from vaccination, Bonten et al. conclude that efficacy persisted throughout the duration of the trial, i.e. around 4 years, without evidence of waning.[22] Unpublished efficacy estimates by cumulative period of time after vaccination, up to 5 years, did not show a clear decline: cumulative VE measured in the 2 years and in the 5 years since vaccination was significant for all outcomes and estimated, respectively, at 50% and 46% for vaccine type CAP, 48% and 45% for vaccine type non-invasive CAP and 75% for both periods for vaccine type IPD.[139] The author concluded that waning of vaccine type protection was not observed. However, available data are only cumulative and not available by (non-cumulative) time after vaccination (e.g. first two years vs. next three years since vaccination).[139]

Table 33 – OPA GMTs levels after initial PCV13 vaccination in subjects 50 years or older, calculated from Frenck et al[140]

Serotype	Post initial PCV13		Ratio
	Year 0 (Table 3)	Year 5 (Table 1)	year 5 vs. year 0
1	217	10	0.05
3	69	8	0.12
4	1,905	88	0.05
5	129	16	0.12
6A	2,779	173	0.06
6B	3,089	209	0.07
7F	2,196	122	0.06
9V	1,343	97	0.07
14	1,169	289	0.25
18C	1,728	120	0.07
19A	879	113	0.13
19F	472	38	0.08
23F	494	50	0.10

OPA: opsonophagocytic activity; GMT: geometric mean titre.

Additional information on changes in immunological markers after vaccination were searched to inform the waning function of the model, but was again limited to the first years after vaccination. Most PCV13 persistence studies do not provide these data.[21, 141] One study covered the 5-year period after initial PCV13 vaccination of adults ≥50 years of age, and showed a marked decline in OPA GMT in the vaccinated group for each vaccine serotype after 5 years, to titres 4 to 20 times lower (i.e. ratio year 5 vs. year 0 ranging 0.05-0.25), Table 33.[140] The titres after 5 years remained higher than baseline pre-vaccination levels (except for serotype 3) and the authors conclude that this indicates that anti-body levels are maintained for at least 5 years after vaccination. However, the publication only describes mean titres, and thus does not inform on the proportion of subjects still protected 5 years after vaccination. There are also no OPA thresholds defined specifically for protection in adults. The OPA threshold for protection in children is set at ≥8. It is unclear whether all vaccinated subjects retain protective titres against serotype 1, 3 and 5 (mean at 10, 8 and 16, respectively) 5 years after vaccination. However, the study was not designed to study the duration of protection.

4.3.2 PPV23 duration of protection

4.3.2.1 Invasive pneumococcal disease

Four studies reported VE against IPD over time after vaccination (Table 34).[29, 130, 132, 135] Three studies show a decline in VE over time, and point estimates over time are relatively similar across studies.[29, 130, 132] This decline was significant in the largest study, from 48% in the first two years to 15% after 5 years, p<0.001.[29]

Table 34 – PPV23 effectiveness against vaccine type IPD in ≥60 years of age, by time after vaccination

Time after vaccination	Andrews, E&W[29]	Wright, NE England[135]	Guttierez[130]	Rudnick[132]
Age	≥65 years	≥65 years	≥60 years	≥65 years
N cases	1270/1272	555/106	588/211	1311/313
VE <2 years	48% (32 to 60)	-9% (-119 to 43)	44.5% (19 to 62)	41.3% (20 to 57)
VE 2-5 years	21% (3 to 36)			
VE 5-9 years	15% (-3 to 30)	38.3% (-6 to 64)	32.5% (-6 to 57)	34.1% (6 to 54)
VE ≥10 years		-21% (-137 to 35)		

The Wright study has inconsistent point estimates, with higher VE in those vaccinated 5-9 years before disease onset compared to those vaccinated within five years before onset. This is not commented in the article but other analyses show discrepant results (see 4.1.3 and 4.1.4) and authors point to a low numbers of controls especially in specific strata (e.g. 15 non-vaccine types in those vaccinated <5 years before onset).[135]

Table 35 – PPV23 effectiveness against vaccine type IPD by time after vaccination and age group[29]

Time after vaccination	65-74 years	75-84 years	85+ years
N cases	369/343	523/524	378/405
VE <2 years	58% (32 to 73)	56% (32 to 71)	12% (-51 to 49)
VE 2-5 years	4% (-42 to 35)	30% (2 to 50)	26% (-10 to 50)
VE ≥5 years	25% (-11 to 49)	8% (-24 to 32)	14% (-20 to 39)

The largest study also stratified VE by time after vaccination and age group (Table 35).[29] VE was significant and above 55% in the first two years after vaccination in those <85 years of age. VE in the ≥85 years of age and in all subjects more than 5 years after vaccination was low (≤26%) and non-significant, despite reasonable numbers of cases per strata (>160).

Two studies stratified by time and risk group (Table 36).[29, 132] Trends are difficult to derive but in both studies VE was relatively high (35-64%) and significant in those non immune-compromised in the first period (<2 or <5 years). A significant VE was observed in immunocompromised subjects in the first two years after vaccination (43%, 95%CI 9 to 65, one study).[29] No significant VE was observed in the immuno-compromised five years or more after vaccination, even in the largest study involving 160 vaccinated cases and 120 non vaccinated cases.

Table 36 – PPV23 effectiveness against vaccine type IPD in ≥65 years of age, by time after vaccination and risk group

Time / Risk group	Andrews, E&W[29]			Rudnick, Canada[132]		
	No risk	HR immuno-competent	Immuno-compromised	No risk	HR immuno-competent	Immuno-compromised
<2 years	35% (0, 58)	63% (40, 78)	43% (9, 65)	64% (15, 85)	50% (23, 68)	3% (-61, 42)
2-5 years	47% (22, 64)	0% (-50, 33)	15% (-22, 40)			
≥5 years	18% (-20, 44)	12% (-48, 33)	20% (-11, 43)	77% (35, 92)	42% (5, 64)	-34% (-154, 30)

HR: high risk.

The Andrews study also stratified VE by age, risk group and time after vaccination. In healthy adults 65-74 years of age, VE was maintained above 60% for up to 5 years after vaccination (65% (23 to 84) and 62% (21 to 82) in the <2 and 2-5 years after vaccination, respectively).[29] In the first two years after vaccination, VE point estimates were higher in high risk immune-competent compared to those with no risk factor, in each age group. This pattern was not observed in longer time after vaccination. VE was also significant in immune-competent subjects <85 years of age in the first two years after vaccination (69%, (95%CI 22 to 88) in the 65-74 years and 70% (95%CI 36 to 86) in the 75-84 years).

4.3.2.2 CAP

No PPV23 study on pneumococcal CAP stratified VE by time after vaccination. Only one cohort study among subjects ≥60 years of age estimated VE in subjects vaccinated in the 5 years before study start and compared it to the VE estimates in subjects vaccinated at any time (Table 29).[42] Although 95%CI are large, VE point estimates against pneumococcal outcomes are higher (+ 9-19%) in those vaccinated within the five years before onset compared to subjects vaccinated at any time. In the same study, VE against all cause CAP was significant at 25% in subjects vaccinated in the five years before study start while it was not significant in subjects vaccinated at any time.

4.4 Selection of efficacy parameters

4.4.1 PCV13

Only one trial provided data on PCV13 efficacy in the elderly. This large trial is considered as suitable to provide parameters for PCV13 efficacy in the Belgian population, with some limitations. Populations from Belgium and the Netherlands are relatively comparable and had similar previous exposure to infant PCV7 vaccination, with a start of the universal PCV7 vaccination in June 2006 in the Netherlands vs. January 2007 in Belgium and a similar uptake in 2009 (95% vs. 90-96% in Belgium according to regions).[142] However recent infant vaccination exposure differs: PCV7 was replaced by PCV10 in May 2010 in the Netherlands while it was replaced by PCV13 in 2011-15 in Belgium (before switching to PCV10 in 2015-2016).

Regarding IPD, the placebo arm of CAPITA (mITT subjects) had a coverage of PCV13 serotypes at 50% in subjects ≥65 years in 2008-13, which is close to the 59% in IPD cases in Belgium for the same age group in 2009-11 (Table 37).[4, 22] The serotype distribution of non-invasive CAP is not available in Belgium. CAPITA data show a higher proportion of PCV13 serotypes compared to recent studies from EU countries using PCV13 (67% in mITT vs. 9-44%, respectively), see 2.4.1. In invasive pneumococcal disease. This is mostly due to a higher frequency of serotypes 19A in CAPITA compared to countries using PCV13 in infants (16% vs. 4% in IPD in CAPITA or ≤9% in invasive and non-invasive pneumonia in other countries). This high prevalence of 19A may be due to differences in recent PCV use, and has been observed in another country using infant PCV10 (Finland).[117] Another possible difference is the absence of policy to vaccinate all elderly with PPV23 in the Netherlands but the low PPV23 uptake in Belgium (around 10% in 2013 in the ≥65 years) is unlikely to have a substantial impact on the pneumococcal epidemiology of the elderly.[143]

Table 37 – Serotype distribution of pneumococcal cases in the CAPITA placebo group (mITT analysis) and comparison with Belgium IPD cases in ≥65 years of age[4, 22, 86]

Serotypes included in	All CAPITA cases, N (%)	NB CAP in CAPITA, N (%)	IPD cases in CAPITA, N (%)	IPD in 65+ Belgium 2009-11, %
PCV13	106 (62%)	73 (67%)	33 (50%)	59%
PCV7	13% (18/144) in PP analysis	15% (13/87) in PP analysis	13% (7/56) in PP analysis	8%
Total cases	174	109	66	669

CAP: community acquired pneumonia; NB: non bacteraemic; IPD: Invasive pneumococcal disease; PP: per protocol analysis.

In the modified intention-to-treat analysis, the CAPITA trial shows a significant and moderate efficacy against IPD (49% against all types and 76% against PCV13 types). Efficacy was lower against pneumococcal CAP (22% against all types and 38% against PCV13 types), including against non-invasive CAP (17% against all types and 41% against PCV13 types). VE estimates showed a significant decline in efficacy by increasing age, with

no protection in subjects above 85 years of age. No significant efficacy against subjects immune-compromised at the time of disease onset could be demonstrated but numbers of subjects are small. There is no data on PCV13 efficacy against outpatient pneumococcal pneumonia.

4.4.2 PPV23

VE estimates on PPV23 effect were extracted from 12 observational studies meeting the inclusion criteria; the only included RCT was very small and could not compute VE due to low numbers of cases. Effectiveness against PPV23 type IPD ranged 24-45% in studies based on the indirect cohort design and as high as 72-77% in two case-control studies. Effectiveness against all pneumococcal CAP ranged 32-53%, and was more than 20% higher in bacteraemic CAP (44-66%) compared to non-bacteraemic CAP (29-42%) in two Spanish studies. Most studies stratifying by age and risk group showed a decline of effectiveness with increasing age, and no evidence of effectiveness among subjects above 85 years of age or among those immune-compromised against both IPD and CAP, with the exception of some studies (see next paragraph).

Case-control studies systematically reported higher VE estimates compared to classical cohort or indirect cohort studies. In two studies conducted in the same population of the Tarragona region in overlapping periods, the case-control study found a 8-32% higher VE for the same outcomes in the same age group compared to the cohort study.[42, 137] This higher VE estimated in classical case-control studies compared to other designs has not been discussed in recent meta-analyses; the 2013 Cochrane review also found higher pooled VE estimates in case-control studies for IPD (53%) compared to cohort studies (43%) but the difference was not significant.[17] However, three out of the four case-control studies found a VE at 67-70% but were pooled with the lower estimate (26%) of a case-control study in a population at higher risk (Navajo adults with frequent risk factors). This difference in estimates may be due to insufficient control for confounding factors, such as those related to the indication bias (i.e. those who receive the vaccine generally differ from those who do not receive it, and this difference introduces a bias in the comparison).

A number of indirect cohort studies also have a low numbers of controls due to a low proportion of pneumococcal cases caused by non-PPV23 serotypes. For instance, one UK study reports inconsistent results, such as a higher VE in immune-compromised subjects compared to the VE in 65-74 years of age with no known risk factors, and a greater protection in those vaccinated 5-9 years before disease onset compared to those recently vaccinated.[135] 95% CI were also very wide as the study included only 106 controls (16% of all events) and inconsistent results are likely related to very small numbers of controls per strata.

Recent meta-analyses conducted on PPV efficacy and effectiveness were not used to inform the PPV23 parameters of our study for the reasons explained above, including a wide mix of settings, age groups, outcomes and the inclusion of very old studies.[16-18, 126] The Cochrane 2013 meta-analysis of RCT among adults found much higher pooled estimates for efficacy:[17] 74% (95%CI 55 to 86) against all IPD, 82% (95%CI 69 to 90) against PPV type IPD, 74% (95%CI 54 to 85) against invasive pneumococcal CAP and 73% (95%CI 13 to 92) against PPV type invasive CAP. But included studies involved all adult ages and pooled estimates are dominated by an old very large 1947 study (with a 2-valent vaccine) showing a 79% effectiveness against IPD and against invasive pneumococcal CAP, with a weight around 55% in these analyses. The Cochrane and the Kraucer-Melamed meta-analyses of observational studies found pooled estimates that are more comparable to our included studies, ranging 50-54% against all IPD. None of these reviews conducted meta-analyses on pneumococcal CAP.

Based on these comparisons, we propose to use the largest indirect cohort study for VE against IPD, conducted in England & Wales.[29] This study has the advantage of matching controls to cases in terms of risk factors, age and periods, and resulting to an equal number of controls and cases and large sample size. The indirect cohort design also presents the advantage of controlling for biases in ascertainment between cases and controls. This study provides numbers and VE across many different strata (by age, risk group and time after vaccination). Additionally, England & Wales present very similar pneumococcal epidemiology and infant vaccine history as Belgium. As this study presents more conservative estimates (i.e. lower values than those from other studies or from recent meta-analyses), we also selected the study from Guttierez et al for higher estimates to use in sensitivity analyses.[130] However, authors stated that the lower estimates are due to a longer time after vaccination compared to other studies. Indeed,

the 56% point estimate in the first two years after vaccination is of similar magnitude than many other studies (Andrews, personal communication).

No single study seems sufficient to provide all VE parameters against pneumococcal CAP, numbers of cases of pneumococcal CAP are small (60-300) and VE values vary substantially across design and settings. Cohort studies should be preferred, in particular due to the likely overestimation of VE in case-control studies and more robust design, but the most complete and recent cohort study 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.[42] However, three analyses indicated a relatively homogeneous ratio in the VE against non-bacteraemic versus bacteraemic CAP, ranging 0.55-0.77, which we will apply on VE against IPD (see further details under 6.2.2. PPV23 efficacy against non-invasive disease).

4.4.3 Comparison between PCV13 and PPV23 protection

Overall, PCV13 seems to provide a better protection against IPD than does PPV23: PCV13 showed a 76% efficacy against PCV13 type IPD compared to a 24-45% PPV23 effectiveness against PPV23 type IPD (Table 25). We could not evidence any difference in VE against pneumococcal CAP between the two vaccines in the included studies due to large confidence intervals and differences in design, populations, outcomes and exposure. When considering all serotypes, VE against all pneumococcal CAP was 22.4% for PCV13 and 32-53% for PPV23, VE against bacteraemic CAP was 48.5% for PCV13 vs. 29-42% for PPV23 and VE against non-bacteraemic CAP was 17.4% for PCV13 and 29-42% for PPV23 (Table 29).

However, comparisons between the two vaccines are difficult because the CAPITA study involved only 3.5% subjects above 85 years of age, no immuno-compromised subjects at entry, a maximum 5 years follow-up, and presents the ideal conditions of a trial study. PPV23 effectiveness studies included all subjects, including a sizeable proportion of persons ≥85 years of age and immunocompromised, and any time after vaccination, which are factors leading to lower estimates. They used different methods, have their own limitations and the case-control design tends to over-estimate VE. Furthermore no straightforward comparison between the two vaccines is possible for similar strata of subjects (e.g. 65-74 years with no risk factor <5 years after vaccination) because the CAPITA study has no separate estimates for IPD and pneumococcal CAP outcomes by age. The proportion of serotypes covered by PPV23 is also larger than those covered by PCV13, and this difference will increase over time under universal infant PCV13 vaccination.

4.4.4 Main limitations of this review

No study including a comparative analysis of PCV13 vs. PPV23 was found. Studies measuring PCV13 and PPV23 protection were not comparable, and each had its limitation to inform parameters for this study. The CAPITA trial had selected subjects (younger and not immunocompromised) that are less representative of the general elderly population, and were vaccinated under the ideal conditions of a trial. Furthermore, limited data were available by age and risk groups. Observational studies were at higher risk of biases and confounding factors and most of them lacked power to provide estimates by age group, risk group and time after vaccination, resulting in large confidence intervals for PPV23 effectiveness. Furthermore, many of these studies were conducted in two Spanish regions (Catalonia and Tarragona), where no high PCV uptake was achieved in infants and thus a low indirect effect in the elderly on PCV7 serotypes is expected.

Key points

- **PCV13 tends to show a better protection against IPD than does PPV23 but included subjects differed in age, risk group and time after vaccination between the two vaccines. VE against CAP did not show clear differences between the two vaccines due to large confidence intervals and variations in subjects, outcomes and exposure. The proportion of cases covered by each vaccine, the population involved and the design also prevented clear comparison between PCV13 and PPV23 protection.**
- **VE against bacteremic CAP tends to be higher compared to non-bacteremic CAP for both vaccines. This difference was more marked in PPV23 studies (24% difference in two studies).**
- **Both PCV13 and PPV23 failed to show significant efficacy/effectiveness against all cause CAP, and point estimates were all under 10%. No study measured vaccine effectiveness against outpatient pneumococcal CAP.**
- **VE in immunocompetent subjects against vaccine types was higher for both vaccines. No significant VE could be shown for immunocompromised subjects with both vaccines.**
- **In the PCV13 trial, efficacy was measured against a first episode of CAP but efficacy against all episodes showed similar estimates for vaccine type IPD. It is thus likely that estimates of protection against a first episode can be used for all episodes, at least for CAP.**
- **VE of both vaccines declined with increasing age in most studies but available data are limited for PCV13.**
- **There is a lack of robust data on waning efficacy. Limited data from CAPITA suggest that VE is maintained in the first five years after vaccination but no detailed data are available to refute (the start of) a potential decline in that period. Data on PPV23 VE according to time after vaccination is available from a few studies and show a progressive decline over time in most studies. However, confidence intervals are wide.**

4.5 Vaccine safety

4.5.1 Safety of PCV13

No systematic review of safety events related to PCV13 in adults was found. The EPAR describes that safety was assessed in six clinical studies including 5,667 adults receiving Prevenar13.[21] A trend to lower frequency of adverse reactions was associated with greater age; adults >65 years of age (regardless of prior pneumococcal vaccination status) reported fewer adverse reactions than younger adults, with adverse reactions generally most common in the youngest adults, 18 to 29 years of age. Overall, the frequencies were similar for all age groups, with the exception of vomiting which was very common (≥1/10) in adults aged 18 to 49 years and common (≥1/100 to < 1/10) in all other age groups. Pyrexia was very common in adults aged 18 to 29 years and common in all other age groups. Severe vaccination-site pain/tenderness and severe limitation of arm movement was very common in adults 18 to 39 years and common in all other age groups.

In the CAPITA trial involving 42 237 vaccinated subjects ≥65 years of age including 1006 subjects in a safety subgroup, the frequency of any local reactions was higher in the PCV13 group (38.4%) than in the placebo group (8.4%).[22] The frequency of any systematic events was similar in both groups (39.5% and 34.7%) but a higher prevalence of muscular pain was observed in vaccinees. Most local reactions and systemic events were mild or moderate in severity. There was no significant difference between the two groups in the frequencies of newly diagnosed chronic medical conditions, serious adverse events, or deaths. No vaccine-related serious adverse events were reported.

4.5.2 Safety of PPV23

PPV is generally considered as safe.[15, 144] In a meta-analysis of nine randomized controlled trials, local reactions were observed among approximately one third or fewer of 7531 patients receiving the vaccine.[145] These consisted mostly in mild, local side effects (pain at the injection site, erythema, and swelling) and usually persist for less than 48 hours. There were no reports of severe febrile or anaphylactic reactions, and no

neurologic disorders such as Guillain-Barre syndrome have been associated with PPV.

A randomized placebo controlled trial of PPV23 (Pneumovax 23) enrolled 1008 subjects of 50-64 years of age and ≥65 years of age, and the safety of an initial vaccination (first dose) was compared to revaccination.[146] Injection-site adverse reaction rate following initial vaccination was 52.9% in subjects aged 65 years or older, 72.8% in subjects aged 50-64 years and typically resolved by 5 days following vaccination. The most common local adverse reactions reported at the injection site after initial vaccination were pain/tenderness/soreness (60.0%), swelling/induration (20.3%), and erythema (16.4%). The rate of vaccine-related systemic adverse reactions following initial vaccination was 21.7% in subjects ≥65 years of age and 35.5% in subjects 50-64 years of age. The most common systemic adverse reactions reported were asthenia/fatigue, myalgia and headache. All of these adverse reactions were reported at a rate lower than 10% after receiving a placebo injection. Six vaccinees had serious adverse experiences within 14 days of vaccination compared to four who received placebo. In this clinical study an increased rate of local reactions was observed with revaccination at 3-5 years following initial vaccination (see below).

In a post-licensure safety assessment in the US covering 1990-2013 (VAERS system), injection site erythema (32%), injection site pain (27%) and injection site swelling (23%) were the most commonly reported non-serious AEs in adults when PPSV23 was administered alone.[147] Fever was most commonly reported in 39% of adults. Clinical review of the 62 death reports in adults did not reveal any concerning patterns that would suggest a causal association with PPV23.

Some earlier studies have suggested that injection site reactions (e.g., pain, swelling, redness) were reported more commonly after PPV23 revaccination than after primary vaccination, but these reactions were mild and typically resolved within 5 days.[148] However, more recent studies of older adults indicate that a second vaccination given five or more years after a first vaccination is well tolerated. The largest assessment of the safety of a pneumococcal polysaccharide revaccination was a prospective study of 1414 adults 50 to 74 years of age.[149] In that study, pneumococcal polysaccharide vaccine was given to 901 pneumococcal vaccine naïve adults and to 513 adults with a history of one prior pneumococcal vaccination five or more years before study enrollment. Local reactions were more frequent in the group given a second vaccination, but the reactions were not severe and were self-limited. Data from two retrospective studies also indicate that a third pneumococcal polysaccharide vaccination is not associated with an increased risk of medically attended adverse events in adults.

4.5.3 Comparative PPV23-PCV13 safety studies

A randomized trial compared the safety of PCV13 (N=417) with PPV23 (N=414) in pneumococcal vaccine-naive adults 60–64 years of age and included an additional 403 subjects 50–59 years of age in an open-label PCV13 arm.[141] Among those 60–64 years of age, the proportion of subjects with severe pain at the injection site was significantly higher after PPV23 compared to PCV13 ($p = 0.003$), and mild pain was significantly higher after PCV13 compared to PPV23 ($p = 0.005$). A higher proportion of 50–59 year old PCV13 recipients reported pain and limitation of arm movement compared to the older age group, while the percentages of subjects with swelling and redness were similar in the two groups. No notable differences in systemic events were observed between the PCV13 and PPV23 groups. The incidence of adverse events was similar between PCV13 (17.0%) and PPV23 (16.7%) recipients and mostly involved conditions commonly observed among older adults, and infectious disorders were the most frequently occurring types of adverse events. There were no vaccine related severe adverse events.

Key points

- **The frequency of local reactions and systemic adverse events was similar in similar age groups after PPV23 and PCV13 vaccination.**
- **Local reactions at injection site are reported in 35-50% of vaccinees ≥65 years of age, consist mostly in mild side effects (pain, erythema, and swelling) and usually resolve by 2-5 days following vaccination. Vaccine-related systemic adverse reactions following vaccination ranged 20-35% in those ≥50 years of age. The most common systemic adverse reactions reported were asthenia/fatigue, myalgia and headache. 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. However, these reactions were mild, resolved within 5 days and more recent studies of older adults indicate that a second vaccination given five or more years after a first vaccination is well tolerated.**

4.6 Vaccination uptake in adults

No data on the use of PCV13 in adults are available as the recommendation is very recent. Uptake data on PPV23 are available from the regular Health Interview Surveys.[19] Table 38 shows a decline in uptake in most ages >60 years between 2004 and 2013. In 2013, uptake 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.

Table 38 – Five year accumulated PPV23 vaccine uptake over 2004-2013 by age group (Health Interview Survey 2004, 2008, 2013)[19]

Age (years)	2004 (%)	2008 (%)	2013 (%)
50-54	1.0	1.6	2.3
55-59	2.6	3.6	3.7
60-64	9.2	7.2	5.1
65-69	12.1	8.1	6.8
70-74	20.5	16.4	9.3
75-79	16.3	16.4	14.1
80-84	14.0	18.3	11.4
85+	14.7	12.7	11.2

4.7 Cost of vaccine and vaccine administration

Based on this study expert group opinion (see list of experts under External expert in Colophon), 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 current retail prices in Belgium:[28] €74.55 for PCV13 and €28.46 for PPV23. In order to explore the influence of the price of the new PCV13 vaccine entering the market for widespread use in adults, the impact of 25% stepwise vaccine price reductions for PCV13 are explored in univariate and multivariate sensitivity analyses.

5 METHODS FOR ECONOMIC EVALUATION

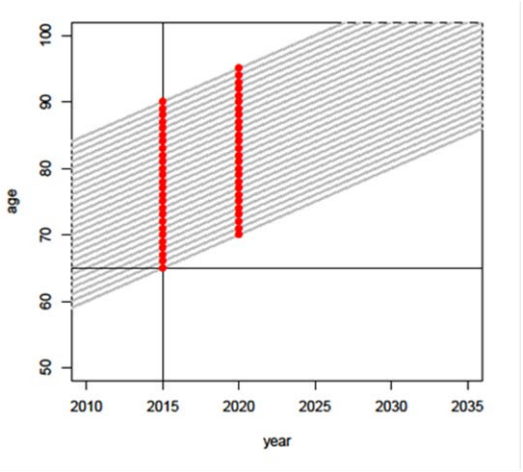
5.1 Model and analytical description

A static model was developed, using a modular design, making it easily adaptable to scenario analysis by modifying the input dataset. The model consists of 1) a core model which processes input data and calls in different functions and 2) modules which have a specific task.

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.[38] 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. We developed and applied an age-structured static multi-cohort model to simulate the costs and effects of pneumococcal conjugate vaccination according to the strategies defined in this report. The model was developed in the R software (R development Core Team, 2012, http://www.R-project.org). 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 (Figure 5). Cohort sizes over time are informed by age specific all-cause mortality and life-expectancy (based on life tables from the National Institute for Statistics, NIS), and were independent of explicit pneumococcal-specific mortality (this commonly made assumption had an insignificant influence on the outcomes).

The vaccines (PCV13, PPV23 or both), their timing and the applied scenario of duration and waning of vaccine-induced protection determine each cohort vaccine efficacy at every age in years post-vaccination, for both IPD and non-IPD and per serotype set ($VE(a,c)$, see Box 1). The interventions and disease burden evolution were modelled such that the comparison of interventions presented in this report start in the year 2017.

Figure 5 – Lexis diagram representing age cohorts between 65 and 90 years old in 2015 (grey lines)



Red dots represent the timing of vaccinating everyone aged 65-90 years old in 2015 with revaccination after 5 years.

A separate *serotype change* module is used to simulate the impact of childhood vaccination (herd immunity or indirect effects) and secular trends on the serotype distribution in adults. It combines the decay in vaccine type (PCV13) incidence per year with the proportion of non-PCV13 type incidence replacement as inputs and calculates an incidence correction factor for both PCV13-serotype specific incidence and non-PCV13-serotype specific incidence (see Box 1). The same correction factor is applied for invasive and non-invasive disease as the few available data do not suggest different indirect effect in invasive and non-invasive disease (see 3. Indirect effect of infant PCV vaccination on adult disease). If children are vaccinated with PCV10 (or any other (future) conjugate vaccine) instead of PCV13, this module can still be used, by simply expressing the PCV10 impact into PCV13-PPV23 vaccine serotype coverage.

Box 1 – Calculation of the population susceptible to IPD and non-IPD

$$F_{IPD} = P_{vac}\left\{\sum_\tau A_\tau(a)\left(1 - VE_{(IPD,\tau)}(a,c)\right)Q_\tau(a,c)\right\} + (1 - P_{vac})\{\sum_\tau A_\tau(a)\,Q_\tau(a,c)\},$$

With

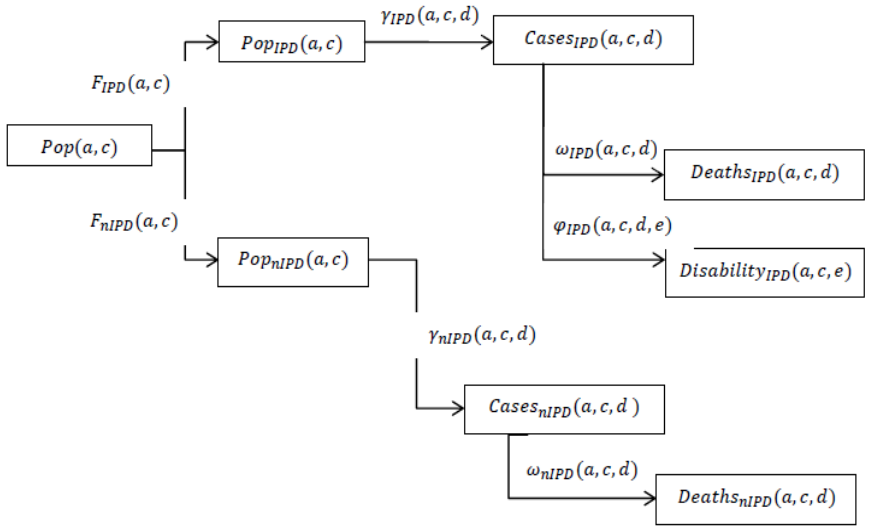
- P_{vac} : the proportion of the population at age a belonging to cohort c that is vaccinated (i.e. vaccination coverage), τ one of four serotype categories which take values from the set {*OPPV23, OPCV13, both, none*}. Here *"OPPV23"* signifies all serotypes included in the PPV23 vaccine but not in PCV13; *"OPCV13"* only serotypes in PCV13 but not in PPV23, *"both"* in both vaccines, *"none"* in neither vaccine.
- A_τ : the age dependent initial proportion of incidence of serogroup category τ at the start of the vaccination program.
- $VE_{(IPD,\tau)}(a,c)$: the vaccine efficacy against IPD for serogroup category τ of cohort *c* at age *a*. It takes into account the vaccine or combination of vaccines used, protection against IPD (as in the notation given here) or non-IPD disease types, the initial vaccine efficacy, the duration of vaccine protection and waning of vaccine efficacy over time.
- $Q_\tau(a,c)$: the ratio of the incidence (in a susceptible population) of serotype category τ of cohort *c* at age *a* and the incidence of that serotype category at the start of the vaccination program. This factor can incorporate PCV13 specific incidence changes due to the childhood vaccination program (PCV10 or PCV13) and the possible replacement of non-PCV13/PCV10 types. Serotype specific incidence changes are assumed proportional to observed serotype specific relative incidences of pneumococcal disease before implementation of the vaccination program.

For non-IPD, the fraction at F_{NIPD} is calculated analogously. Note that the population at risk for non-IPD and the population at risk for IPD will be largely overlapping and are only used as intermediates to calculate disease cases.

The vaccination coverage together with the calculated 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 (Figure 6). On those calculated population sizes per cohort-age combination, we apply age- and serotype-specific yearly incidence rates of the different hospitalised disease categories (meningitis, septicaemia, non-invasive pneumonia and invasive pneumonia) and outpatient non-invasive pneumonia; and their consequences in terms of deaths (Figure 6).

For outpatient cases only pneumococcal pneumonia is included because we considered the direct vaccine impact on acute otitis media (AOM) negligible in adults. The distinction between different disease categories was made based on how physicians classified hospitalised patients based on ICD9 coding in administrative databases. Possible long-term consequences of meningitis (hearing loss or neurological sequelae) are also taken into account.

Figure 6 – Structure of the model



From left to right: population, population at risk for invasive or non-invasive pneumococcal disease, disease cases and disease consequences (fatality or long term effects).
Pop(a,c): population size of cohort c at age a, Pop(a,c) is multiplied with the proportion that is not vaccine protected against IPD or non-IPD (FIPD(a,c) or FnIPD(a,c) respectively) to calculate the number of people at risk of IPD or non-IPD disease respectively (see Box 1). γIPD(a,c,d) and γnIPD(a,c,d): yearly rate to develop IPD or non-IPD respectively, with d indicating the disease category, i.e. bacteraemic hospitalised pneumonia, bacteraemia without focus or meningitis for IPD; outpatient pneumonia or non-invasive hospitalised pneumonia for non-IPD (impact of otitis media is assumed negligible). ωIPD(a,c,d) and ωnIPD(a,c,d): age- and cohort-specific death rates of the different IPD and non-IPD disease categories, respectively. φIPD(a,c,d,e): rate at which meningitis cases develop sequelae of category e (hearing problems or neurological sequelae). Other IPD disease categories do not have such long term outcomes attached.

5.2 Outcomes and comparators

Key outputs of the model include: averted hospitalised pneumococcal pneumonia, meningitis, bacteraemia without focus and other unspecified IPD, sequelae from meningitis, outpatient pneumonia, fatalities; quality adjusted life years (QALYs) gained and cost-effectiveness. 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.

Direct medical costs and QALYs associated with these outcome categories were included in order to compare the costs and QALYs of the current with increased vaccine uptake scenarios. A description of the vaccination scenarios modelled can be found in section 5.5.

Results are presented over all vaccination scenarios, as well as per age group, by plotting the proportion of simulations which are cost-effective for the most cost-effective vaccination strategy (i.e. the strategy with the highest expected net benefits) for each willingness to pay level for a QALY gained over a wide range from €0 to €350 000 (i.e. using “cost-effectiveness acceptability frontiers (CEAF)”, see section 5.4.1).

5.3 Perspective, time horizon, discounting

In accordance with the Belgian KCE guidelines on economic evaluations,[102] a health care payer perspective was used under which morbidity and mortality-associated productivity losses to society were excluded. All costs are expressed in Euro from the year 2015. Costs from previous years were updated to 2015 values using consumer price indices (Eurostat) if needed.

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% as recommended by the Belgian KCE guidelines.[102]

5.4 Uncertainty analysis

5.4.1 Probabilistic sensitivity analysis

Where appropriate, uncertainty around input parameter estimators was specified in terms of probability distributions (Table 40 with Input parameters). To assess the uncertainty of the ICERs, we conducted Monte-Carlo sampling with 1000 draws taken from the joint input distribution, assuming independence of the uncertain inputs (i.e. Probabilistic Sensitivity Analysis, PSA). These results are summed by appropriate age groups over cohorts for each outcome, and subsequently summarized by taking means and medians with their 95% uncertainty interval.

Furthermore cost-effectiveness acceptability frontiers (CEAFs) are constructed where informative. CEAFs have the attractive feature of summarizing parameter uncertainties in the ICERs in relation to a range of willingness to pay values. The CEAFs we present in this report are constructed as follows. The costs and health outcomes of an option for vaccination are compared to all other options for vaccination with a parameter value drawn from data driven distributions on most of the input parameters that determine the outputs. This process is repeated 1000 times per comparison of all options. Thus we obtain for each comparison 1000 sets of incremental costs and QALYs. These sets of comparisons can be categorised based on where they fall in the cost-effectiveness plane. Model runs are ranked at the highest (most favorable) end if they fall in the South East (SE) quadrant (i.e. they achieve cost savings and improve effectiveness (from most to least cost-saving)) and at the lowest end if they fall in the North West (NW) quadrant (i.e. cost more and are less or equally effective) as their comparator. The CEAFs are constructed such that for each willingness to pay value, we calculate the net benefit of vaccinating, i.e. calculating the monetary difference between the QALYs gained valued at the corresponding willingness to pay value and the incremental cost of implementing a vaccination option. In the CEAFs, the probability estimate of having the highest net-benefit is plotted for the options with highest average net-benefit at each willingness to pay value. Furthermore, the PSA results are also shown in cost-effectiveness planes.

5.5 Vaccination scenarios to compare

All incremental strategies in Table 39 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). Table 39 below presents the vaccination strategies. Uptake values are for the in 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).

These scenarios were defined after discussion with the expert group of this study (list provided under External experts in Colophon), and the Vaccination subcommittee of the Superior Health Council in Belgium. Uptake levels of the more expansive strategies (2 to 7) were informed by influenza uptake levels by age. Uptake levels were assumed to have relatively lower attainability in 85+ than for the other (younger) age groups based on the expert opinion and experience regarding medical practice in primary care.

Table 39 – 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)	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)	15% revaccination	25% revaccination	25% revaccination	20% revaccination
(6) as in (3) with PCV13 revaccination once after 5 years versus option (3)	15% revaccination	25% revaccination	25% revaccination	20% revaccination
(7) as in (4), with PPV23 revaccination once after 5 years versus option (4)	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 currently observed. The uptakes in options 2-7 are assumed, conditional on these options being funded (hence higher uptake). This potentially achievable uptake in other options is loosely based on observed influenza and PPV23 vaccination in the elderly (KCE Reports 204A).*

6 SUMMARY OF INPUT DATA FOR ECONOMIC EVALUATION

6.1 General overview of input parameters

Table 40 – General overview of assumptions and model input parameter values

Parameter	Scale/detail	Values and distribution	Source /Reference	Report section where described
Vaccine parameters				
Current vaccine uptake	Per year of age	Varying from 1% to 20% by age group, 2013	Health Interview Survey data[19]	Table 38 in 4.6. Vaccination uptake in adults
Targeted vaccine uptake (target for new unvaccinated cases)	Per age group	See Table 39	Expert committee	Table 39 in 5.5. Vaccination scenarios to compare
Vaccine efficacy of PCV13	Average over age, per time after vaccination and clinical syndrome	See Table 41 Waning: Table 42	CAPITA[22] Waning: assumptions based on CAPITA,[22] Frenck et al,[140] and expert opinion	Literature review under 4.1. Efficacy and effectiveness of the 13-valent conjugate vaccine and 4.3. Duration of vaccine protection
PCV13 vaccine efficacy age dependency	Per age in years	See Table 41	Van Werkhoven et al[123]	Table 23 and literature review in section 4.1.3. Effect of age on efficacy.
Vaccine efficacy of PPV23	Per age group, clinical syndrome and time after vaccination	See Table 41 Waning: Table 43.	IPD: Andrews et al for base case, Guttierez et al for sensitivity analyses[29, 130] Non-IPD: Andrews et al, scaled at a 0.55 ratio for VE non-IPD/IPD (base case) from Ochoa-Gondar et al.[29, 42] Sensitivity analysis: Andrews et al, scaled to the 0.77 ratio non-IPD/IPD, Vila-Corcoles case-control, 2009[29, 137] Waning assumption based on VE by time in Andrews et al[29]	IPD: 4.2.1. Invasive pneumococcal disease. Non-IPD: 4.2.2 Community acquired pneumonia Waning: 4.3. Duration of vaccine protection
Cost of vaccine administration	2015	€11.7 (half a GP visit or €23.32/2)	Tariff of one GP visit	4.7. Cost of vaccine and vaccine administration
Cost per PCV13 dose	Per dose	€74.55 current retail price, reduced prices explored in sensitivity analyses (25% stepwise reductions)	Belgisch centrum voor farmacotherapeutische informatie[28]	4.7. Cost of vaccine and vaccine administration

Cost per PPV23 dose	Per dose	€28.46 (2015 retail price), reduced prices explored in sensitivity analyses		
Epidemiological and demographical parameters				
Size target group	Per year of age	Non-random, 2015	Eurostat 2015 population data (http://ec.europa.eu/eurostat/data/database)	NA
Vaccine serotype coverage	IPD: in ≥50 years of age (2015) Non-IPD: percentage	- IPD (Table 13): PCV13: 25% PPV23: 66% - Non-IPD (Table 47): PCV13: 25% PPV23: 51%	IPD: NRC 2015 data for serogroups, Vanderlinden et al. for serotype distribution within vaccine serogroups (Germany)[77] Non-IPD: Benfield et al.[40]	IPD: Table 13 in section 2.4.1. In invasive pneumococcal disease Non-IPD: Table 14 under Benfield et al. in section 2.4.2. In non-invasive pneumococcal disease
Incidence of outpatient pneumococcal disease (non-invasive)	Per disease category and per age group	Outpatient all-cause pneumonia incidence: Table 4 Proportion of outpatient CAP attributable to pneumococcal infections: 10.5% (95%CI 7.7-13.2) Estimated incidence of outpatient pneumococcal pneumonia: Table 44	INTEGO 2013 R81 for incidence of all-cause pneumonia Proportion of outpatient CAP due to pneumococcus: pooled estimate from Capelastegui et al and Holm et al[47, 48]	Parameters in Table 44. Further details in section 2.1.3. Outpatient non-invasive pneumococcal disease
Incidence of hospitalised invasive pneumococcal disease	Per disease category and per age group	Table 2. All IPD assumed to be hospitalized	National Reference Centre (NRC), 2015, and Verhaeghen et al for the distribution of clinical syndromes.[4]	Table 2 in section 2.1.1. Hospitalised invasive pneumococcal disease
Incidence of hospitalised non-invasive pneumococcal pneumonia	Per disease category and per age group	Proportion of hospitalised adult pneumococcal CAP that is non-invasive: 82.7% (95%CI 80-86), based on IPD incidence data from Table 2	NRC for IPD incidence data. Pooled estimate of four studies for the proportion of hospitalised adult pneumococcal CAP that is non-invasive[41-44]	Literature review in section 2.1.2. Hospitalised non-invasive pneumococcal disease. Details in 6.3.2. Hospitalised pneumococcal disease
Proportion of long term consequences of meningitis	Per disease category	Sequelae in 25.7% of meningitis survivors, assuming 50% hearing loss and 50% other neurological sequelae - Percentage hearing loss in meningitis survivors: 12.9% (25.7/2%) in base case, 20% in sensitivity analysis - Percentage neurological sequelae in meningitis survivors: 12.9% in base case, 22% in sensitivity analysis	Proportion of meningitis sequelae: Jit[65] Proportion of neurological and hearing loss sequelae from literature review, Table 11 Sensitivity analysis for hearing loss: Worsoe et al[67] Sensitivity analysis for other neurological sequelae: Ostergaard et al[52]	Section 2.3.1. Pneumococcal meningitis

Case fatality ratio of IPD	Per disease category and age group	Table 6, Table 7 and Table 8	Based on MZG/RHM deaths during hospitalisations, in IPD cases matched between NRC and MZG/RHM	Table 6, Table 7 and Table 8 in section 2.2.1.1. IPD mortality in Belgian databases
Case fatality ratio (CFR) in outpatient pneumonia	Percentage	2/118 (1.7%) All ages (mean age study=74 years) Sampled from beta distribution	Vila Corcoles et al 2009[11]	Section 2.2.3. Mortality due to outpatient pneumococcal pneumonia
Ratio CFR invasive versus non-invasive pneumonia	Per age group, based on the counts	Adjusted hazard ratio for invasive versus non-invasive pneumonia 2.8 (1.6-5.1) Sampled from log-normal distribution	Capelastegui et al 2014[57] To inform CFR non-invasive pneumonia	Section 2.2
Indirect effect of PCV infant vaccination on PCV13 serotype incidence	Annual percentage	PCV13: Yearly decline of 16% (base case) For sensitivity analyses (including PCV10 infant vaccination): Table 48	SPIDNET 2010-15 analysis[35]	Section 3.1. Indirect effect of PCV13 vaccination
Proportion of serotype replacement due to infant vaccination	Annual percentage	Yearly compensation of 76.3% of the PCV13 decline (proportion of the PCV13 decline that is compensated by the non-PCV13 serotype increases) Scenarios for sensitivity analyses: Table 48	SPIDNET 2010-15 analysis[35]	Section 3.1. Indirect effect of PCV13 vaccination
Life expectancy	General population per age in years	Belgian national institute of statistics (2014 last available year)	(http://statbel.fgov.be/nl/statistieken/cijfers/bevolking/sterfte_leven/tafels/)	NA
Background mortality	All-cause mortality per age in years	Belgian national institute of statistics (2014 last available year)	(http://statbel.fgov.be/nl/statistieken/cijfers/bevolking/sterfte_leven/tafels/)	NA
Costs of treatment				
Hospitalisation cost	Per disease category and age in years	Table 18	MZG/RHM linked with NRC	Section 2.6.1. Cost of hospitalised episodes of pneumococcal disease
Out of hospital cost for hospitalised patients	NR	Not included	NR	NR
Out of hospital cost of outpatient pneumonia episodes	Average for all ages	€80.9 per outpatient episode Sensitivity analysis: €104.2 (adding a 2nd GP visit)	Table 67, derived from EU project GRACE,[46] (personal communication, Raymond Oppong, 2015)	Section 2.6.2. Cost of outpatient pneumococcal CAP
Cost of long term consequences of meningitis	Per long term cost category and age in years	- Hearing loss: Average €11 619 1st year	KCE report n° 231[150]	Table 46, Section 6.5. Costs of pneumococcal disease.

		€1498 / year in following years - Neurological sequelae: €35 000 /year		
QALY utilities				
QALY loss for hospitalised cases	Disease specific, per age in years	Table 16, PNEUMOCOST SURVEY France, uncertainty by bootstrapping, taking up QALY loss until 12 months after hospitalisation	PNEUMOCOST SURVEY France, personal communication of Gerard de Pouvourville, ESSEC, 2016 [94]	2.5.2.3. Conclusions for QoL input data used
QALY loss for non-hospitalised pneumonia	Disease specific, per age in years	Utility value QoL: 0.508 (0.442 – 0.575) sampled from normal distribution, applied during 8.5 days	Galante et al[94]	2.5.2.3. Conclusions for QoL input data used
QALY loss long term consequences of meningitis	Age independent	Utility weight for hearing loss: 0.635 (lifelong) Utility weight for neurological sequelae: 0.319 (lifelong). Sampled from normal distribution	Galante et al[94]	2.5.2.3. Conclusions for QoL input data used
UK population norms to use with Galante et al (average age: 31 years) disease-specific UK-derived utilities	Age independent	0.93	Age group 25-35 years from Kind et al[151]	2.5.2.3. Conclusions for QoL input data used
Discounting				
Discount rate for costs	Percentage	3%	Cleemput et al[102]	NA
Discount rate for health outcomes (life years, QALYs)	Percentage	1.5%	Cleemput et al[102]	NA

*NA: not available; NR: non relevant; NRC: National Reference Centre; MZG/RHM: Minimale Ziekenhuis Gegevens / Résumés Hospitaliers Minimum; *: SHA/AZV: Séjour Hospitalier Anonyme / Anoniem Ziekenhuis Verblijf; mITT; modified intention-to-treat analysis.*

6.2 Vaccine efficacy parameters

We assume no vaccine protection >85 years for IPD and >80 years for non-IPD, due to negative average VE. For scenarios in which vaccine efficacy is made age independent, we assume no vaccine protection in persons above 85 years consistent with efficacy against IPD and the maximum age of PPV23 vaccine protection, as emerged from our literature reviews (Table 41). VE against non-invasive CAP is assumed to be similar for both hospitalised and non-hospitalised CAP.

Because we used conservative estimates for the PPV23 effectiveness against IPD (see 4.4.2. PPV23), we also used the estimates from another more vaccine-favourable study in sensitivity analyses (Table 41).[130]

Table 41 – Summary of PCV13 and PPV23 efficacy selected as input for the model, by age and outcome

Age group	PCV13 (mITT analysis)	PPV23
Initial efficacy	≤4 years since vaccination	<2 years since vaccination
IPD, vaccine type		
50-84 years (average)	Base: 75.8% (47 to 90)*	Base: 56% (40 to 68) SA: 82% (69-90)
≥85 years	0%	0%
Non-invasive CAP, vaccine type		
50-79 years (average)	Base: 41.1% (12.7%-62%) and 0%	Base: 30.8% (22 to 37) and 0% SA: 43.1% (31 to 52) and 0%
≥80 years	0%	≥85 years: 0%
Age-specific function (IPD and non-IPD)	Scale to the hazard rate f_{HR}= 1.058 (1.008 to 1.111) per year of age	None (stratified by age group)
Waning (IPD and non-IPD)	Table 42 and Figure 7	2 years fixed then exponential decay, half-life value of 1.5 years, Table 43

**: <65 year olds assumed to have the same vaccine protection as 65 year olds; SA: sensitivity analysis.*

6.2.1 PCV13 vaccine efficacy over time

Vaccine efficacy estimates are used to derive vaccine effectiveness to estimate the cost-effectiveness of the various vaccination strategies. The waning functions for PCV13 efficacy was informed by the literature (see section 4.3 4.3) and by the expert committee's opinions. PCV13 protection is assumed to follow the same waning function against non-invasive CAP and IPD, but with different age-specific starting values.

From the CAPITA trial it appears that the minimum duration of protection without waning can be assumed to be 5 years. We therefore chose to assume after vaccine administration a constant period of full protection as reported by the CAPITA trial, followed by a period of logistic waning. The logistic waning function can be written as:

$$VE * \left(1 - \frac{1}{1+e^{-k(t-t_{50\%})}}\right)$$

With t the years after vaccination; VE the initial vaccine efficacy; $t_{50\%}$the time at which the current vaccine protection is reduced to 50% of initial VE and k parametrising the waning speed.

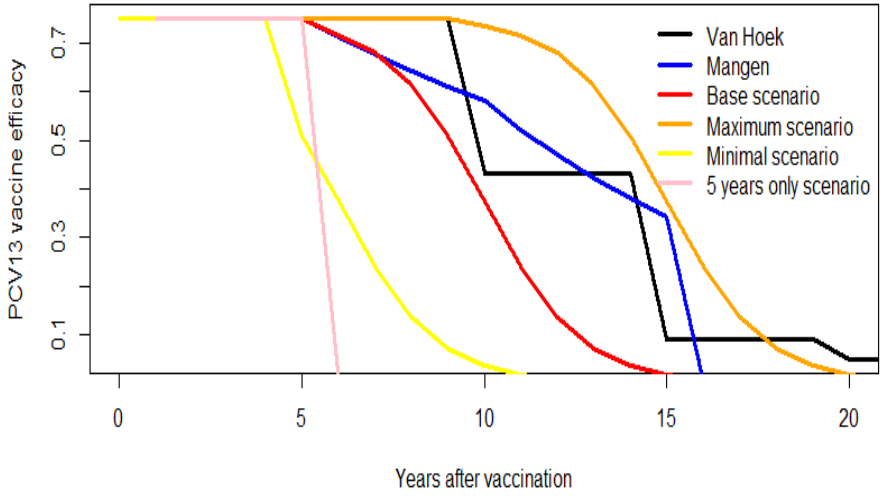
Table 42 summarises the minimum, baseline and maximum scenario for waning vaccine efficacy over time, and this is also visualized in Figure 7 Table 9, comparing these assumptions with those of previous economic evaluations.

Table 42 – Baseline and sensitivity PCV13 vaccine efficacy waning assumptions, 50-84 year olds

	Translation to logistic waning (see Figure 7)		
Scenario	**Period of "fixed vaccine protection**	**50% point ($t_{50\%}$)***	**Waning rate (k)**
5 years only scenario	5 years (then 0%)	-	-
Min. scenario	4 years	6 years	75%
Base case	5 years	10 years	75%
Max. scenario	9 years	15 years	75%

**: The time at which the current vaccine protection is reduced to 50% of initial VE.*

Figure 7 – Baseline and sensitivity PCV13 vaccine efficacy waning assumptions in 50-84 year-olds, compared to two recent studies[92, 152]



6.2.2 PPV23 efficacy against non-invasive disease

No single study could be used to derive this VE parameter (see 4.4.2. PPV23). In the three analyses of two studies, the ratio of VE non-bacteraemic pneumococcal CAP on bacteraemic CAP ranged 0.55-0.77.[42, 137] We apply the lowest and most trustworthy of these ratios (55% from Ochoa-Gondar et al cohort, analysis vaccinated anytime vs. non-vaccinated),[42] on the selected VE against IPD, informed by a much more robust study,[29] to derive the VE against non-invasive CAP used in baseline analyses (Table 41). This choice is more conservative than using parameters from any other retrieved study. Not only do we test the choice of the above ratio in univariate sensitivity analysis, but because the confidence interval of most estimates of VE against non-bacteraemic CAP do not include 0%, we also produce an equivalent series of (alternative baseline) analyses based on the assumption that PPV23 has 0% VE against non-invasive CAP.

This 50-84 year value is sampled from the log-normal distribution. In our analyses, we pay special attention to the very wide uncertainty of VE against non-invasive CAP, by using it in its parameterized form as shown in Table 41, as well as by assuming it is 0% with certainty.

The same efficacy estimates are used for hospitalised and outpatient non-invasive CAP.

6.2.3 PPV23 vaccine efficacy over time

PPV23 efficacy assumptions were informed by the literature review (see section 0.Efficacy and effectiveness of the 23-valent polysaccharide vaccine) and the expert committee. The estimates listed in Table 43 and Table 41 are used to inform the input distribution for the efficacy against IPD and non-IPD, by age and over time, respectively.

Table 43 – PPV23 efficacy against IPD by age and time, estimated by merging counts of 65-74 and 75-84 year groups as reported in Andrews et al[29]

Time after vaccination / age group	50-84 years of age	≥85 years of age
First 2 years after vaccination	VE= 0.56 (95%CI 0.40, 0.68)	0
>2 years after vaccination	Exponential waning starting from the second year with half-life value 1.5 years	0

We implement PPV23 waning – in the same way for IPD and non-IPD - by assuming 2 years of fixed vaccine protection, followed by exponential waning with a half time value of 1.5 years (i.e. reducing vaccine protection to 15% over the course of 3 years). The duration of PPV23 protection is varied between 2 and 5 years in sensitivity analysis.

6.3 Incidences of pneumococcal disease

6.3.1 Outpatient pneumococcal disease

Table 44 – Incidence of outpatient pneumonia per 100 000 persons (INTEGO, 2013)

Age group	All cause pneumonia (INTEGO)*	Estimated pneumococcal pneumonia incidence
50-64 years	599	63
65-74 years	672	71
75-84 years	1009	106
≥ 85 years	1505	158

**: R81 code; the estimated practice population is used as denominator. The yearly incidence rate of pneumonia is sampled from a beta(cases, denominator-cases) distribution to take uncertainty into account.*

The rates of all cause outpatient pneumonia are derived from the Intego 2013 database, see details in Table 4 in section 2.1.3.1. We estimated the proportion of pneumococcal pneumonia in all-cause outpatient CAP based on two selected studies from similar settings, from the literature review (see 2.1.3.2): 10.5% (95%CI 7.7-13.2).[47, 48] Table 44 present the rates used as final parameters by age.

6.3.2 Hospitalised pneumococcal disease

Table 2 describes the rates of hospitalised invasive pneumococcal disease, including invasive pneumonia.

As no Belgian data is available on non-invasive hospitalised pneumococcal pneumonia, due to the inaccuracy of ICD9 coded episodes in the MZG/RHM database, we used literature review estimates to derive these rates. The pooled estimate from four recent studies of high quality, i.e. using urine assay/test to detect non-bacteraemic cases in >80% of CAP cases, indicate that 82.7% (95%CI 80-86) of hospitalised pneumococcal CAP are non-invasive (see section 2.1.2.). We use that proportion of non-invasive pneumococcal pneumonia within hospitalised pneumococcal pneumonia (termed Pr(n. bac.)), 82.7%, together with the incidence of invasive pneumonia (Table 2 termed IBp) to estimate the incidence of non-invasive pneumonia (InBp) according to the following formula:

InBp = IBp Pr(n. bac.)/ (1- Pr(n. bac.))

The incidence of non-invasive pneumococcal pneumonia is thus a factor 4.78 larger than the incidence of invasive pneumococcal pneumonia among hospitalised cases.

In sensitivity analysis we varied the assumed percentage of IPD cases which are reported from 94% in the base case to 100% (thus lowering the estimated incidence). Additionally we assessed the impact of assuming higher hospitalised pneumococcal pneumonia incidences (invasive and non-invasive) by varying this incidence once to 150% and once to 200% of the base case incidence.

6.4 Mortality of pneumococcal disease

The case fatality ratio (CFR) of IPD has been directly derived from Belgian cases, based on MZG/RHM deaths during hospitalisations, in IPD cases matched between NRC and MZG/RHM. CFR of IPD are described by clinical syndrome in Table 6, Table 7 and Table 8, see section 2.2.1.1., and summarised below in Table 45. We made the assumption that the CFR of septicaemia can be used as parameter for the CFR of other IPD (such as peritonitis, arthritis etc.).

Table 45 – 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£
50-64 years	10.7%	2.2%	1.7% (for all ages)
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 MZG/RHM; **: by applying a factor derived from the hazard ratio of 1/(2.8) to the case fatality ratio of invasive pneumococcal CAP to derive non-invasive CAP; £: based on Vila-Corcoles et al.[11]*

As no mortality data on non-invasive disease are available from Belgian databases, we used literature review data.

To estimate the CFR of hospitalised non-invasive pneumococcal pneumonia, we employ the findings of Capelastegui 2014, which found a adjusted hazard rate of 2.8 (1.6-5.1) for the 30-day mortality of bacteraemic versus non-bacteraemic pneumococcal pneumonia (HR(bac. vs n. bac.)). This HR was sampled from the log-normal distribution. The CFR of non-invasive pneumonia is then calculated as follows, assuming that the ratio of mortality of bacteraemic on non-bacteraemic disease is a good proxy of the ratio of mortality of invasive on non-invasive disease:

$CFR_{nBp} = CFR_{Bp}$/HR(bac. vs n. bac.), with

- CFR_{nBp} = *case fatality ratio of hospitalised non bacteraemic pneumococcal pneumonia*
- CFR_{Bp} = *case fatality ration of hospitalised bacteraemic pneumococcal pneumonia*

To estimate the CFR of outpatient pneumococcal pneumonia, we used the findings of Vila-Corcoles et al 2009, i.e. 1.7%, sampled from beta distribution and for all ages, see section 2.2.3. Mortality due to outpatient pneumococcal pneumonia.[11] Uncertainty in CFR was taken into account by sampling from a distribution. For CFR following hospitalisation we performed additional sensitivity analysis by varying the CFR 50% up and 50% down.

6.5 Costs of pneumococcal disease

Costs of pneumococcal disease, for hospitalised and outpatient episodes, are described in the chapter on disease burden (2.6. Costs of pneumococcal disease) in Table 17 and Table 18. We used the costs of pneumococcal septicaemia (ICD9 code) in our analysis as an approximation for the costs of other IPD.

No costs of follow-up management of sequelae are available from Belgium. Based on the literature review, we assumed in the base case that half of the meningitis sequelae cases (estimated at 25.7%) present with hearing loss and half of them present with other neurological sequelae (see section 2.3.3. Conclusions). In hearing loss, one third was unilateral and two third bilateral.[54, 66] We also assumed that all those with hearing loss (defined as >30dB) need a hearing aid if loss 30-90 dB or a cochlear implant if loss >90 dB in accordance with INAMI/RIZIV rules for reimbursement.

We thus assumed that three quarter of hearing loss patients would need hearing aid (68-82% loss 30-90 dB in the two studies providing data) and the remaining one quarter would need cochlear implant (18-42% loss >90 dB).[54, 66] The cost of hearing aid was estimated based on INAMI/RIZIV data (Table 46).[150] For the sensitivity analyses, we varied the proportion of hearing loss and other neurological criteria according to other published studies (Table 46).[52, 67]

Table 46 – Cost estimates for meningitis sequelae

Parameter	Value	Source
Proportion of hearing loss in meningitis survivors	12.9% in base case*, 20% in sensitivity analysis	Jit,[65] and literature review 2.3, Worsoe et al[67]
Proportion of hearing loss requiring hearing aid (>30dB and <90dB)	75%	Literature review 2.3, Kastenbauer and Weisfelt[54, 66]
Proportion of hearing loss requiring cochlear implant (≥90dB)	25%	
First year cost per hearing aid	€529	Hanquet et al[150]
Cost for every following year per hearing aid	€339	
First year cost per cochlear implant	€26 298	
Cost for every following year per cochlear implant	€2577	
Number of implants needed per hearing loss patient (average number of ears affected)	5/3	Unilateral in one third and bilateral in two third in literature review[54, 66]
Average cost of treatment of hearing loss, per patient, first year	€11 618.75	Calculated from the respective proportion cost of hearing aid and cochlear implant
Average cost of treatment of hearing loss, per patient, in the following years	€1497.5	
Proportion other neurological sequelae in meningitis survivors	12.9% in base case* 22% in sensitivity analysis	Jit et al, literature review 2.3, Ostergaard et al[52]
Average cost of treatment for neurological sequelae, per year	€35 000	Beutels et al[153]

**: 50% of the total proportion of meningitis sequelae from Jit et al (25.7%).*

6.6 Serotype coverage and scenarios serotype replacement scenarios

Serotype coverage counts from NRC and Benfield et al (Table 13 and Table 14), updated to 2015, are used in base case analysis, focusing on ≥50 year olds.

Table 47 – 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,[40] 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.*

Changes in vaccine and non-vaccine serotype incidence influenced by the indirect effects of PCV13 infant vaccination are based on a multicentre European study comparing IPD incidence rates in elderly between the pre-PCV13 and 5 years post infant PCV13 vaccination in five countries with high uptake (France, Ireland, Scotland, Norway and Denmark) during 2010-15 (see section 3.1. Indirect effect of PCV13 vaccination).

Table 48 – Serotype change scenarios informed by SPIDNET data

Scenario	Description	PCV13 serotype decline (per year)	% replacement of PCV13 serotype decline by non-PCV13 increase	Relapse
Baseline scenario	Average of SPIDNET of changes of non-PCV7 PCV13 serotypes	-16%	76.3%	no
Min. scenario	Rounded minimum yearly decline SPIDNET data of changes of non-PCV7 PCV13 serotypes	-10%	76.3%	no
Max. scenario	Rounded maximum yearly decline SPIDNET data of changes of non-PCV7 PCV13 serotypes	-20%	76.3%	no
Quick relapse	Same as baseline	-16%	0%	With logistic curve ($t_{50\%}$=5 years, k=1)
Slow relapse	Same as baseline	-16%	0%	With logistic curve ($t_{50\%}$=10 years, k=0.5)

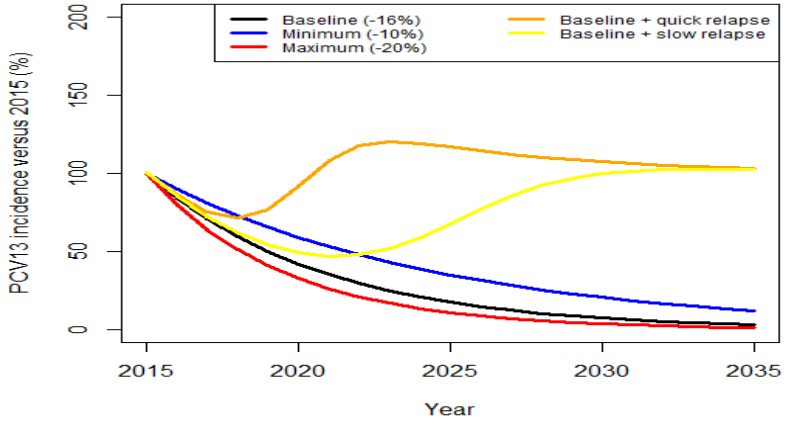
Indirect effects generated by infant PCV vaccination differ between PCV13 and PCV10, as described under "13. Indirect effect of infant PCV vaccination on adult disease".

The 76.3% value used for PCV13 replacement is calculated on the basis of SPIDNET data, where we find a yearly increase of 4% of non-PCV13 types (that represented 75.3% of 2015 IPD incidence in Belgium) and an average 16% decline of PCV13 types (24.7% of 2015 Belgian IPD incidence). This yields a proportion loss of PCV13 incidence compensated by the non-PCV13 serotype increases of: (4%*75.3%)/(16%*24.7%) = 76.3%. Therefore the per year compensation of the incidence decline due to the non-PCV13 increase is 76.3%.

Under PCV10 infant vaccination, increases in serotypes included in PCV13 but not in PCV10 showed a marked increase, and this potential risk is

modelled in the two “relapse” scenarios (one quick and one slow relapse scenario) of Table 48. In these scenarios, we make the PCV13 serotype incidence evolution different from a persisting trend over time, derived from our observations up to 2015, in an attempt to mimick the “comeback” of PCV13 serotypes for which PCV10 vaccine in infants does not provide sufficient indirect protection in adults (i.e. in the first place serotype 19A). That is - as shown in Figure 8 - we increase the incidence of PCV13 serotypes to attain slowly (“slow relapse”), or to exceed rapidly (“quick relapse”) the incidence level observed in 2015. Under the quick relapse scenario, PCV13 incidence departs from the downward trend after 2 years and temporarily exceeds its 2015 level after 7 years to return to its 2015 level after 15 years. Under the slow relapse scenario, PCV13 incidence starts to depart from the trend after 5 years to attain and stay at its 2015 level after 15 years. Note that our interventions are modelled to take place in 2017, accounting for the projected serotype incidence evolution up to that time. In both relapse scenarios the increase is specific for PCV13 types, since we assume 0% replacement by non-PCV13 types for these evolving incidences.

Figure 8 – Assumed proportion of PCV13 incidence over time versus the reference year 2015 (2015=1) according to various serotype change scenarios



7 RESULTS

7.1 Current disease burden

Table 49 shows the annual disease and cost burden by age. It shows that with current PPV23 vaccination recommendations in place, we expect about 5800 hospitalisations and 3600 additional patients treated in ambulatory care, as well as about 440 deaths, and about 4150 QALYs lost. The health care costs for treatment amount to about €33 million. The number of fatalities, and particularly those of 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, and this explains also the decreasing trend in costs by age group

Table 49 – Current annual disease and cost (€2015) burden related to *S. pneumoniae* in adults 50 years and older (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)

7.2 Effectiveness and cost-effectiveness analyses

In line with our expert group recommendations, we present three “base case” calculations, one in which PPV23 and PCV13 each have baseline (fully parameterised) efficacy against non-invasive CAP (see section 0. Vaccine efficacy parameters), one in which only PPV23 has no efficacy against non-IPD (i.e. it is then assumed to have 0% efficacy, without uncertainty) and one in which both PPV23 and PCV13 have no efficacy against non-IPD.

We use CEAFs showing for each willingness to pay (WTP) level over a wide range, 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 (when a QALY is valued at the WTP level shown).

When we inspect the CEAFs of all strategies and age groups put together, a common feature of all three baseline scenarios shown in the current section and other comparable figures below is that the current situation remains the option with the highest probability of yielding the highest net benefits at the lowest range of the WTP spectrum shown. This means that the value of the number of QALYs gained by any of the strategies with higher uptake (e.g. when the vaccine is subsidised) pneumococcal vaccination (with either PPV23 or PCV13) is unlikely to surpass the additional vaccination costs incurred minus the additional health care costs avoided, if each QALY is valued at less than about €50 000 by a policy maker (see e.g.Figure 9).

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 none of the vaccines has conclusive evidence to show efficacy in that age group. In line with that assumption, vaccination of 85+ individuals would imply 0 effects on health outcomes and an infinitely high cost-effectiveness ratio. Therefore, in the presentation of the results we do not show any specific results for this age group, but we do return to vaccination costs for this age group in the budget-impact section, as they could still be considered for vaccination for reasons of equity.

7.2.1 Assuming fully parameterised efficacy for both PPV23 and PCV13

Using fully parameterised information 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 65-84 years with PPV23 (from about €60 000 to €80 000 per QALY) and further to 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 9). This implies that it is better, in terms of cost-effectiveness, to have high uptake PPV23 in 75-84 year olds, before expanding this strategy to younger age groups.

Figure 9 – Cost-effectiveness acceptability frontier for all strategies and age groups combined, assuming baseline fully parameterised efficacy against non-invasive CAP for both vaccines

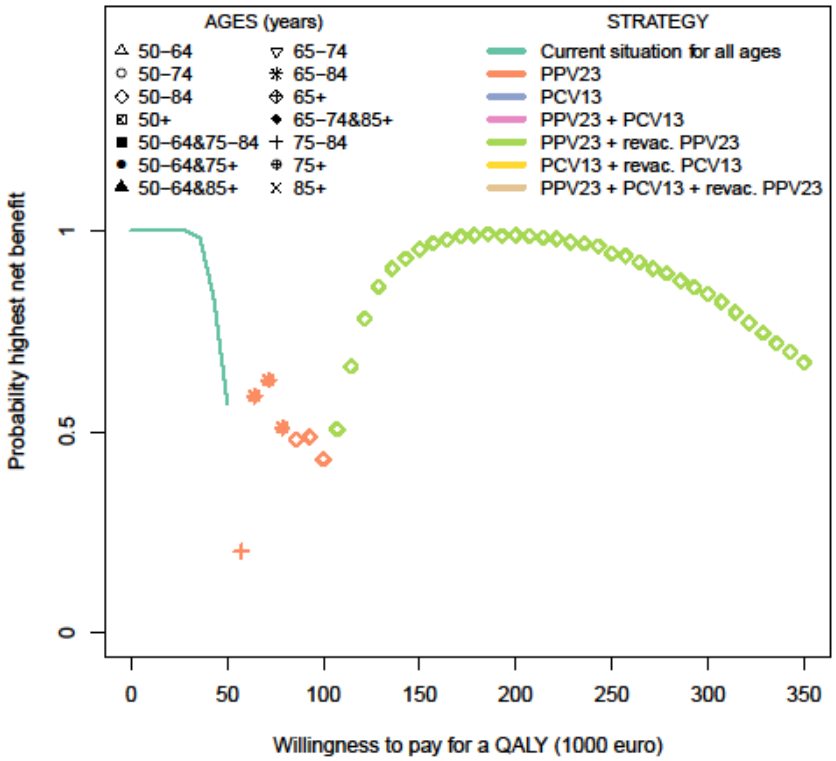


Table 50, Table 51, Table 52 show for each age group, more precise details of the incremental effects and cost-effectiveness versus the next most effective strategy, indicating that versus the current situation, introducing high uptake PPV23 and PCV13 vaccination is most effective. However versus high uptake PPV23, this strategy has much less to gain at relatively large incremental vaccination costs. The incremental effectiveness of further expansive strategies (e.g. PPV23+PCV13+PPV23 versus PPV23+PCV13) is less impressive, i.e. it is clear that vaccination costs at current prices are relatively high compared to the additional effects yielded at the margin. In terms of specific health outcomes, clearly PCV13 containing strategies have a larger impact on hospitalisations for pneumococcal pneumonia. On average, versus the current situation, high uptake PPV23 vaccination would cost about €52 000 - 83 000 per QALY gained, depending on age group, whereas high uptake PCV13 vaccination would cost more than twice that amount, about €171 000 - 338 000 per QALY gained.

In the 50-65 year olds over the remaining lifetime of the vaccinated cohorts, introducing PPV23+PCV13 vaccination at 25% uptake would prevent 24 deaths and gain 478 QALYs (see Table 50) versus the current situation, but would only gain 190 QALYs and 10 deaths versus PPV23 25% uptake, at incremental vaccination costs of €48 million. 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 (see column PPV23 versus current situation). PPV23 vaccination would cost about €83 000 per QALY gained in 50-64 y olds compared to PCV13 at about €201 000 per QALY gained, using 25% uptake for both.

Table 50 – Avoided burden and cost-effectiveness of vaccination in 50-64 year olds (mean(median) based on 1000 simulations, rounded to the nearest unit)

Outcomes	PPV23 versus current situation	PCV13 versus current situation	PPV23 + PCV13 versus current situation	PPV23 + PCV13 versus PPV23	PPV23 + PCV13 versus PCV13	PPV23 + revac. PPV23 versus PPV23 once	PCV13 + revac. PCV13 versus PCV13 once	PPV23 + PCV13 + revac. PPV23 versus (PPV23 + PCV13) once
Meningitis cases	9(9)	5(5)	12(12)	3(3)	7(7)	4(4)	0(0)	4(4)
Bacteraemia without focus and other IPD	9(9)	6(6)	13(13)	4(4)	7(7)	5(5)	1(1)	5(5)
Pneumococcal CAP hospitalisations	217(218)	269(268)	411(410)	194(194)	142(143)	86(86)	29(29)	66(67)
Outpatient pneumococcal CAP cases	127(126)	202(199)	274(270)	146(144)	71(70)	28(28)	17(17)	16(15)
Deaths meningitis	1(1)	1(1)	2(2)	0(0)	1(1)	1(0)	0(0)	0(0)
Deaths bacteraemia without focus and other IPD	1(1)	1(1)	2(2)	1(1)	1(1)	1(1)	0(0)	1(1)
Pneumonia deaths	11(11)	13(13)	21(20)	9(9)	8(8)	6(6)	2(2)	5(5)
Total deaths	14(14)	14(14)	24(24)	10(10)	10(10)	7(7)	2(2)	6(6)
Undiscounted QALY lost	288(285)	275(268)	478(470)	190(186)	203(201)	117(116)	25(24)	98(98)
Discounted QALY lost	239(237)	227(222)	395(388)	156(153)	168(167)	93(93)	19(19)	78(78)
Total medical cost undiscounted (€)	2 273 774 (2 304 334)	2 141 852 (2 150 497)	3 758 030 (3 754 478)	1 484 256 (1 487 532)	1 616 178 (1 632 994)	907 389 (917 913)	204 203 (204 526)	753 607 (763 893)
Total medical cost discounted (€)	1 897 853 (1 922 192)	1 814 202 (1 819 553)	3 140 474 (3 130 975)	1 242 621 (1 245 382)	1 326 272 (1 342 424)	662 624 (670 614)	144 029 (144 161)	543 429 (549 124)
Total vaccination costs (administration and purchase) discounted	-21 723 637 (-21 723 637)	-47 457 504 (-47 457 504)	-69 858 085 (-69 858 085)	-48 134 448 (-48 134 448)	-22 400 581 (-22 400 581)	-11 169 539 (-11 169 539)	-24 001 146 (-24 001 146)	-11 169 539 (-11 169 539)
ICER: mean(cost)/mean(QALY) (median ICER) of the ICER distribution	82 814 (83 728)	201 172 (206 351)	168 879 (171 883)	301 246 (307 561)	125 313 (126 149)	113 132 (113 080)	1 262 175 (1 290 100)	136 910 (136 704)

CAP: community acquired pneumonia; ICER: Incremental cost-effectiveness ratio; QALY: quality adjusted life years lost.

In 65-74 year olds over the remaining lifetime of the vaccinated cohorts, substantially more deaths and hospitalisations can be avoided, and slightly more QALYs can be gained (see Table 51), with PPV23 than with PCV13 (both at 50%), except for pneumococcal pneumonia outpatients and hospitalisations. For instance, about 45 deaths and 600 hospitalisations are averted and 500 QALYs are gained by a combined high uptake PPV23 and PCV13 program versus the current situation. It is important to remember though, that these effects are obtained with twice the vaccine uptake compared to these strategies in the 50-64 year olds. This may help explaining that on average PCV13 and PPV23 vaccination cost about €60 000 and about €170 000 per QALY gained, respectively, versus the current situation in this age group.

Table 51 – Avoided burden and cost-effectiveness of vaccination in 65-74 year olds (mean(median) based on 1000 simulations, rounded to the nearest unit)

Outcomes	PPV23 versus current situation	PCV13 versus current situation	PPV23 + PCV13 versus current situation	PPV23 + PCV13 versus PPV23	PPV23 + PCV13 versus PCV13	PPV23 + revac. PPV23 versus PPV23 once	PCV13 + revac. PCV13 versus PCV13 once	PPV23 + PCV13 + revac. PPV23 versus (PPV23 + PCV13) once
Meningitis cases	7(7)	4(4)	10(10)	3(3)	6(6)	3(3)	0(0)	3(3)
Bacteraemia without focus and other IPD	14(15)	8(8)	19(20)	5(5)	11(11)	6(6)	1(1)	6(6)
Pneumococcal CAP hospitalisations	342(344)	349(351)	575(574)	232(229)	226(227)	101(102)	16(15)	78(79)
Outpatient pneumococcal CAP cases	134(132)	180(179)	256(254)	122(121)	76(75)	27(26)	7(7)	15(15)
Deaths meningitis	1(1)	1(1)	1(1)	0(0)	1(1)	1(1)	0(0)	1(1)
Deaths bacteraemia without focus and other IPD	2(2)	1(1)	3(3)	1(1)	2(2)	1(1)	0(0)	1(1)
Pneumonia deaths	25(25)	23(22)	41(40)	16(15)	18(18)	10(10)	1(1)	9(9)
Total deaths	29(28)	25(24)	45(44)	17(16)	20(20)	12(12)	2(2)	10(10)
Undiscounted QALY lost	337(333)	272(266)	511(503)	174(170)	239(236)	102(101)	11(11)	85(86)
Discounted QALY lost	301(298)	240(235)	452(447)	152(148)	213(211)	86(86)	9(9)	72(72)
Total medical cost undiscounted (€)	2 559 386 (2 575 999)	2 268 919 (2 275 051)	4 023 606 (4 014 425)	1 464 220 (1 461 007)	1 754 687 (1 768 112)	703 101 (710 144)	83 592 (81 846)	569 559 (575 383)
Total medical cost discounted (€)	2 340 219 (2 355 593)	2 034 813 (2 042 580)	3 624 245 (3 613 952)	1 284 026 (1 279 330)	1 589 432 1 602 632)	550 574 (556 219)	59 156 (57 756)	442 472 (446 616)
Total vaccination costs (administration and purchase) discounted	-19 545 248 (-19 545 248)	-43 107 470 (-43 107 470)	-63 617 697 (-63 617 697)	-44 072 449 (-44 072 449)	-20 510 227 (-20 510 227)	-7 978 159 (-7 978 159)	-17 143 496 (-17 143 496)	-7 978 159 (-7 978 159)
ICER: mean(cost)/mean(QALY) (median ICER) of the ICER distribution	57 212 (57 716)	171 344 (174 491)	132 590 (134 364)	281 970 (288 510)	88 929 (89 579)	86 217 (86 564)	1 954 873 (2 005 960)	104 198 (104 021)

CAP: community acquired pneumonia; ICER: Incremental cost-effectiveness ratio; QALY: quality adjusted life years lost.

In 75-84 year olds (Table 52), we see that effectiveness against many outcomes further improves (but with 10% higher uptake than in the previous age group) and that the balance tips further in favour of PPV23. Note also that the uncertainty on the pneumococcal pneumonia hospitalisations and outpatient cases averted becomes larger (also for PCV13 now with a lower negative bound on the uncertainty interval). The ICER becomes greater for PCV13 containing strategies and lower for PPV23 containing strategies, in comparison to the previous age groups.

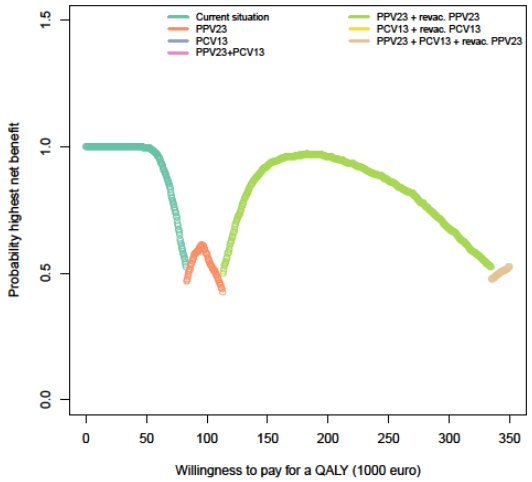
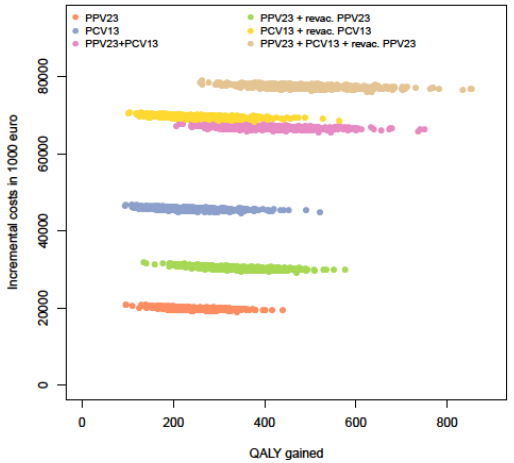
Table 52 – Avoided burden and cost-effectiveness of vaccination in 75-84 year olds (mean(median) based on 1000 simulations, rounded to the nearest unit)

Outcomes	PPV23 versus current situation	PCV13 versus current situation	PPV23 + PCV13 versus current situation	PPV23 + PCV13 versus PPV23	PPV23 + PCV13 versus PCV13	PPV23 + revac. PPV23 versus PPV23 once	PCV13 + revac. PCV13 versus PCV13 once	PPV23 + PCV13 + revac. PPV23 versus (PPV23 + PCV13) once
Meningitis cases	9(9)	4(4)	11(11)	2(2)	7(7)	1(2)	0(0)	1(1)
Bacteraemia without focus and other IPD	18(18)	8(8)	22(22)	4(4)	14(14)	3(3)	0(0)	3(3)
Pneumococcal CAP hospitalisations	422(423)	151(159)	505(501)	83(78)	354(350)	47(47)	4(2)	39(39)
Outpatient pneumococcal CAP cases	161(159)	51(53)	188(185)	27(21)	137(132)	11(11)	2(0)	8(7)
Deaths meningitis	3(3)	1(1)	3(3)	1(1)	2(2)	1(1)	0(0)	0(0)
Deaths bacteraemia without focus and other IPD	3(3)	1(2)	4(4)	1(1)	3(3)	1(1)	0(0)	1(1)
Pneumonia deaths	45(45)	18(18)	56(55)	10(10)	38(38)	6(6)	1(0)	6(6)
Total deaths	51(51)	20(21)	63(63)	12(12)	43(42)	8(8)	1(1)	7(7)
Undiscounted QALY lost	297(294)	115(118)	356(353)	59(58)	241(239)	34(34)	3(2)	30(30)
Discounted QALY lost	277(275)	105(109)	330(328)	54(52)	225(223)	30(30)	2(2)	26(26)
Total medical cost undiscounted (€)	2 190 270 (2 199 671)	804 301 (846 006)	2 610 605 (2 604 577)	420 335 (401 840)	1 806 304 (1 799 159)	238 671 (240 687)	19 739 (10 013)	201 883 (204 520)
Total medical cost discounted (€)	2 037 593 (2 048 091)	720 635 (759 370)	2 400 162 (2 394 913)	362 570 (345 028)	1 679 527 (1 668 893)	189 543 (191 253)	16 478 (7 106)	159 723 (162 038)
Total vaccination costs (administration and purchase) discounted	-16 465 506 (-16 465 506)	-36 383 438 (-36 383 438)	-53 721 416 (-53 721 416)	-37 255 910 (-37 255 910)	-17 337 978 (-17 337 978)	-4 497 254 (-4 497 254)	-9 663 716 (-9 663 716)	-4 497 254 (-4 497 254)
ICER: mean(cost)/mean(QALY) (median ICER) of the ICER distribution	52 147 (52 606)	338 159 (325 811)	155 395 (156 659)	688 486 (701 802)	69 655 (70 189)	143 642 (143 834)	4 058 817 (6 148 401)	165 978 (165 633)

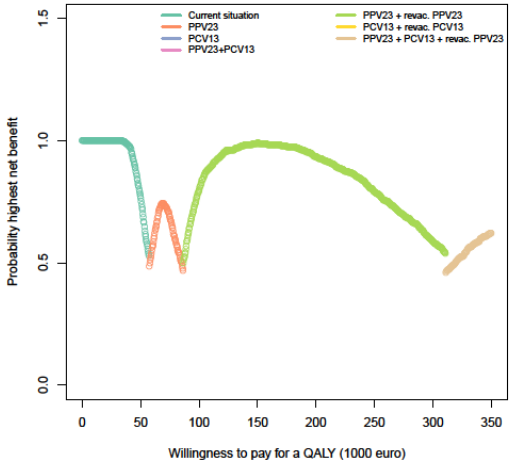
For a visual overview of the effectiveness and cost-effectiveness of the different strategies in the different age groups, Figure 10 shows CEAFs and cost-effectiveness planes by age group targeted. In the cost-effectiveness planes the realizations of 1000 simulations in terms of costs and effects (QALYs), results in clouds of 1000 points – one cloud for each incremental strategy - plotted versus the origin, where the origin of the plane represents the current situation. Note that the same 1000 simulations per strategy are used to produce the other results we present under uncertainty.

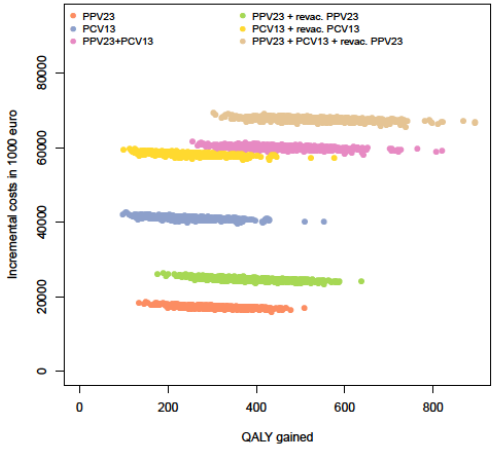
The cost-effectiveness planes show by the axis scales and the position of the ellipsoid clouds that most of the parametric uncertainty relates to uncertainty around the QALYs gained. The positions of the clouds also indicate that at the mean, the PCV13 containing strategies are dominated by the PPV23-only strategies in above 65 year olds. The CEAFs per age group confirm this by showing that increasing PPV23 uptake is the preferred change from the current situation in all age groups, followed by PPV23 with PPV23 revaccination, and, in 50-74 year olds only, PPV23+PCV13 and revaccination with PPV23 when WTP exceeds €300 000 per QALY gained.

Figure 10 – Cost-effectiveness acceptability frontiers (CEAFs, on the left) and cost-effectiveness planes (CE planes, on the right) by targeted age group assuming fully parameterized vaccine efficacy for both vaccines

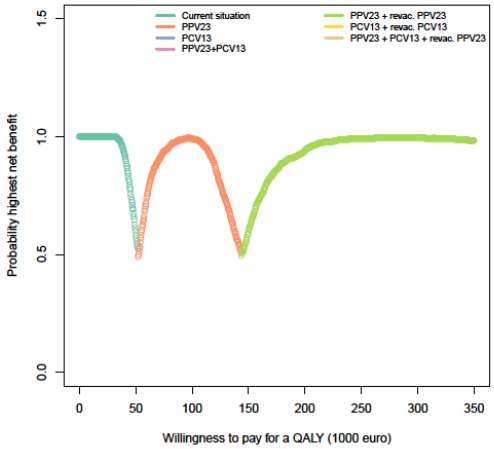
Age group	Cost-effectiveness acceptability frontiers	Cost-effectiveness plane
50-64 years		

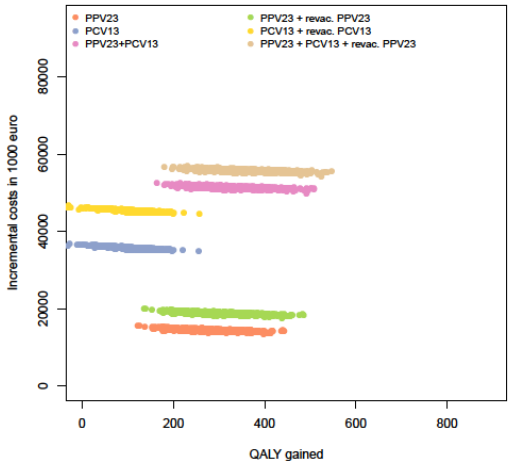
65-74 years





75-84 years





7.2.2 *Assuming fully parameterised efficacy for PCV13 and no protection against non-invasive CAP for PPV23*

When we assume that PPV23 has 0% efficacy (with certainty) and PCV13 has baseline (fully parameterized uncertainty) efficacy against non-invasive CAP, the best options with increasing WTP for a QALY are to (1) vaccinate the age group 75-84 years with PPV23 only (for WTP €70 000 to €100 000), which expands to (2) 65-84 years with PPV23 (WTP: €100 000 to €120 000) only and with (3) the addition of PPV23 revaccination (from WTP €120 000) expanded to all ages (50-84 y) from €150 000 and the final (4) addition of PCV13 at WTP>280 000 per QALY (see Figure 11). This implies that the overall choice of strategies is similar (though less cost-effective versus the current situation) compared to the completely parameterized efficacy, except in the highest region of WTP considered, where PPV23+ PCV13+PPV23, the only PCV13 containing strategy, emerges as the most beneficial one.

These observations are nearly uniform across the different age groups, as shown in Figure 13. Assuming no PPV23 protection against non-invasive CAP makes PCV13 containing strategies the most beneficial when WTP per QALY exceeds €250 000 and €200 000 in the 50-64 year and 65-74 year age groups, respectively. In 75-84 year olds PCV13 is not selected as a component of the most beneficial strategy at any WTP level up to €350 000.

Figure 11 – Cost-effectiveness acceptability frontier assuming fully parameterised efficacy against non-invasive CAP by PCV13 only, and 0% such efficacy by PPV23

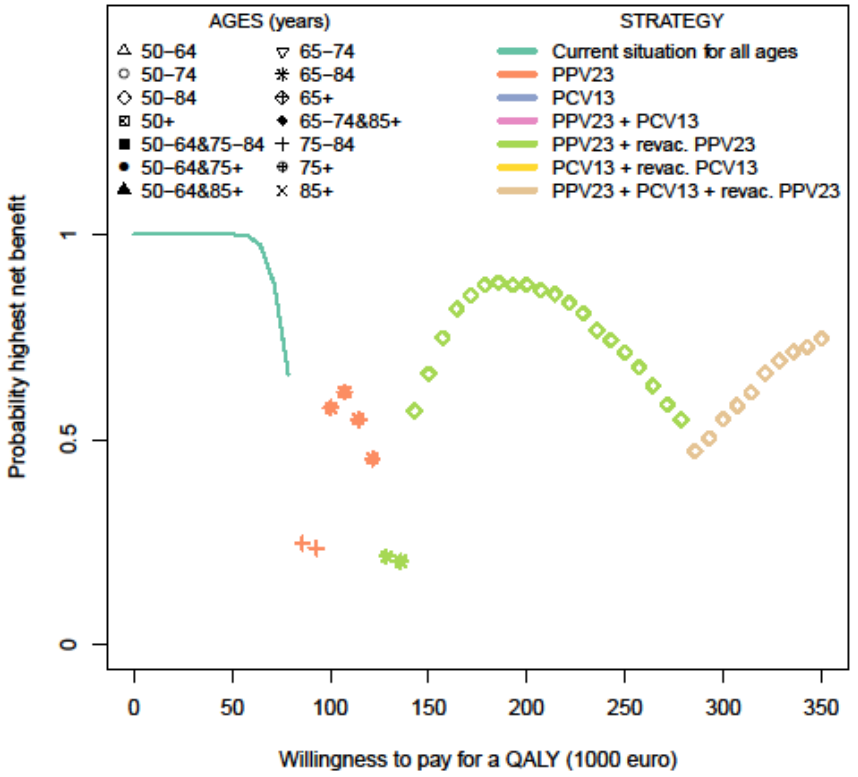
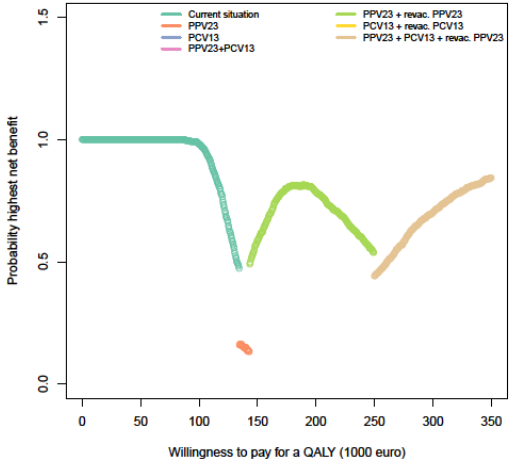
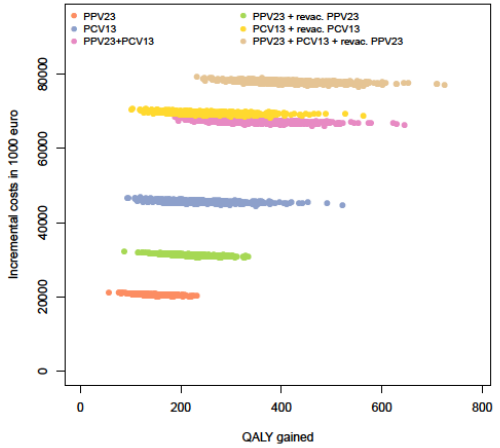
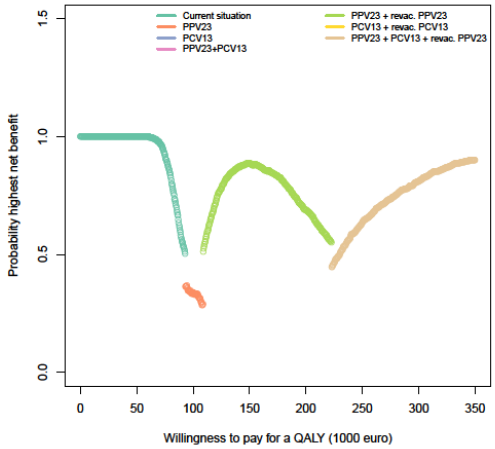
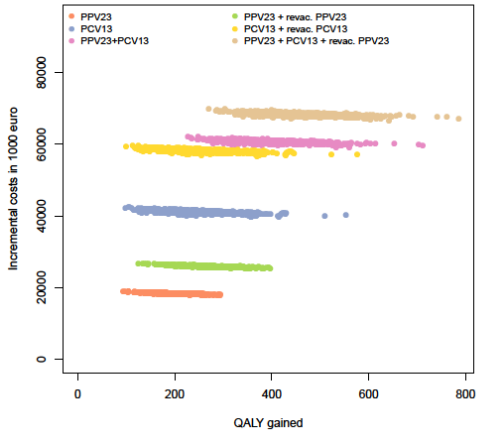


Figure 12 – Cost-effectiveness acceptability frontiers (CEAFs, on the left) and cost-effectiveness planes (CE planes, on the right) by targeted age group assuming fully parameterised efficacy against non-invasive CAP by PCV13 only, and 0% such efficacy by PPV23

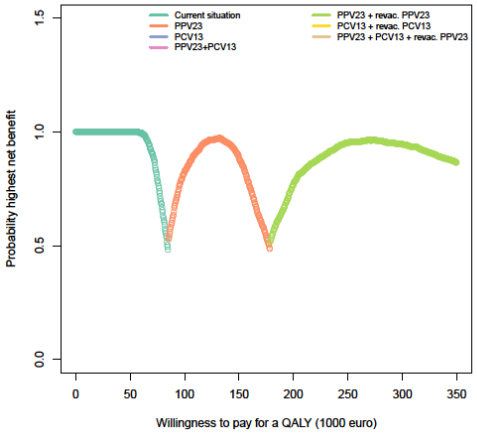
Age group	Cost-effectiveness acceptability frontier	CE plane
50-64 years		

65-74 years





75-84 years



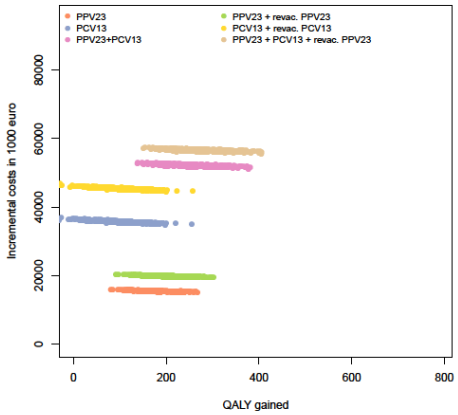


Table 53, Table 54 and Table 55 show for the three age groups that the strategies involving PPV23 now have a substantially reduced impact on the pneumonia outcomes, and therefore also in terms of deaths and QALYs. Therefore the ICERs with strategies using PPV23 become less attractive. Note that the strategies using only PCV13 remain as they were depicted above in Table 50, Table 51 and Table 52.

Table 53 – Avoided burden and cost-effectiveness of vaccination in 50-64 year olds (mean(median) based on 1000 simulations rounded to the nearest unit), focusing on outcomes differentially affected by assuming 0% PPV23 protection against non-invasive CAP

Outcomes	PPV23 versus current situation	PPV23 + PCV13 versus current situation	PPV23 + PCV13 versus PPV23	PPV23 + PCV13 versus PCV13	PPV23 + revac. PPV23 versus PPV23 once	PPV23 + PCV13 + revac. PPV23 versus (PPV23 + PCV13) once
Pneumococcal CAP hospitalisations	91(92)	340(340)	249(249)	72(73)	53(54)	48(48)
Outpatient pneumococcal CAP cases	0(0)	202(199)	202(199)	0(0)	0(0)	0(0)
Pneumonia deaths	6(6)	18(18)	12(11)	5(5)	4(4)	4(4)
Total deaths	9(9)	21(21)	13(12)	7(7)	6(6)	5(5)
Undiscounted QALY lost	185(186)	420(415)	235(229)	145(146)	94(94)	85(85)
Discounted QALY lost	153(154)	347(342)	194(188)	120(120)	75(75)	67(68)
Total medical cost undiscounted (€)	1 544 001 (1 560 490)	3 350 223 (3 357 728)	1 806 222 (1 812 282)	1 208 371 (1 221 041)	715 758 (724 050)	646 305 (653 404)
Total medical cost discounted (€)	1 198 029 (1 211 728)	2 749 371 (2 754 083)	1 551 342 (1 552 508)	935 169 (946 770)	504 164 (510 044)	454 701 (459 934)
ICER: mean(cost)/mean(QALY) (median ICER) of ICER distribution	134 520 (133 754)	193 672 (195 888)	240 215 (247 945)	179 448 (178 542)	143 114 (142 471)	159 132 (158 365)

CAP: community acquired pneumonia; ICER: Incremental cost-effectiveness ratio; QALY: quality adjusted life years lost.

Table 54 – Avoided burden and cost-effectiveness of vaccination in 65-74 year olds (mean(median) based on 1000 simulations, rounded to the nearest unit), focusing on outcomes differentially affected by assuming 0% PPV23 protection against non-invasive CAP

Outcomes	PPV23 versus current situation	PPV23 + PCV13 versus current situation	PPV23 + PCV13 versus PPV23	PPV23 + PCV13 versus PCV13	PPV23 + revac. PPV23 versus PPV23 once	PPV23 + PCV13 + revac. PPV23 versus (PPV23 + PCV13) once
Pneumococcal CAP hospitalisations	142(145)	461(463)	319(320)	112(114)	62(63)	56(57)
Outpatient pneumococcal CAP cases	0(0)	180(179)	180(179)	0(0)	0(0)	0(0)
Pneumonia deaths	15(15)	35(34)	20(19)	12(12)	8(8)[	7(7)
Total deaths	19(19)	40(39)	21(20)	15(15)	10(10)[	9(9)
Undiscounted QALY lost	221(221)	445(440)	224(219)	173(173)	82(83)	74(75)
Discounted QALY lost	197(197)	393(390)	197(192)	154(154)	70(70)	63(63)
Total medical cost undiscounted (€)	1 407 644 (1 422 650)	3 370 651 (3 377 205)	1 963 008 (1 964 573)	1 101 732 (1 115 574)	506 897 (513 110)	457 520 (462 632)
Total medical cost discounted (€)	1 231 614 (1 246 499)	2 995 547 (3 003 829)	1 763 934 (1 767 914)	960 734 (973 552)	387 714 (392 483)	349 445 (353 452)
ICER: mean(cost)/mean(QALY) (median ICER) of ICER distribution	93 164 (93 035)	154 073 (155 640)	214 884 (220 802)	127 148 (126 935)	108 886 (108 234)	121 233 (120 303)

CAP: community acquired pneumonia; ICER: Incremental cost-effectiveness ratio; QALY: quality adjusted life years lost.

Table 55 – Avoided burden and cost-effectiveness of vaccination in 75-84 year olds (mean(median) based on 1000 simulations, rounded to the nearest unit), focusing on outcomes differentially affected by assuming 0% PPV23 protection against non-invasive CAP

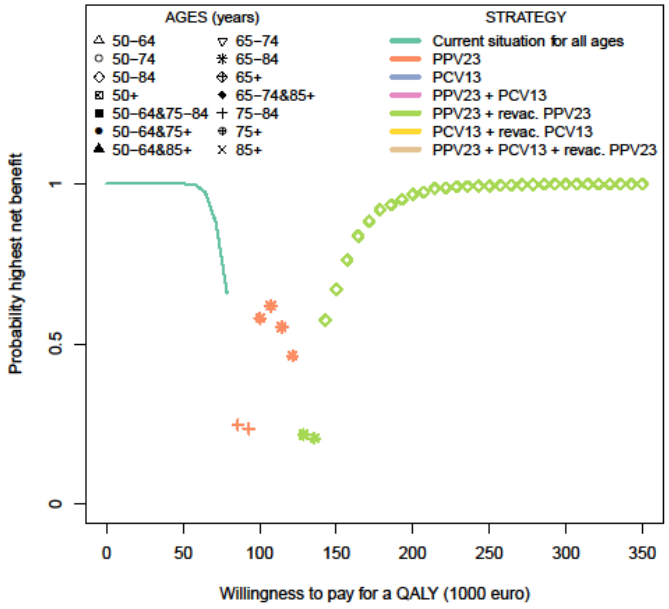
Outcomes	PPV23 versus current situation	PPV23 + PCV13 versus current situation	PPV23 + PCV13 versus PPV23	PPV23 + PCV13 versus PCV13	PPV23 + revac. PPV23 versus PPV23 once	PPV23 + PCV13 + revac. PPV23 versus (PPV23 + PCV13) once
Pneumococcal CAP hospitalisations	175(178)	298(299)	123(123)	147(145)	29(29)	26(27)
Outpatient pneumococcal CAP cases	0(0)	55(53)	55(53)	4(0)	0(0)	0(0)
Pneumonia deaths	28(28)	41(41)	13(13)	23(23)	5(5)	5(5)
Total deaths	34(35)	49(48)	14(14)	28(28)	6(6)	6(6)
Undiscounted QALY lost	195(197)	274(273)	78(77)	159(158)	28(28)	26(26)
Discounted QALY lost	182(183)	253(252)	71(70)	148(147)	24(25)	22(22)
Total medical cost undiscounted (€)	1 140 457 (1 153 939)	1 742 765 (1 744 464)	602 308 (605 272)	938 464 (934 312)	166 954 (168 459)	151 503 (152 679)
Total medical cost discounted (€)	1 025 739 (1 040 724)	1 563 189 (1 563 209)	537 451 (541 760)	842 555 (837 547)	130 001 (131 248)	117 838 (118 911)
ICER: mean(cost)/mean(QALY) (median ICER) of the ICER distribution	85 001 (84 274)	206 160 (206 720)	514 585 (522 877)	111 806 (112 348)	178 542 (177 869)	196 832 (195 995)

CAP: community acquired pneumonia; ICER: Incremental cost-effectiveness ratio; QALY: quality adjusted life years lost.

7.2.3 *Assuming no protection against non-invasive CAP from either PPV23 or PCV13*

When the efficacy of both vaccines against non-invasive CAP is set at 0% with certainty, PCV13 loses an important advantage over PPV23 and the attractiveness of PPV23 is reinforced, with PPV23 + PPV23 revaccination in 50-84 year olds being the strategy resulting in the highest net benefits – with certainty (as the probability is 1), dominating the other strategies - when WTP exceeds about €130 000 (see Figure 13).

Figure 13 – Cost-effectiveness acceptability frontier showing the probability of achieving the highest net benefits with the selected vaccination strategy and age group at each level of willingness to pay for a QALY gained (€2015) assuming efficacy against non-invasive CAP is 0% for both vaccines



The results per age group confirm that PPV23 vaccination dominates PCV13 containing strategies in all age groups over the entire range of WTP values considered. These more detailed figures and tables can be found in supplementary files.

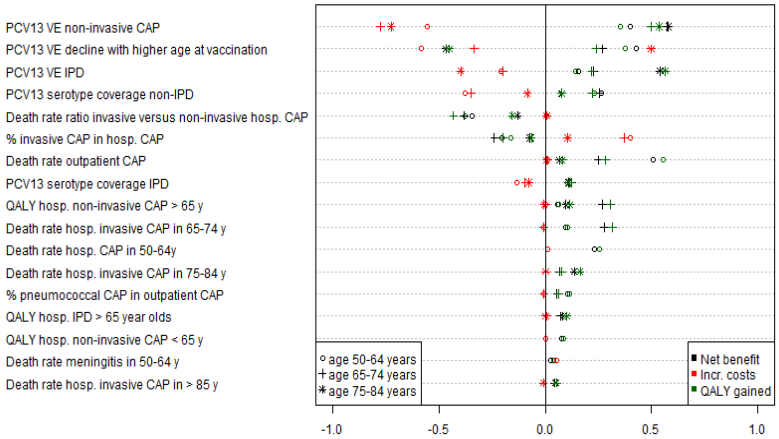
7.3 Sensitivity and scenario analyses

7.3.1 *Probabilistic sensitivity analysis*

In this section, variable importance is analysed in relation to parametrised uncertainty (i.e. which determines the width of the uncertainty intervals reflected implicitly or explicitly in CEAFs, cost-effectiveness planes and all results tables produced in this report). Variable importance is shown graphically in tornado graphs by plotting the standardized coefficients in a linear regression model with as response (a) incremental costs avoided, (b) incremental QALYs gained, and (c) net benefits. The higher the absolute value of the standardized coefficient, the larger its relative influence on these outcomes. We use the net benefits instead of the ICER, since the ICERs under parametric uncertainty cover multiple quadrants of the cost-effectiveness plane, which could lead to misleading results. These importance analyses are produced using a single WTP value per QALY gained (set at €35 000), knowing that increases/decreases in this value would increase/decrease the relative importance of parameters driving the QALY estimates (which dominate the net benefits as illustrated above and below). We show only coefficients with at least an absolute value of 5% on one of the three outcomes.

The most influential parameters are the same for incremental costs, QALYs and net benefits, and the regression coefficients for QALYs and net benefits are almost identical. This implies that the uncertainty on the net benefits stems almost entirely from uncertainty on the QALYs (i.e. the effectiveness of the vaccines and the disease burden estimates, Figure 15). The parameters related to vaccine effectiveness (especially against non-invasive CAP, and the degree of age dependence imposed) are of major importance, whereas those related to IPD become more important if protection against non-invasive CAP is no longer subject to parameterized uncertainty (Figure 15). The other influential parameters are mainly those related to death rates, and those that determine the estimation of non-invasive incidence.

Figure 14 – Variable importance of PCV13 vaccination per age group, if PCV13 is assumed to offer baseline parameterised protection (left panel) or no protection (right panel) against non-invasive CAP



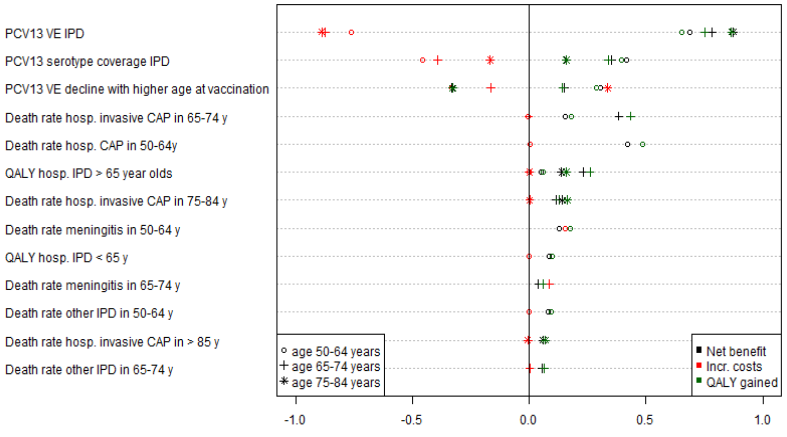
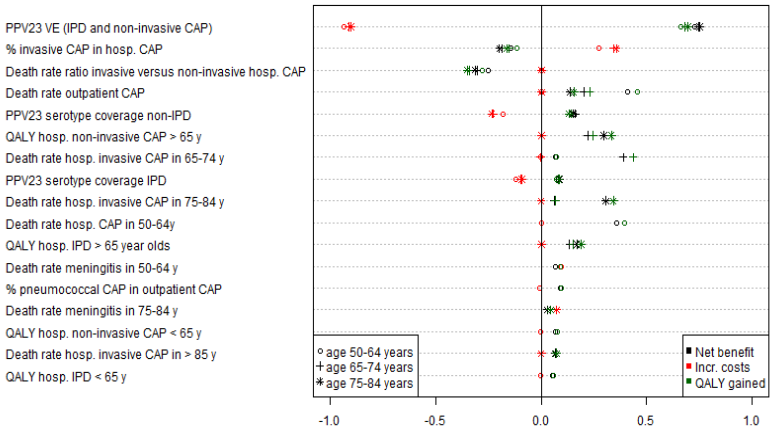
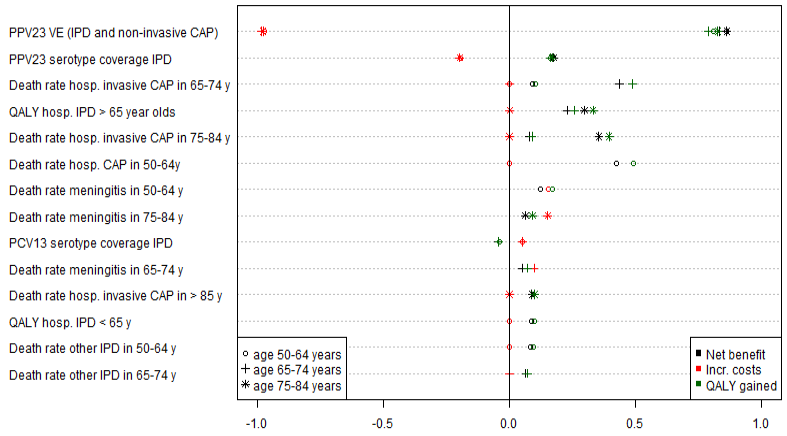


Figure 15 – Variable importance of PPV23 vaccination per age group, if PPV23 is assumed to offer baseline parameterised protection (left panel) or no protection (right panel) against non-invasive CAP





7.3.2 Scenario and univariate sensitivity analysis

In addition to the parametric sensitivity and the three scenarios for vaccine efficacy against non-invasive CAP shown above, we also explore uncertainty in relation to other assumptions that were not parameterized, while keeping all other assumptions and parameters the same as in the analysis which uses baseline (fully parameterized) vaccine efficacy against non-invasive pneumonia for both PCV13 and PPV23, unless stated otherwise.

A detailed results supplementary file including CEAFs and CE planes for the analyses shortly discussed below, as well as analyses in which vaccine efficacy against non-invasive CAP is simultaneously altered for PPV23 only or both vaccines, is available online. In this section we highlight a few notable results from the univariate (or one way) sensitivity analyses, including the influence of PCV13 price reductions. We report here results for WTP levels up to €350 000 per QALY gained, so when we say an option is unlikely the most beneficial at any WTP level, it is implied that this is for any WTP level per QALY up to €350 000.

7.3.2.1 *Higher PPV23 protection against non-invasive CAP, by assuming ratio vaccine effectiveness non-IPD/IPD = 0.77 (instead of baseline 0.55)*

This change makes especially PPV23 vaccination more cost-effective, lowering the WTP level to about €40 000 per QALY for 65-84 year olds. PCV13 containing strategies are no longer the most beneficial over the entire WTP range considered.

7.3.2.2 *5 years of PCV13 protection followed by no protection, and baseline PPV23 protection*

As in the baseline, when assuming only 5 years of PCV13 vaccine protection, PPV23 vaccination (with or without revaccination) targeted at 65-84 year olds and 50-64 year olds dominates the other options in those age groups when WTP exceeds €50 000 and €80 000 per QALY, respectively. PCV13 is unlikely to be the most cost-effective option at any WTP level considered.

7.3.2.3 *Minimum duration of PCV13 protection, and with baseline PPV23 protection*

In this scenario, we applied the minimum observed duration of PCV13 protection (4 years fixed protection followed by rapid waning to no protection at 10 years), and baseline PPV23 protection. The results are very similar to those of the previous scenario.

7.3.2.4 *Maximum duration of PCV13 protection, and with baseline PPV23 protection*

Here we assume 9 years fixed protection followed by slow waning to no protection at 20 years, and baseline PPV23 protection. Increasing the duration of PCV13 vaccine protection, lowers the WTP level at which strategies with PCV13 are retained in 50-74 year olds to about €250 000-€275 000 per QALY. In 75-84 year olds, PCV13 is still not included as part of the most beneficial strategies at any WTP level considered.

7.3.2.5 *PCV13 efficacy age independent (<85y), and with baseline PPV23 vaccine protection*

In this scenario we assume constant overall vaccine efficacy (as reported in CAPITA) in all ages between 50-84 year olds (and still 0% efficacy in 85+). This makes PCV13 containing options less likely beneficial versus the other options. PCV13 is now unlikely to be the most cost-effective option in any age group at any WTP level considered. While this seems logical for those aged 50-64 years, it may sound counter-intuitive for older age groups. For 65-74 year olds, at a willingness to pay around 350 000 euro per QALY, there is a clear difference between the baseline result and the result when assuming an age independent PCV13 vaccine efficacy. The tilting point of age dependence is 72 years (average age CAPITA study), meaning that under age independence, 65-72 year olds will have a lower PCV13 VE and 73-74 year old will have a higher PCV13 VE. The 65-72 years however dominate the result of the age category 65-74, meaning that PCV13 scenario's become less attractive when assuming an age independent PCV13 VE. For 75-84 year olds, the improved efficacy estimate lowers the certainty by which the PPV23-only strategies dominate PCV13 containing strategies over the range of WTP considered. When WTP exceeds

€400 000, PPV23+PCV13+revaccination with PPV23 becomes the strategy with the highest expected benefits.

7.3.2.6 Two years of complete PPV23 protection followed by no protection, and with baseline PCV13 vaccine protection

This assumption is somewhat influential in that it lowers the effectiveness of PPV23, requiring the WTP to exceed €90 000 for any PPV23 vaccination strategy to become cost effective. PCV13 is unlikely to be the most cost-effective option at any WTP level below €300 000 per QALY.

7.3.2.7 5 years of complete (without waning) PPV23 protection followed by no protection, and with baseline PCV13 vaccine protection

When PPV23 offers baseline protection without waning over 5 years, it becomes yet more cost-effective vis-à-vis PCV13 for all age groups, and overall becomes more rapidly a more attractive strategy versus the current situation, especially in the age groups 65-74 and 75-84 years, from a WTP threshold of about €40 000 per QALY. PCV13 containing strategies are never preferred in any age groups.

7.3.2.8 Five years of complete (without waning) protection followed by no protection for both PCV13 and PPV23

This is almost identical to the previous change, except that the likelihood of PCV13 containing strategies being the most beneficial is even lower (and PPV23 is more certain to be the most beneficial over the entire WTP range).

7.3.2.9 Minimum serotype shift: PCV13 serotype incidence decline -10% per year, and baseline (76%) replacement

All vaccination options become slightly more cost-effective. Ages 65-84 years remain the most beneficial to subsidise pneumococcal vaccination using PPV23 at the lower end of WTP (from about €45 000 per QALY). In 50-64 year olds, vaccination becomes likely beneficial from about €70 000 with PPV23, and from about €220 000 with PPV23+PCV13+PPV23 (€200 000 for 65-74 year olds). For 75-84 year olds PCV13 containing strategies are not selected as the most cost-effective.

7.3.2.10 Maximum serotype shift: PCV13 serotype incidence decline -20% per year, and baseline (76%) replacement

This maximum serotype evolution scenario echoes our baseline analyses (though slightly less favorable towards vaccination), in which PPV23 is not likely cost-effective until WTP exceeds about €50 000-70 000 per QALY. PCV13 containing options are not the most cost-effective in any age group.

7.3.2.11 Quick serotype relapse: PCV13 incidence returns to 2015 value within 7 years

Following the introduction of infant PCV10 in other countries, overall IPD did hardly decline and non-PCV10 types increased rapidly, most often driven by a 19A rise. If these trends would continue, overall disease incidence could increase above pre-vaccination levels, as observed in Finland in 2015, five years after PCV10 introduction.[118] When the PCV13 incidence relapses quickly (within 7 years) to return to its 2015 level, all vaccination options become more attractive, and in particular PCV13 containing options and PPV23 revaccination options (the latter appears as the most beneficial also at the lower end of WTP with PPV23+PPV23 in 65-84 year olds) become much more attractive in <75 year olds. PPV23 + PCV13 + PPV23 is now cost-effective from WTP of about €130 000 per QALY. In 75-84 year olds, PPV23+PCV13+PPV23 becomes the most beneficial at WTP>€230 000.

7.3.2.12 Slow serotype relapse: PCV13 incidence returns to 2015 value within 15 years

When the PCV13 incidence relapses slowly (within 15 years) to return to its year 2015 level, all vaccination options become more attractive, but less so than in the “quick” relapse scenario described above. PCV13 only strategies are again never selected, but PPV23+PCV13+PPV23 becomes the most beneficial in the age groups 50-74 year olds (from >€175 000). PCV13 containing strategies are not the most beneficial in 75-84 year olds at any WTP level considered.

7.3.2.13 Higher hospitalised pneumococcal pneumonia incidence: twice the baseline

Doubling the baseline incidence of pneumococcal pneumonia hospitalisations makes PPV23 likely cost-effective at a willingness to pay value of €50 000 per QALY gained for 50-84 year olds (and specifically in 75-84y and 65-84 y age groups from about €25 000 and €30 000 per QALY gained, respectively). In the age groups 50-64y and 65-74y, it makes PCV13 containing strategies (in combination with PPV23) likely the most cost-effective at a WTP per QALY exceeding €200 000 and €160 000, respectively. In 75-84 year olds a PCV13 containing strategy is never the most beneficial.

7.3.2.14 Higher percentage of pneumococcal pneumonia in outpatient CAP (27% (Said 2013) instead of 10.5%)

A higher proportion of outpatient CAP makes all vaccination options more attractive, especially PPV23. As with most other scenarios with increasing WTP, first the current situation, then PPV23 alone and subsequently with PPV23 revaccination is preferred. Finally at WTP > €250 000, PPV23+PCV13+PPV23 is the most beneficial for the age group 50-74 years, but not for those over 75 years of age.

7.3.2.15 PCV13 price reductions

Figure 16 shows that 25% to 50% reductions in the price of PCV13 makes little difference to the overall picking order of age groups and strategies, whereas PCV13 price reductions of 75% do have an effect when we simultaneously assume that PPV23 has 0% efficacy against non-invasive CAP. In that case, especially the age groups of 50-64 and 65-74 years are more likely to favour PCV13 containing strategies. The minimum WTP level at which PCV13 containing strategies are favoured over PPV23 alone when the price is reduced by 25%, 50% and 75% is at about €250 000, €200 000 and €55 000 for 50-64 year olds and at about €250 000, €170 000 and €50 000 for 65-74 year olds (see Figure 16). None of these price reductions show the highest expected benefits for a PCV13 containing strategy in 75-84 year olds at below a WTP of €250 000 per QALY (results shown in supplementary files).

In the age group 75-84 years (not shown in Figure 18), a price reduction of 75%, and assuming no protection of PPV23 against non-invasive CAP, still only leads to the selection of PPV23 based strategies, with the only one of these including a PCV13 component - strategy PPV23+PCV13+revaccination PPV23 having the high expected net benefits when WTP attains about €250 000.

Figure 16 – Univariate influence of increasing PCV13 price reductions (left to right, using 75%, 50% and 25% of the baseline, current list price) illustrated by CEAFs for all age groups combined. Top row: assuming baseline fully parameterized efficacy for both vaccines; bottom row: assuming 0% efficacy against non-invasive CAP for PPV23 and baseline efficacy for PCV13

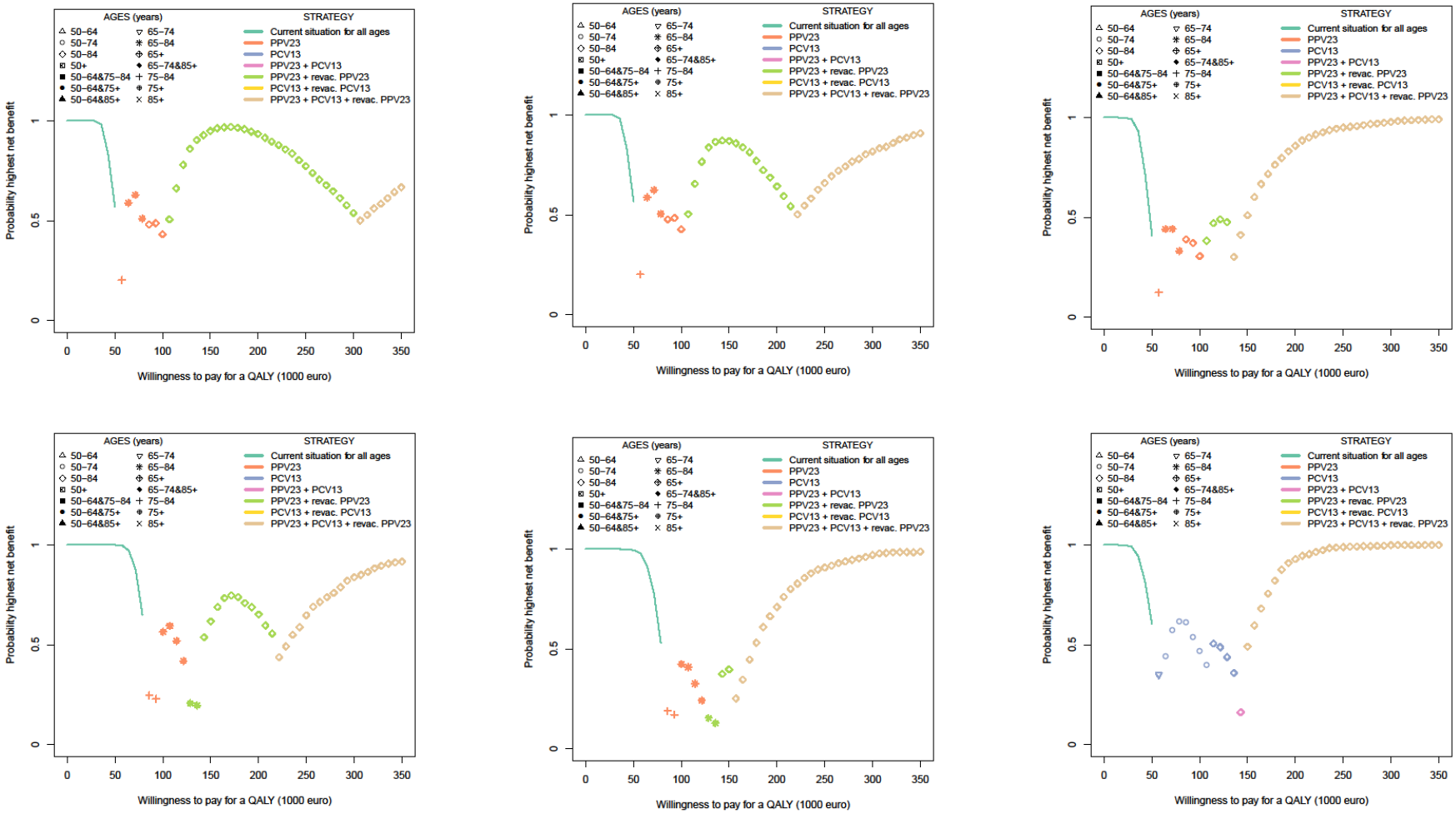


Figure 17 – Univariate influence of increasing PCV13 price reductions (left to right, using 75%, 50% and 25% of the baseline price) illustrated by CEAFs for age groups 50-64 years (top row) and 65-74 years (bottom row), using the baseline fully parameterized vaccine efficacy of PPV23 and PCV13

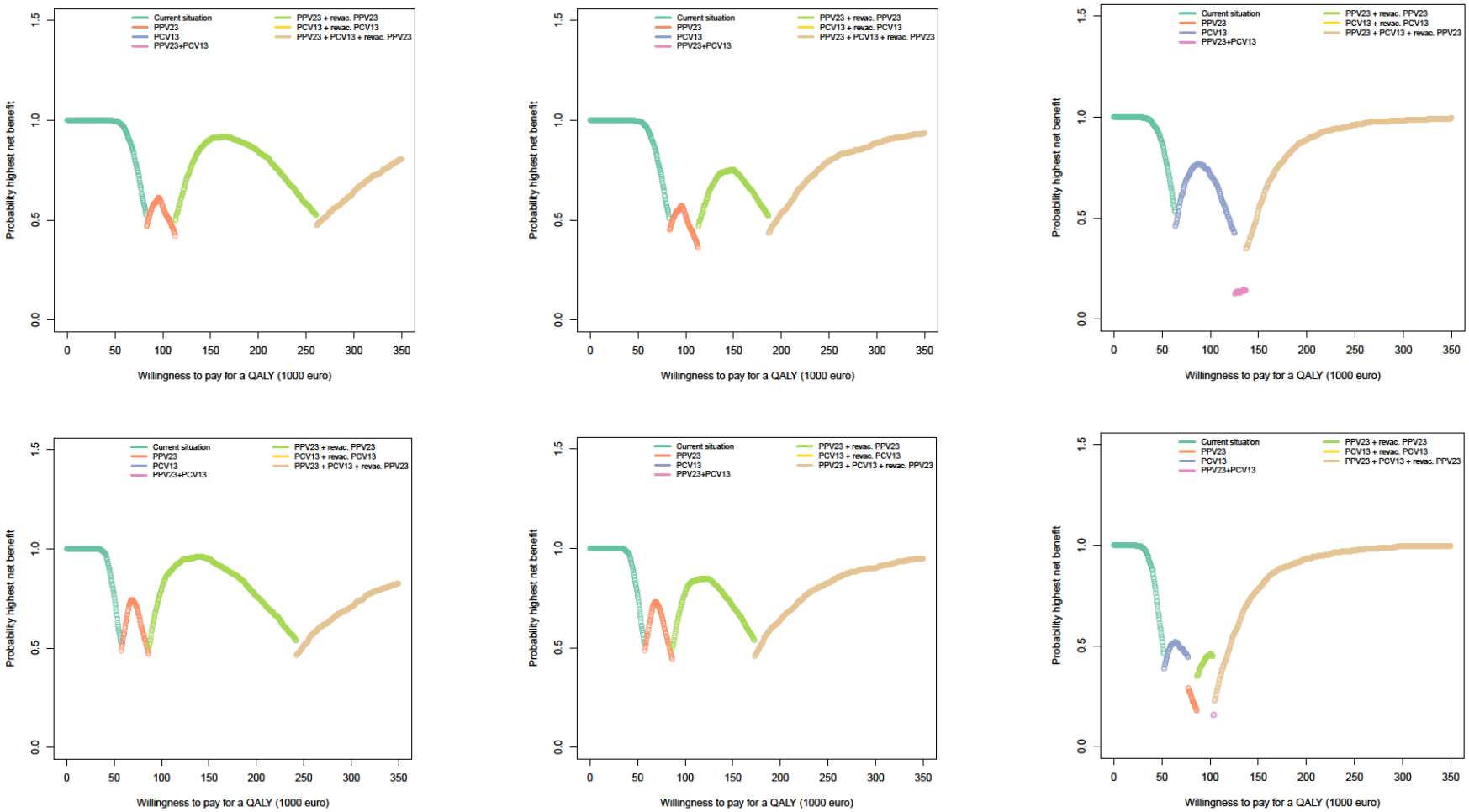
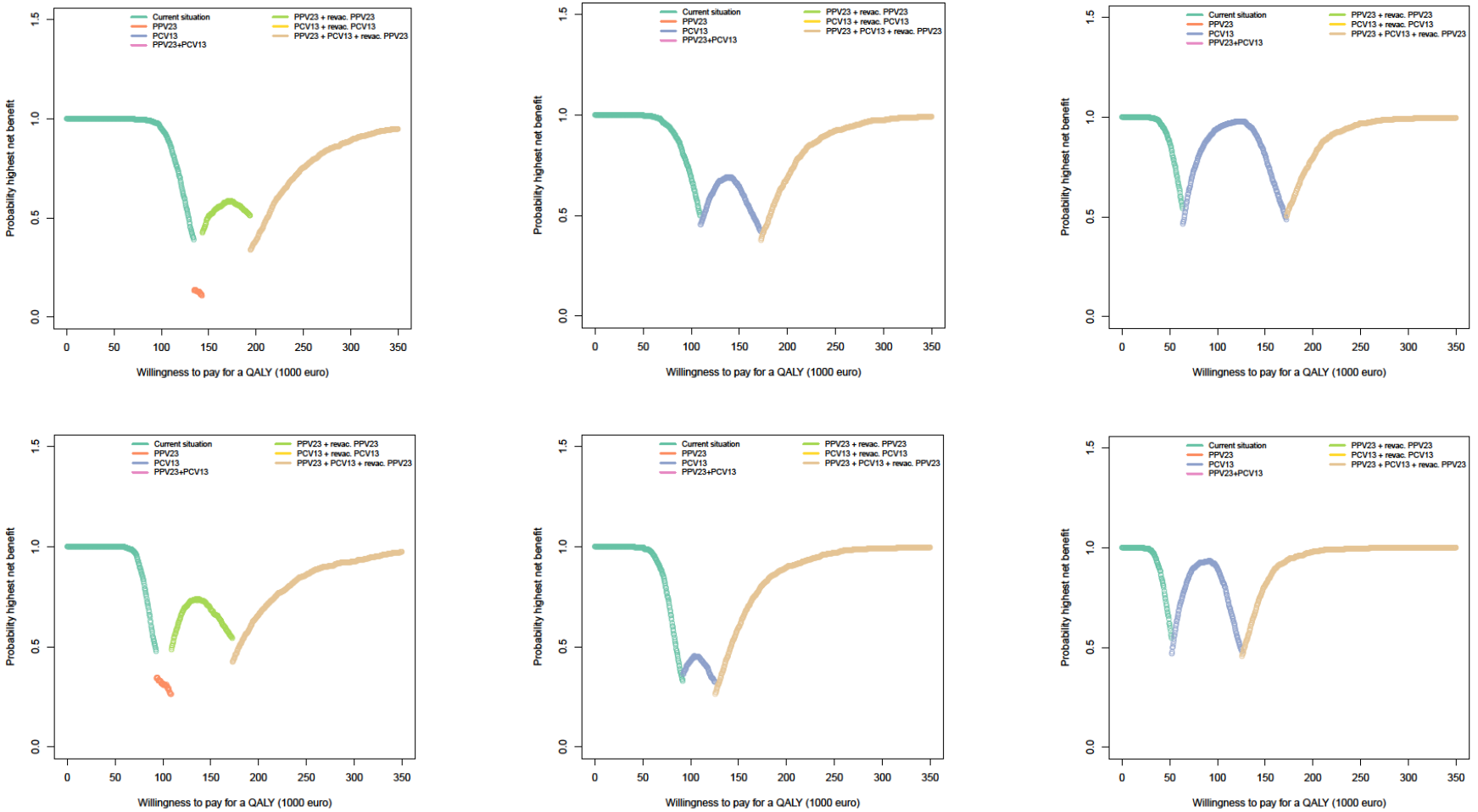


Figure 18 – Univariate influence of increasing PCV13 price reductions (left to right, using 75%, 50% and 25% of the baseline price) illustrated by CEAFs for age groups 50-64 years (top row) and 65-74 years (bottom row), assuming PPV23 has 0% efficacy against non-invasive CAP, and using the baseline fully parameterized vaccine efficacy of PCV13



7.3.2.16 PPV23 price reductions

The current retail price of PPV23 (€28.46 per dose), as modelled throughout this report (unless mentioned otherwise), is higher than in some other countries. For instance it is in France €12.46 per dose. We therefore also investigated the influence of reductions in the price of PPV23.

As expected, and as can be seen in Figure 19 and Figure 20, such price reductions make PPV23 containing strategies more attractive. As illustrated in Table 56, such price reductions are more influential for strategies that use more vaccine doses, but single dose PPV23 use remains most cost-effective in 75-84 year olds, whereas the incremental cost-effectiveness of 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.

Table 56 – Incremental direct costs per QALY gained for strategies using only PPV23, given a range of PPV23 price reductions (€2015, mean(median)), both with and without PPV23 vaccine efficacy against non-invasive pneumonia

PPV23 price reduction	Higher uptake PPV23 versus current situation			PPV23 with PPV23 revaccination versus PPV23 alone		
	-25%	-50%	-75%	-25%	-50%	-75%
Baseline protection of PPV23 versus non-invasive pneumonia						
50-64 years	66 722(67 442)	50 629(51 191)	34 537(34 849)	91 803(91 840)	70 475(70 473)	49 147(49 039)
65-74 years	45 686(46 114)	34 160(34 482)	22 633(22 814)	69 794(69 977)	53 370(53 501)	36 947(37 037)
75-84 years	41 593(42 066)	31 039(31 395)	20 485(20 649)	117 047(117 195)	90 453(90 528)	63 858(63 842)
0% protection of PPV23 versus non-invasive pneumonia						
50-64 years	109 271(108 612)	84 023(83 441)	58 774(58 293)	116 534(116 005)	89 954(89 506)	63 374(63 046)
65-74 years	75 531(75 363)	57 898(57 719)	40 265(40 176)	88 589(88 037)	68 293(67 823)	47 996(47 669)
75-84 years	68 925(68 263)	52 849(52 325)	36 773(36 406)	145 936(145 325)	113 331(112 783)	80 725(80 298)

Figure 19 – Univariate influence of increasing PPV23 price reductions (left to right, using 75%, 50% and 25% of the baseline price) illustrated by CEAFs for age groups 50-64 years (top row), 65-74 years (middle row) and 75-84 years (bottom row), using the baseline fully parameterized vaccine efficacy of PPV23 and PCV13

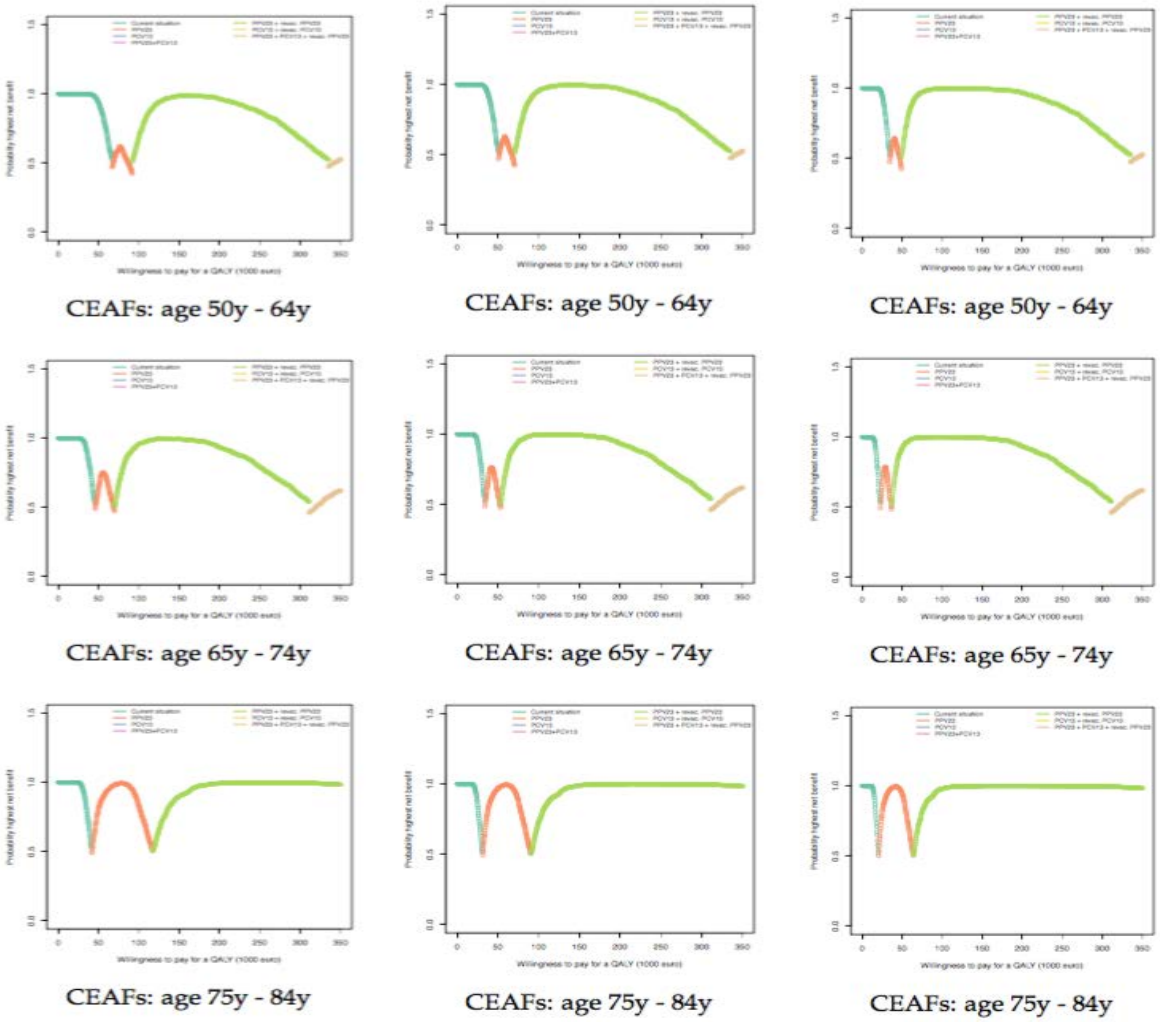
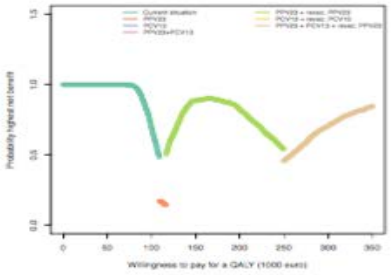
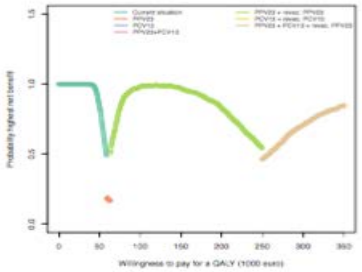
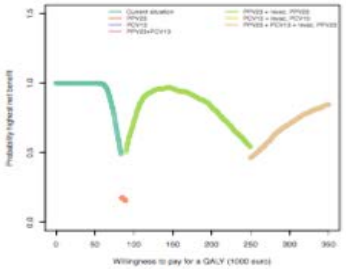
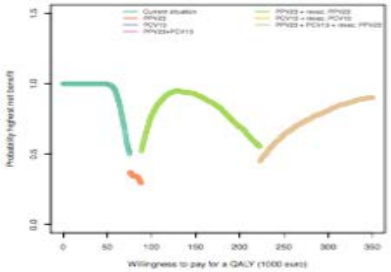


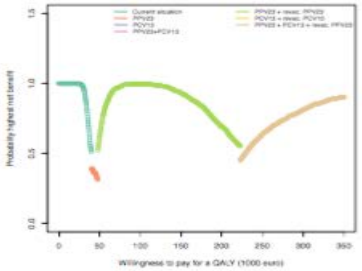
Figure 20 – Univariate influence of increasing PPV23 price reductions (left to right, using 75%, 50% and 25% of the baseline price) illustrated by CEAFs for age groups 50-64 years (top row) and 65-74 years (bottom row), assuming PPV23 has 0% efficacy against non-invasive CAP, and using the baseline fully parameterized vaccine efficacy of PCV13

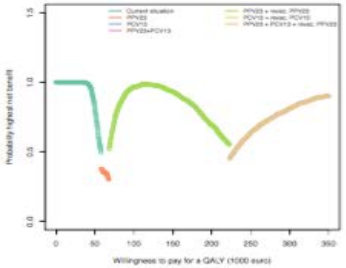

CEAFs: age 50y - 64y

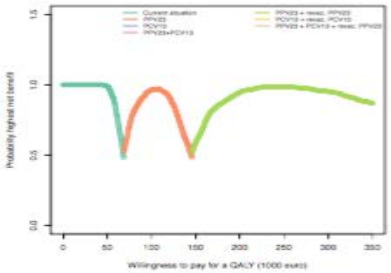

CEAFs: age 50y - 64y

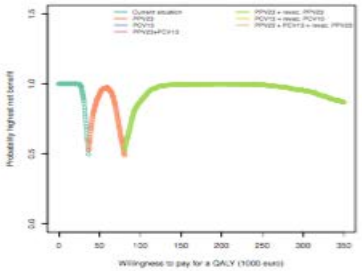

CEAFs: age 50y - 64y

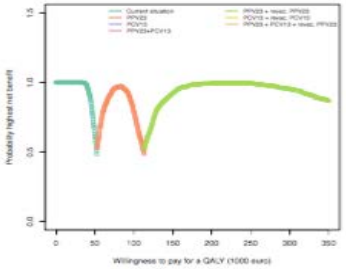

CEAFs: age 65y - 74y


CEAFs: age 65y - 74y


CEAFs: age 65y - 74y


CEAFs: age 75y - 84y


CEAFs: age 75y - 84y


CEAFs: age 75y - 84y

7.3.2.17 Higher PPV23 vaccine efficacy against IPD

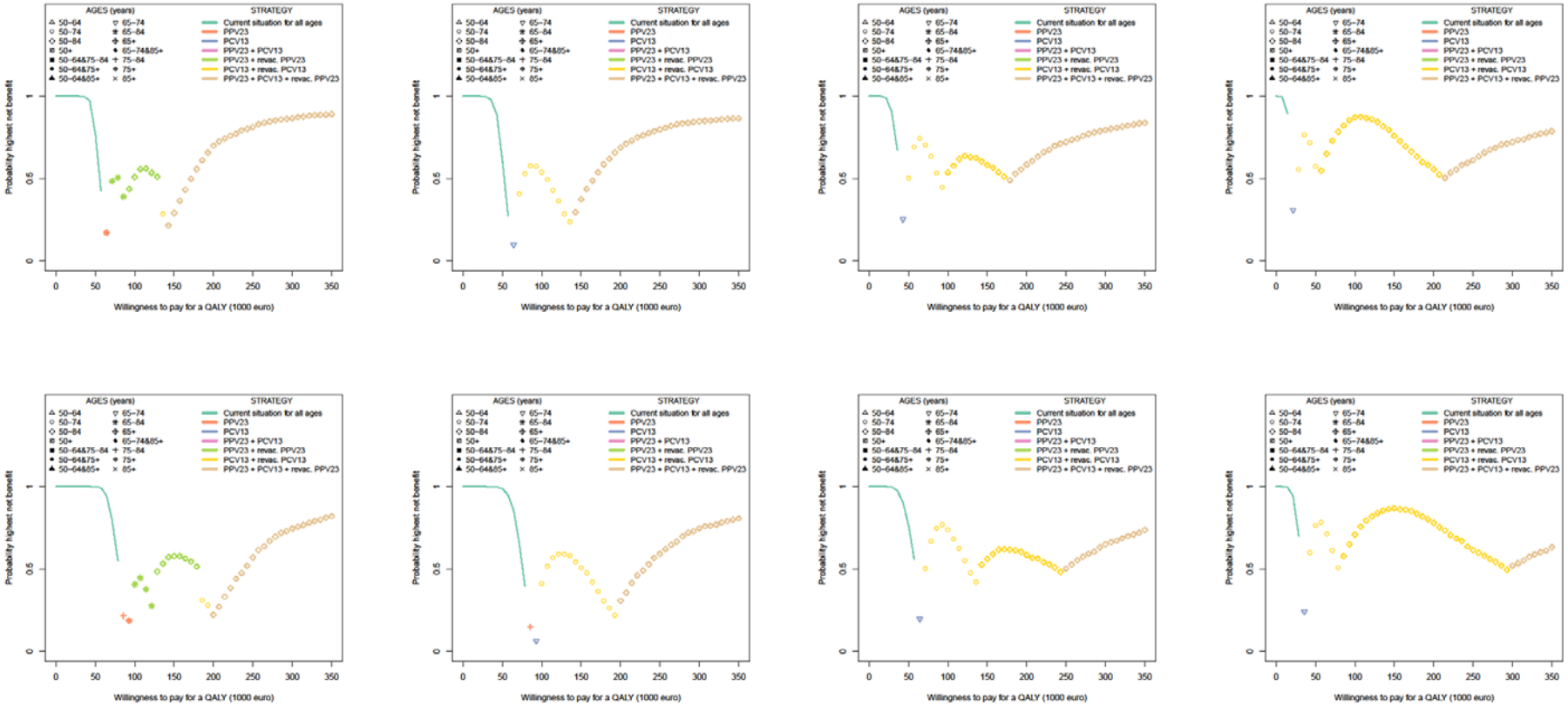
When we assume a higher vaccine efficacy for PPV23 against IPD (82% versus 56% in the baseline) and non-IPD (43% versus 31% in the baseline), all PPV23 containing strategies become more attractive. However, the influence of this variation is not very large, and there is no change in the relative attractiveness of the different strategies. With this higher efficacy, the ICERs of increased PPV23 uptake for 50-64y, 65-74y and 75-84y decline to about €55 000, €37 000 and €34 000, respectively if PPV23 protects against non-invasive CAP, and €89 000, €61 000, €56 000 if it does not. A 50% PPV23 price reduction would further make these values decline to €33 000, €21 000, €19 000 and €55 000, €37 000, €34 000, respectively.

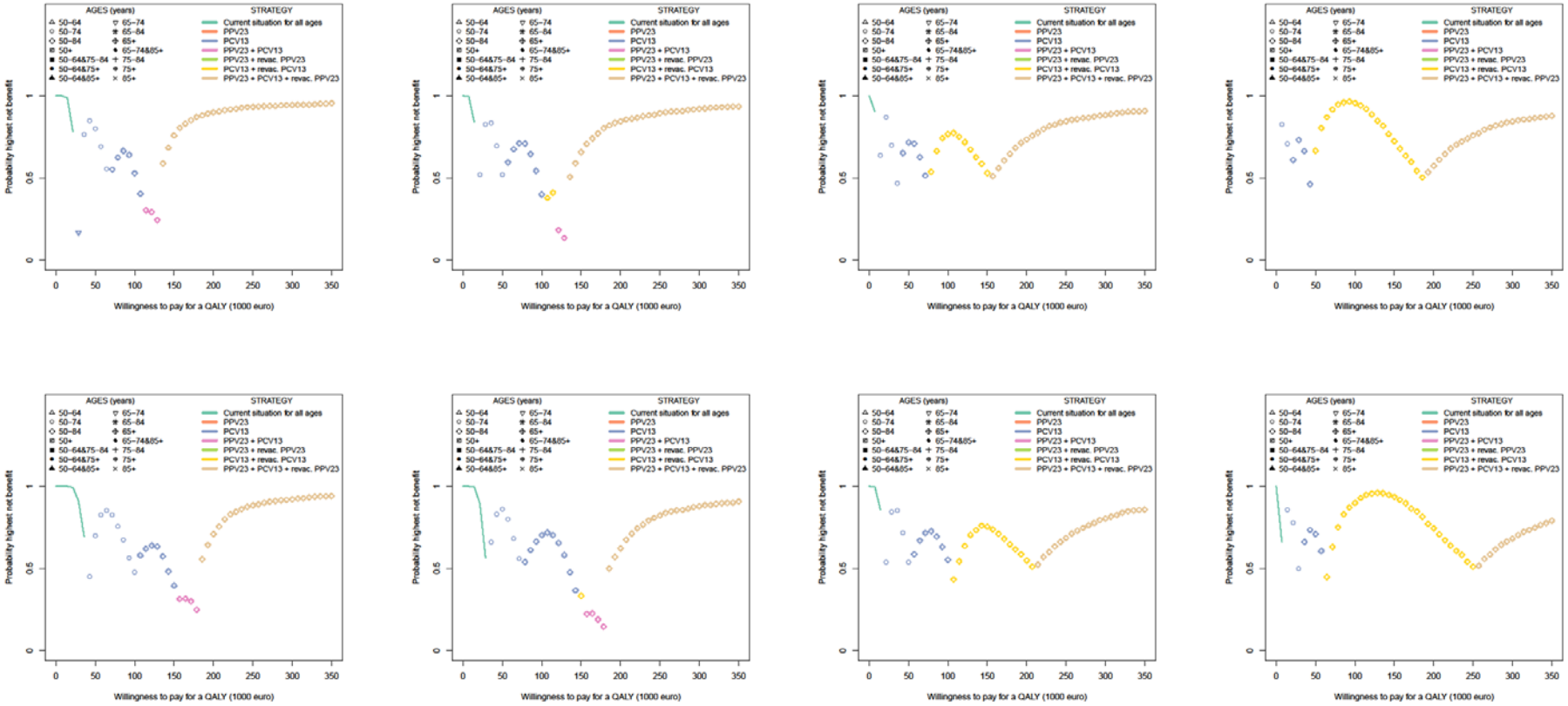
7.3.3 Multivariate sensitivity analysis (MVSA)

In multivariate sensitivity analyses, we simultaneously varied a number of influential assumptions and parameter choices discussed in the previous section. We point out some notable aspects in this section (see supplementary files for a more extensive MVSA). Numerous combinations can be made with the univariate sensitivities we showed in the previous section. Here we give only some examples. Figure 22 shows the impact of simultaneous changes in serotype coverage, vaccine prices, duration of protection and incidence of pneumococcal pneumonia.

The supplementary files with this report contain on the one hand results as shown using CEAFs (as in Figure 21), entitled “Supplementary appendices with multivariate sensitivity analyses Part 1: CEAFs and CE planes”) and on the other hand as shown using net benefit box plots (as in Figure 22 and Figure 23, for 3 different WTP levels, entitled “Supplementary appendices with multivariate sensitivity analyses Part 2: Net benefit box plots”). These explorations, which are largely self-explanatory, show that the most dominant influence comes from potential price reductions, but also the assumed duration of protection and serotype relapse are important. The incidence of pneumococcal pneumonia is influential, but less so than these other variable assumptions, unless the change in incidence is combined with other changes in severity of illness (such as all incidences and death rates). The combined impact of these changes is best illustrated through the box plots shown in Figure 22 and Figure 23.

Figure 21 – CEAFs across all age groups, PPV23 0% efficacy against non-invasive CAP, quick serotype relapse scenario





Left to right decreasing PCV13 prices (baseline, 25%, 50% and 75% reduction). First row with minimum duration of protection for PCV13 and 50% higher incidence of pneumococcal pneumonia. Second row with minimum duration of protection for PCV13 and baseline incidence of pneumococcal pneumonia. Third row with maximum duration of protection for PCV13 and 50% higher incidence of pneumococcal pneumonia. Fourth row with maximum duration of protection for PCV13 and baseline incidence of pneumococcal pneumonia.

When the net benefits are positive (>0 in the graphs, Figure 22 and Figure 23) for a given willingness to pay value, that means that it is cost-saving versus the current situation at that particular willingness to pay level. The parametric uncertainty remains fully reflected by the position of the box plot versus 0 in each scenario considered. For ease of reference we also show the box plot of the baseline scenario and we show direct comparisons in these plots between PCV13 and PPV23 versus the current situation only. When a given box plot is with its average or completely more to the right than another one (say if PPV23 base is more to the right than PCV13 base), that means that the strategy and scenario it represents is on average or completely more beneficial (i.e. PPV23 base is on average more beneficial than PCV13).

Figure 22 and Figure 23 show the same information for each of 4 age groups (as previously mentioned the age group >85 years can be ignored here). For reference the "PCV13 base" and "PPV23 base" labels at the bottom show the expected net benefits of our baseline analysis (so not subject to the changes outlined in the title), in which vaccine efficacy against non-IPD is parameterised. The "PPV23: nIPD protection" and "PPV23: no nIPD protection" refer to the modified analysis specified in the title of the figure together with the stated specific change in the label. For instance in Figure 22 and Figure 23, "PPV23: no nIPD prot; Hosp DR100%" means that in addition to the changes in the title of the figure (double incidence + QALY loss of a medium risk person + WTP of €35 000 per QALY) and the assumption that PPV23 offers 0% protection against non-IPD (with certainty), the death rate for hospitalised patients is kept as in the baseline. "PPV23: no nIPD prot; Hosp DR150%" additionally assumes a 50% higher death rate in hospitalised patients, in comparison to the baseline (and therefore also in comparison to "PPV23: no nIPD prot; Hosp DR100%". The difference between Figure 22 and Figure 23 is that in Figure 23 the quick serotype relapse scenario is also included as a change from the baseline.

Figure 22 indicates that when PPV23 has some protection against non-IPD ("PPV23 nIPD prot"), the changes specified in the title are by themselves sufficient to make PPV23 cost-saving at a WTP of €35 000 per QALY for all age groups <85 years (and more so for the older than the younger age groups), but not if PPV23 has 0% protection against non-IPD. Such savings only occur for PCV13, if the PCV13 price decreases by at least 50%. An increase in the in-hospital death rate by 50% keeps the relative advantage of PPV23 over PCV13 constant in the two youngest age group, but increases it in 75-84 year olds. Figure 23 shows that the addition of a serotype relapse scenario makes PCV13 in these circumstances clearly preferable to PPV23, except in the 75-84 year olds where PPV23 still yields the highest net benefits.

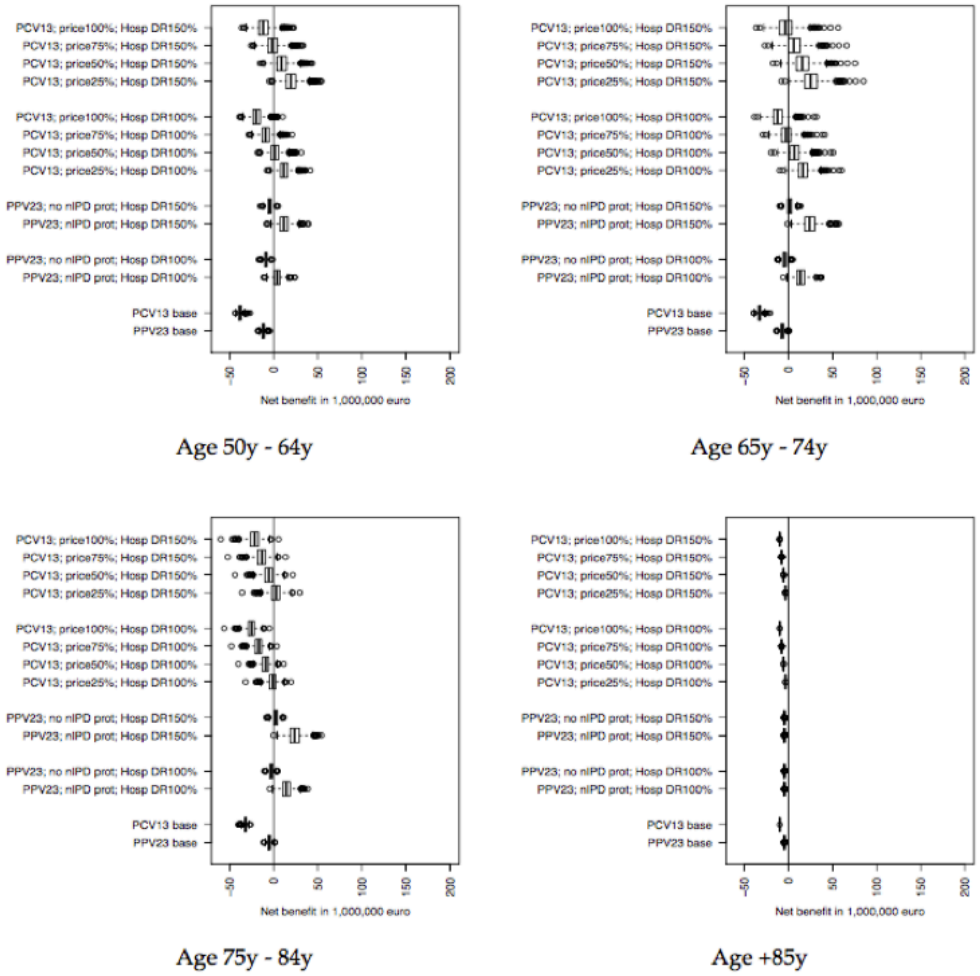
So for PCV13, the combination of vaccine price decreases and an increase in PCV13 non-PCV10 serotypes (i.e. relapse) scenarios is more important to make it preferable to PPV23 than other parameter combinations.

In the supplementary files we illustrate these multivariate sensitivities also for different WTP thresholds per QALY, which are quite influential as well.

We also explored in multivariate sensitivity analyses some changes in parameter choices that influence mainly the attractiveness of PPV23 containing strategies.

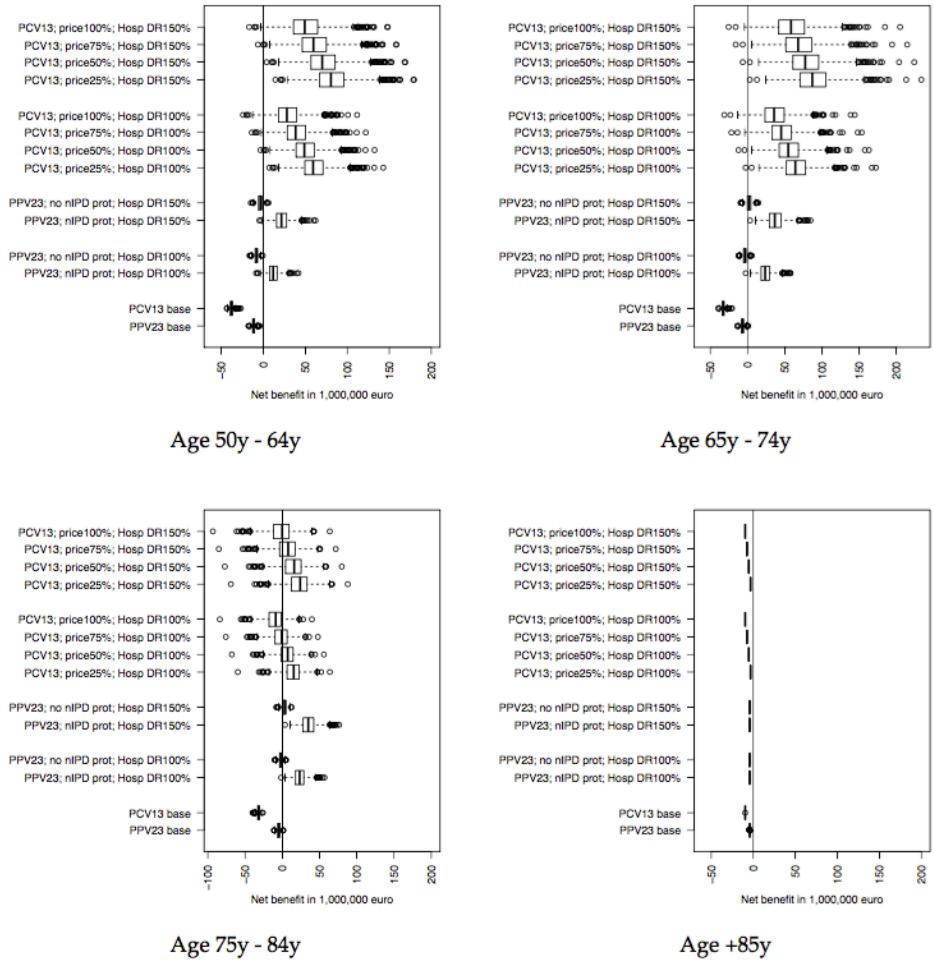
Figure 24 and Figure 25 illustrate again the critical role of vaccine price, and of the assumption of PPV23 protection against non-invasive pneumonia. Indeed, if we assume that PPV23 has baseline protection against non-invasive pneumonia, then two by two combinations of price reductions with either a higher pneumonia incidence and higher vaccine efficacy are sufficient to yield net benefits at a WTP of €35 000 per QALY gained in each age group <85 years. However, when we assume PPV23 has 0% protection against non-invasive pneumonia, then price reductions need to be combined with higher incidence estimates, and the influence of vaccine efficacy against invasive pneumonia is less important. In the supplementary files (with a separate supplement containing uni- and multivariate analyses that are more optimistic for PPV23), we also illustrate these multivariate sensitivities for different WTP thresholds per QALY.

Figure 22 – Net benefit box plots of PPV23 use and PCV13 use versus the current situation when doubling all incidences, while using QALY impact of the medium risk group (baseline low risk group), and assuming a willingness to pay of € 35 000 per QALY gained



Hosp DR: death rate in hospitalised cases; nIPD protection: some protection against non-IPD.

Figure 23 – Net benefit box plots of PPV23 use and PCV13 use versus the current situation when assuming quick serotype relapse (PCV13 incidence returns to 2015 value within 7 years) and doubling all incidences, while using QALY impact of the medium risk group (baseline low risk group), and assuming a willingness to pay of € 35 000 per QALY gained



Hosp DR: death rate in hospitalised cases; nIPD protection: some protection against non-IPD.

Figure 24 – Net benefit box plots of PPV23 use and PCV13 use versus the current situation showing the influence of PPV23 price reductions combined with a doubling of hospitalised pneumococcal incidence and a higher PPV23 vaccine efficacy, while assuming PPV23 protects against non-invasive pneumonia and a willingness to pay of € 35 000 per QALY gained

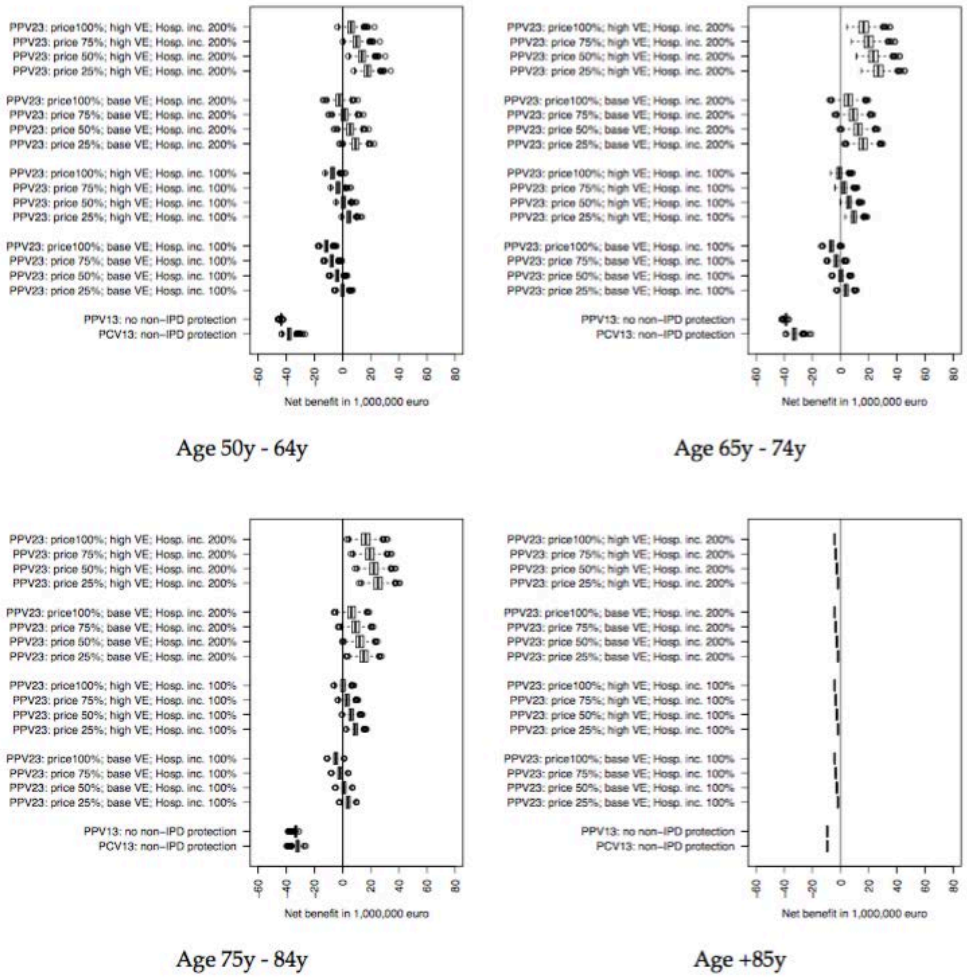
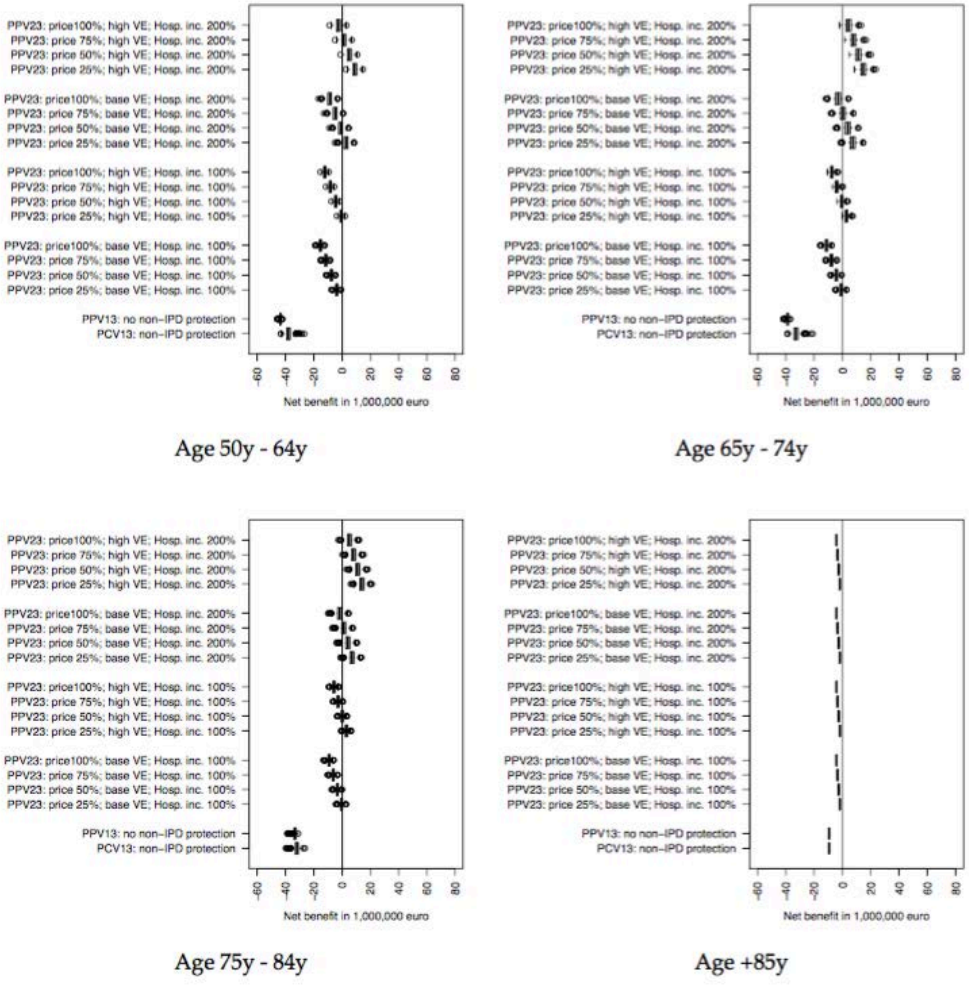


Figure 25 – Net benefit box plots of PPV23 use and PCV13 use versus the current situation showing the influence of PPV23 price reductions combined with a doubling of hospitalised pneumococcal incidence and a higher PPV23 vaccine efficacy, while assuming PPV23 has 0% protection against non-invasive pneumonia and a willingness to pay of € 35 000 per QALY gained



7.4 Budget-impact analyses

The budget-impact of increasing current PPV23 vaccination up to our baseline assumptions, versus the current situation, is shown in Table 57 assuming baseline parameterized efficacy of both vaccines against non-IPD. It shows that the avoided treatment costs (< €10 million for ages 50+ combined), benefiting mainly the national health insurer RIZIV/INAMI and patients, are much lower than the required vaccination costs (> €80 million for 50-84 year olds) incurred by the funder of preventive vaccination, expected to be mainly regional governments (Flanders, Wallonia, Brussels) and patients. This results in a low (< 11%) return on investment, and net costs in excess of €70 million for 50-84 year olds. There is little difference between these 5 or 10 year time spans because the change in uptake under a change in vaccination policy is modelled as having the largest impact in the first year of the introduction. Phased introduction in different age groups is also possible, and the budget impact is therefore also shown by age group.

The budget-impact of introducing PCV13 versus the current situation is shown in Table 58, using the baseline (retail) price and uptake levels (see Table 39 above) for single dose PCV13 vaccination. It shows that the avoided treatment costs (< €4-6 million for ages 50+ combined), benefiting mainly the national health insurer RIZIV/INAMI and patients, are much lower than the required vaccination costs (> €170 million for 50-84 year olds) incurred by the funder of preventive vaccination, expected to be mainly regional governments (Flanders, Wallonia, Brussels) and patients, resulting in a low (< 5%) return on investment, and net costs in excess of €170 million for 50-84 year olds.

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 64-75 years at 9% after 5 and 10% after 10 years. Naturally, the highest net costs (or negative direct net benefits) occur for the highest uptake levels.

Our supplementary excel file allows inspecting the budget-impact for the different vaccination strategies over a wide range of PPV23 and PCV13 uptake and PCV13 price levels, and conditional on our three main analytical approaches regarding vaccine effectiveness against non-IPD.

Table 57 – Mean vaccination costs, treatment costs avoided, return on investment and direct net benefits over 5 and 10 year periods for improved baseline uptake of PPV23 vaccination versus the current situation

Age group	Avoided treatment costs over 5 years (disc)	Avoided treatment costs over 10 years (disc)	Vaccination costs over 5 years (disc)	Vaccination costs over 10 years (disc)	Return on Investment over 5 years (%)	Return on Investment over 10 years (%)	Direct net benefits over 5 years	Direct net benefits over 10 years
50-64 years	2 058 792	2 635 906	27 950 833	34 767 582	7.4	7.6	-25 892 040	-32 131 676
65-74 years	2 795 305	3 738 451	28 522 064	38 348 749	9.8	9.7	-25 726 759	-34 610 298
75-84 years	2 446 399	3 222 201	23 694 979	31 608 894	10.3	10.2	-21 248 580	-28 386 693
85-105 years	0	0	7 100 373	10 120 288	0	0	-7 100 373	-10 120 288
50-84 years	7 300 496	9 596 559	80 167 876	104 725 226	9.1	9.2	-72 867 380	-95 128 667
50-105 years	7 300 496	9 596 559	87 268 249	114 845 514	8.4	8.4	-79 967 753	-105 248 955

Table 58 – Mean vaccination costs, treatment costs avoided, return on investment and direct net benefits over 5 and 10 year periods for baseline uptake of PCV13 vaccination versus the current situation

Age group	Avoided treatment costs over 5 years (disc)	Avoided treatment costs over 10 years (disc)	Vaccination costs over 5 years (disc)	Vaccination costs over 10 years (disc)	Return on Investment over 5 years (%)	Return on Investment over 10 years (%)	Direct net benefits over 5 years	Direct net benefits over 10 years
50-64 years	1 504 155	2 169 300	60 931 281	75 680 673	2.5	2.9	-59 427 126	-73 511 373
65-74 years	1 941 276	2 876 329	62 782 002	84 319 197	3.1	3.4	-60 840 725	-81 442 868
75-84 years	773 499	1 170 738	52 370 638	69 871 409	1.5	1.7	-51 597 139	-68 700 671
85-105 years	0	0	15 796 465	22 514 983	0	0	-15 796 465	-22 514 983
50-84 years	4 218 930	6 216 367	176 083 921	229 871 279	2.4	2.7	-171 864 991	-223 654 912
50-105 years	4 218 930	6 216 367	191 880 386	252 386 261	2.2	2.5	-187 661 456	-246 169 894

8 DISCUSSION AND CONCLUSION

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 childhood 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.

We estimate that the current annual disease burden of pneumococcal disease in adults over 50 years is important, at about 5800 hospitalisations and 3600 additional patients treated in ambulatory care, as well as at about 440 deaths, and about 4150 QALYs lost. The associated health care costs for treatment amount to about €33 million.

8.1 Based on cost-effectiveness, if we are to use (one of) these vaccines, how should we do this?

For this question of technical efficiency 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 €171 000, €201 000 and €338 000, respectively.

It was shown that the strong preference for PPV23 over PCV13 would only change when joint (i.e. a single variable change is not sufficient) changes would occur in PCV13 vaccine price (with large, up to 75%, reductions required), in disease burden preventable by PCV13 (e.g. facilitated by a relapse in the ongoing PCV13 serotype incidence decline in adults through the switch from PCV13 to PCV10 that has occurred in the Belgian infant PCV program, if the Finland situation would become true in Belgium), 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 PCV13 serotypes, then the choice between the two vaccines 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.

These analyses, pertaining to the choice between PPV23 and PCV13, included some relatively conservative estimates for PPV23 efficacy against invasive disease and price, and may therefore be seen as optimistic for PCV13, given the current state of the evidence.

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

This question of allocative efficiency depends entirely on the WTP for a QALY. We have shown that when WTP levels are in the lower – likely more acceptable magnitude ranges – of the levels we explored (mainly €0 to €350 000, but up to €5 million in analyses not shown), use of PPV23 could be considered cost-effective, particularly in the age group 75-84 years, where the fully parameterised baseline puts the average cost-effectiveness at around €50 000 per QALY. For the age group 65-74 years and 50-64 years, the WTP for a QALY has to be 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.

We have shown that PPV23 price reductions, more in line with PPV23 prices observed in other EU countries, would further improve the cost-effectiveness of PPV23 containing strategies. Furthermore, large - though realistic - PPV23 price reductions, combined with higher estimates of pneumococcal disease incidence and a more optimistic parameter choice for PPV23 vaccine efficacy would bring more expansive use of single dose PPV23, below an average of €35 000 per QALY gained in all age groups (with cost savings closely for the age group 75-84 years). It would also bring the ICER of revaccination with PPV23 down to about €15 000 per QALY gained in 65-74 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 €80 million over a 5 year period when we use the baseline list price for the vaccines.

8.3 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.[154] 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.

8.4 Findings from other economic evaluations

Three 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 and the US.[92, 152, 155]

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). The England study 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.[152] Relying on the explicit WTP threshold of £20 000 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.[92] 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. In terms of parameters, 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-€10500 versus €1700-€5900 for inpatient CAP (depending on age group). 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 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.[156] 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,[157] 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.

8.5 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 (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.[158] However there is no willingness-to-pay threshold defined in Belgium for deciding on the introduction of health interventions.[154]

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 additional hospitalisations and 12 additional deaths in the 75-84 years of age for a cost of €688 500 per QALY gained.

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 by 75%, under the assumption of PPV23 effectiveness against non-invasive pneumonia.

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.

Changes in the incidence of PCV13 and PPV23 serotypes may change the conclusions of our analyses. The serotype is currently not determined in pneumococcal cases in Belgium (only the serogroup is determined). It is thus essential that the incidence and serotypes of pneumococcal disease in the elderly are determined and monitored, to detect any change in the epidemiology that would put into question the conclusions from the present study.

Clinicians should also be aware that the proportion of disease covered by vaccine serotypes in adults is much smaller for PCV13 than for PPV23, and continues to decline under the influence of infant PCV vaccination. If PCV13 is administered, a better clinical protection is offered if it is followed by PPV23 as this will protect against the additional serotypes (representing today 42% of all invasive disease).

APPENDICES

APPENDIX 1. METHODS FOR LITERATURE REVIEWS

Appendix 1.1. General methodology

The literature search was limited to Pubmed articles. As vaccines, detection methods, blood culture rates and serotype distribution changed over the last decades and across settings, only studies covering periods after 2000, conducted in similar settings (i.e. preferably Europe, and North America if too few studies were retrieved from EU settings), and including pneumococcal specific outcomes in all adults (no sub-group with risk factor), and covering adults, were included. In a first step, the search selected eligible systematic reviews and references of studies included in these reviews that fulfilled the criteria were included as well.

Were excluded studies based on ICD code only, without revision of medical files, and studies with all-cause CAP as outcomes.

Appendix 1.2. Literature review on serotype distribution and proportion of pneumococcal disease

Invasive and non-invasive disease: recent studies comparing serotype distribution between invasive and non-invasive pneumococcal pneumonia in settings similar to Belgium, i.e. European settings in which PCV7 has been widely used (>50% uptake in children). Design: observational studies comparing the two groups of patients in the same population, adjusting for potential confounding factors in the difference between invasive and non-invasive disease.

Appendix 1.3. Literature review on mortality and sequelae related to CAP

CAP was defined as an X-ray confirmed clinical picture.

- For the review on case fatality ratio in outpatient CAP: search strings were composed with key words fatality, mortality, death, elderly, Pneumococcal pneumonia, pneumonia, burden, adult, outpatient, and NOT childhood, NOT hospital.
- For the review on mortality due to invasive and non-invasive CAP: search strings were composed with key words fatality, mortality, death, elderly, Pneumococcal pneumonia, pneumonia, invasive pneumococcal disease, burden, adult, and NOT childhood.
- For the review on sequelae due to pneumococcal disease: search strings were composed with key words elderly, Pneumococcal pneumonia, invasive pneumococcal disease, “infection, *Streptococcus pneumoniae*”, burden, adult, meningitis, empyema, complications, sequelae, outcome, and NOT childhood, NOT vaccine, NOT vaccination.

Appendix 1.4. Literature review on vaccine efficacy and effectiveness against IPD and CAP

Clinical trials and observational studies adjusting for the main confounding factors and including a minimum of 100 cases were selected. Observational studies in which PCV7 has been widely used (>50% uptake), e.g. after 2001 in US and 2006 in most EU countries. IPD studies without laboratory confirmation, or mixing outcomes, were excluded. As studies using the screening method lack adjustment for the main confounding factors, these were excluded. VE should be available for vaccine serotypes by age.

APPENDIX 2. FURTHER DATA FROM LITERATURE REVIEW ON DISEASE BURDEN

Appendix 2.1. Literature review on serotype distribution in invasive and non-invasive pneumococcal CAP

Table 59 – Serotype distribution in bacteraemic/invasive and non-bacteraemic/non-invasive pneumococcal CAP in adults

Study, country, period, design	Age of cases	Numbers of cases, disease definitions, case characteristics	Infant PCV programme	Serotype	% in bacteraemic / invasive CAP	% serotypes in non-bacteraemic / non-invasive CAP
Benfield, Denmark 2011 Prospective study in 15 hospitals[40]	≥15 years Mean 68 years (both) 60% ≥65 years	- 272 non-bacteraemic CAP (NBP), 20% COPD - 192 bacteraemic CAP (BP), 44% COPD Culture only, from: - BP: blood - NBP: airway sample and negative blood culture Unknown for pleural fluid. 27% NBP had no blood culture 98.5% hospitalized	Universal PCV7: 2007-10 PCV13: 2010-11 Uptake 92% for 2 doses in 2011 [81]	PCV7 serotypes	6.8% (13/192)	11.8% (30/272)
				6 add. PCV13	52.6% (101/192)	22.4% (61/272)
				5 add. PCV13 in PPV23*	51.5% (99/192)	22.0% (60/272)
				PCV13 overall	59%	34%
				11 PPV23 additional	~ 28%	~ 23%
				PPV23 overall	87%	57%
				Non covered by PPV23	13%	43%
				Major serotypes	1, 7F, 3, 8, 19A	3, 11A (8%), 19A
				1	20%	3%
				7F	13%	2%
				3	12%	10%
				19F	1%	3%
				19A	7%	7%
Ochoa-Gondar, Tarragona, Spain 2008-11 Prospective cohort[42]	≥60 years Mean of cohort 71.7 years	- 109 non-invasive CAP - 16 invasive CAP Culture and/or urine assay: - Invasive CAP: any sterile site (+) - Non-invasive CAP: sputum or urine assay (+) with blood culture (done in 68%) (-)	Non-universal PCV7: 2001-09 PCV13: 2010 Uptake 45-51% in 2008-11[84]	PCV7 serotypes	6% (1/16)	1% (1/109)
				6 add. PCV13	31% (5/16)	8% (9/109)
				5 add. PCV13 in PPV23*	31% (5/16)	7% (8/109)
				PCV13 overall	38% (6/16)	9% (10/109)
				1	12% (2/16)	0% (0/109)
				7F	6% (1/16)	0% (0/109)
				3	6% (1/16)	4% (4/109)
				19F	0% (0/16)	1% (1/109)
				19A	6% (1/16)	4% (4/109)
Horacio, Portugal 2009-2011 Prospective study in 30 laboratories [78, 79]	≥18 years, 40% ≥65 years	- 1300 non-invasive CAP - 1265 IPD: any, not only pneumonia Culture only, from: - IPD: any sterile fluid	Non-universal PCV7: 2001-09 PCV13: 2010-11 Uptake: 82% 2 doses[85]	PCV7 serotypes	19%; 14.2% in 65+ (2010)	10.3%; 8.4% in 65+ (2010)
				6 add. PCV13	41.0%	33.4%
				5 add. PCV13 in PPV23*	40.5%	30.7%
				PCV13 overall	59%	43.7%; 40.6% in 65+
				11 PPV23 additional	20.5%	22.3%
				PPV23 overall	80%	66%; 67% in 65+
				Non covered by PPV23	20%	34%

		- non-invasive pneumonia: sputum, bronchial secretions or BAL (8% of all) (+), with sterile fluid (-) NBP without blood culture performed: unknown		Major serotypes	3, 7F, 19A, 14 (8%), 1	3, 11A (7%), 6C (6%), 19F, 22F (5%)
				1	7%	2%
				7F	10%	3%
				3	13%	16%
				19F	2%	6%
				19A	9%	8%
Domenech, Barcelona, Spain 2001-08 Prospective study in one hospital[83]	Adults (no age defined)	COPD cases only: - 161 non-bacteraemic CAP, including 7 pleural fluid - 94 bacteraemic CAP Culture only, from: - BP: blood - NBP: sputum, pleural fluid, BAL, transthoracic NBP without blood culture performed: unknown	Non-universal PCV7 2001-09 Uptake 50%[159] (PCV13 in 2010)	PCV7 serotypes	20% (19/94)	32% (51/161)
				6 add. PCV13	50% (47/94)	29% (47/161)
				5 add. PCV13 in PPV23	47% (44/94)	27% (44/161)
				PCV13 overall	70% (66/94)	61% (98/161)
				Major serotypes	3, 1 , 5 (9%), 19A	3, 19F, 23F (6%), 11A (6%), 6B (6%)
				1	9%	5%
				7F	3%	3%
				3	18%	15%
				19F	4%	12%
				19A	7%	4%
CAPITA (Bonten), Netherlands, 2008-13, not immune-compromised Placebo arm of RCT[22, 86]	≥65 years	- 56 invasive disease - 87 non-invasive CAP Culture or urine detection: - IPD: any sterile fluid (+) - non-invasive CAP: urine test (+) and sterile fluid (-) First episode, per protocol subjects Analysis of all pneumococcal CAP/IPD in PP analysis	Universal PCV7: 2006-2010 PCV10: 2011-13 Uptake >94%[87]	PCV7 serotypes	13% (7/56)	15% (13/87)
				6 PCV13 additional	38% (21/56)	55% (47/87)
				5 add. PCV13 in PPV23*	34% (19/56)	52% (45/87)
				PCV13 overall	50% (28/56) mITT: 61%	70% (60/87) mITT: 67%
				Major serotypes	7F, 1, 3*	19A, 7F, 3, 1*
				1	9%	7%
				7F	13%	15%
				3	7%	14%
				19A	4%	16%
				19F	2%	2%

**: major serotypes are limited to those included in PCV13 because non-vaccine types have not been typed. BP: bacteraemic pneumonia; NBP: non-bacteraemic pneumonia; CAP: community acquired pneumonia; COPD: Chronic obstructive pulmonary disease; BAL: bronchoalveolar lavage.*

Appendix 2.2. Literature review on the proportion of hospitalised pneumococcal pneumonia that are non-invasive CAP

Table 60 – Findings of studies reporting the proportion of hospitalised pneumococcal pneumonia that are non-invasive CAP

Study	Setting and study design	Patients characteristics	Outcome definition	Number cases	% non-invasive/NB pneumonia
Said[5]	Meta-analysis, all settings	Adults (age not described) Majority hospitalised	X-Ray (+) Culture or urine assay (+) Proportion tested by urine assay: variable.	28 studies, total cases unknown	75% (95%CI: 71, 79)
Sordé 2011[44]	Spain, Barcelona, 2007-08 Prospective study of CAP patients in one hospital,	≥16 years All CAP: mean 64 years, 23% ≥80 years All hospitalised	X-Ray (+) Culture or urine assay/test (81% cases): - invasive: culture of blood or PF (+) or PCR (+) - non-invasive: sputum or urine assay (+), blood (-). Urine detection in 90% Pnc cases	171 pneumococcal CAP	66% (113/171)
Benfield 2013[40]	Denmark, 2011 Design unclear	≥15 years Mean 68 years, 60% ≥65 years 98.5% hospitalised	X-Ray (+) and pneumococcal isolate. Culture only: - BP: blood culture (+) - NBP: airway sample (+) and blood culture (-). Probably include pleural fluid	464 pneumococcal CAP - 272 NBP, 20% are COPD	59% (272/464)
Blasi 2013 (REACH study)[45]	10 EU countries, incl. BE, 2010-11 Retrospective study of CAP cases in 128 centres	≥18 years Mean 64 years, 56% ≥65 years All hospitalised (severe)	Severe hospitalised CAP only (requiring intravenous antimicrobials) Culture or urine assay/test (35% cases): - BP: blood culture (+) - NBP: Sputum (+), BAL (+), pleural fluid (+) or urine antigen test (+)	228 pneumococcal CAP	68% (154/228)
Bewick 2012[41]	England, 2008-10. Prospective cohort study in one hospital	≥16 years Median 71 years, 62% ≥65 years All hospitalised in large hospitals	X-Ray (+), Culture or urine assay (100%): - BP: blood culture (+) - NBP: airway sample (+) or urine assay Binax (+) and blood culture (-)	253 pneumococcal CAP	84% (213/253)*
Ochoa-Gondar 2014[42]	Spain, Tarragona, 2008-11 Prospective cohort study of patients from 9 primary health centers	Cohort: ≥60 years Mean 72 years (unknown for cases) All hospitalised	X Ray (+), Culture or urine assay (81% cases): - BP or invasive CAP: any sterile site (+) - non-invasive CAP: sputum or urine assay (+), blood (-) (done in 68%)	125 pneumococcal CAP	87% (109/125)
Sherwin[43]	US, 2010-11 Prospective multicentre cohort study	≥50 years Median 62 years, 40% ≥65 years 97% hospitalised	X-Ray (+) Culture or urine assay (100% cases): - invasive: blood culture (+) - non-invasive: sputum or urine assay (+) and blood (-)	98 pneumococcal CAP	88% (86/98)

**: calculated on those with blood culture results only; BP: bacteraemic pneumonia; NBP: non-bacteraemic pneumonia; CAP: community acquired pneumonia; COPD: Chronic obstructive pulmonary disease; Pnc: pneumococcal*

APPENDIX 3. MATCHING OF THE MZG-RHM AND NRC DATABASES

Data from the NRC have been linked to MZG-RHM/AZV-SHA data after obtaining authorisation from the Belgian Commission for the protection of privacy in April 2015.

Data from the NRC from year 2007 to year 2014 have been selected based on the isolation source to restrict matching to invasive pneumococcal disease. Selected cases were then matched to the MZG-RHM/AZV-SHA data based on the patient's gender and year of birth along with the hospital identification number associated with the stay for MZG-RHM/AZV-SHA data and with the laboratory for the NRC data. Matching was done only if the date of the sample reception was in the period of 10 days leading up to, and 14 days after a matching hospital stay. Moreover, the patient zip code was also considered, and when multiple matches were possible, the record with the date closest to the hospital admission date was selected, with a preference for analysis occurring during the stay over analysis occurring before or after the stay. Whenever the patient's zip code did not match, the laboratory's zip code was considered, and manually accepted or rejected. Only one hospital record per patient was kept.

More than 70% of the NRC cases were matched for the years 2008-2011.

APPENDIX 4. LITERATURE REVIEWS OF HEALTH UTILITY VALUES

Appendix 4.1. General methods

The first literature search focused on utility values related to outcomes of pneumococcal infections in adults. The second literature search was broader and covered utility values for similar outcomes caused by any other pathogens (e.g. Meningococcus…). The following inclusion criteria were used:

The following inclusion criteria were used:

- Population:
  - Search 1: adults who suffered from pneumococcal infection as well as sub-groups of patients experiencing a particular clinical manifestation of pneumococcal infection (i.e. pneumonia, meningitis, bacteraemia, septicaemia, empyema) or long-term sequelae due to pneumococcal infection. All serotypes of *Streptococcus pneumoniae* were considered.
  - Search 2: adults who suffered the clinical manifestations and sequelae specified in search 1, caused by any bacteria (i.e. bacterial meningitis, bacterial pneumonia, bacteraemia, empyema) or pathogen (community-acquired pneumonia (CAP), septic shock).
- Outcome: papers reporting utility measures, i.e. measures that lead to a single score for the HRQoL of a particular health state and that are obtained using preference- or choice-based methods. Profile measures giving separate scores for each dimension of a particular health state are excluded as they cannot be directly converted into quality-adjusted life-years (QALYs) to be used in cost-utility analyses. Papers must value HRQoL utility indexes based on a generic descriptive instrument (EQ-5D, HUI, SF-6D, SF-12 or SF-36[e]) or directly from the patient (TTO, PTO, SG, VAS)[f].

[e] Although generating profile health status measures and although being non-preference-based measures, SF-12 and SF-36 instruments were still considered as they may have been converted into SF-6D health states and a corresponding single preference-based utility score.

[f] TTO: time trade-off, PTO: person trade-off, SG: standard gamble, VAS: visual analogue scale, EQ-5D: EuroQol 5 dimensions, HUI: health utilities index, SF-36: short-form 36, SF-12: short-form 12, SF-6D: short-form 6 dimensions.

- Design: original primary QoL studies are considered. Reviews and methodological papers are excluded. For the review on pneumococcal infections (search 1), published cost-utility analyses of adult pneumococcal vaccination are also retained with the aim to provide an overview of their QoL assumptions and inputs.
- Geographical coverage: studies performed in countries with comparable culture and epidemiology of pneumococcus were preferably considered.

The following databases were searched in January/February 2015 for papers published up to early 2015: CRD HTA, CRD NHS EED, Medline(Ovid), Medline(Ovid) in-process and other non-indexed citations, PsycInfo(Ovid), Econlit(Ovid) and Embase. A combination of MeSH, EMTREE and text words terms related to S*treptococcus pneumoniae* and to bacterial meningitis, bacterial pneumonia, bacteraemia, empyema, CAP and septic shock, were combined with those related to quality of life and age groups (see appendix). Early March 2016, an update of the literature searches was performed in order to identify studies published in the 2015-early 2016 interval (see appendix).

Identified citations were assessed in a two-step procedure: initial assessment of the title, abstract and keywords; followed by full-text assessment if the title or the abstract or the keywords suggested relevant information or if no abstract was available. Reference lists of the selected studies were scrutinized for additional relevant citations. The flow charts of the selection processes can be found below.

Appendix 4.2. Studies identification - Health utility values for pneumococcal diseases in adults

Appendix 4.2.1. Search strategies

Database		Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present	
Date			20/01/2015
Date covered			1946 to present
Search strategy	**#**	**Searches**	**Results**
	1	exp Streptococcus pneumoniae/	18497
	2	exp Pneumococcal Infections/	16581
	3	1 or 2	27034
	4	"Quality of Life"/	121111
	5	Quality-Adjusted Life Years/	7177
	6	(health utilit* index or HUI).mp.	1176
	7	(short form health survey or SF-36 or SF36 or SF-6D or SF6D).mp.	15841
	8	(EuroQol or EQ-5D or EQ5D).mp.	4490
	9	(quality-adjusted life year* or quality-adjusted life-year* or quality adjusted life year* or quality adjusted life-year* or QALY).mp.	10618
	10	(quality of life or HRQL).mp.	203902
	11	(standard gamble or SG).mp.	6494
	12	(time-trade off or time trade-off or TTO).mp.	1088
	13	utilit*.mp.	126865
	14	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	335183
	15	"Aged, 80 and over"/ or Aged/ or Middle Aged/	3903943
	16	3 and 14 and 15	84
Note	mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier. Similar searches performed on PsynINFO(OVID) and Econlit(OVID) returned 0 results. Updated search performed in March 2016.		

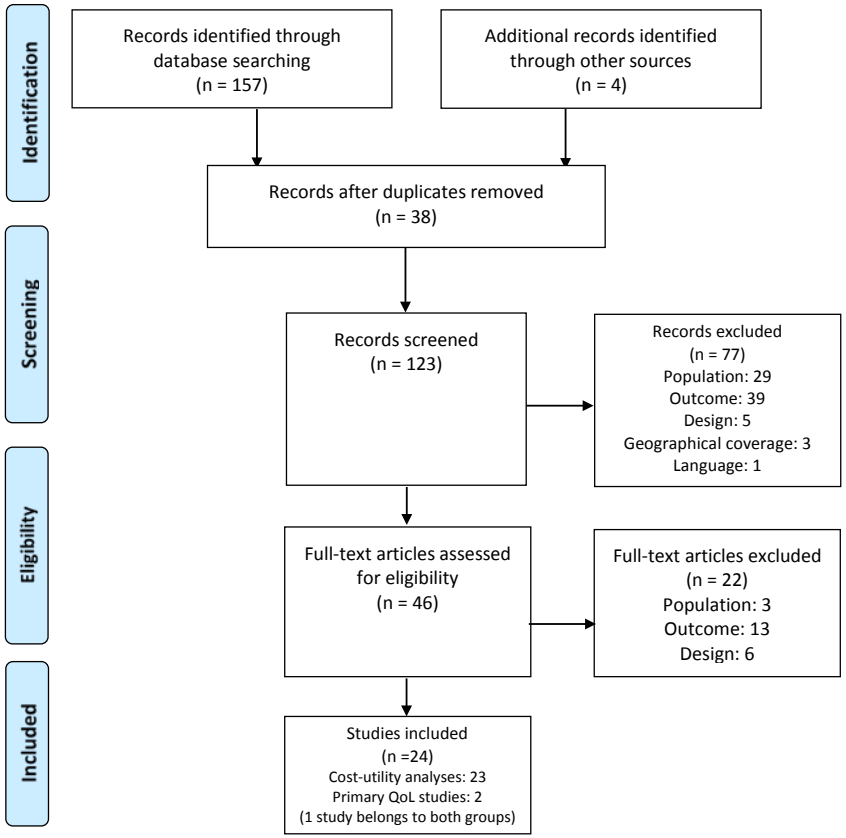
Database		Embase	
Date			20/01/2015
Date covered			No restriction
Search strategy	**#**	**Searches**	**Results**
	#1	'pneumococcal infection'/exp	8901
	#2	'middle aged'/exp OR 'aged'/exp	2690011
	#3	'pneumococcal infection'/exp AND ('middle aged'/exp OR 'aged'/exp)	1132
	#4	'quality of life'/exp OR 'cost utility analysis'/exp	287594
	#6	'health utility index' OR 'hui':ab,ti	2065
	#7	'short form health survey' OR 'sf-36' OR 'sf36' OR 'sf-6d' OR 'sf6d':ab,ti	23906
	#8	'euroqol' OR 'eq-5d' OR 'eq5d':ab,ti	7989
	#11	'quality-adjusted life year' OR 'quality adjusted life year' OR 'qaly':ab,ti	16388
	#12	'quality of life' OR 'hrql':ab,ti	318812
	#13	'standard gamble' OR 'sg':ab,ti	8621
	#14	'time-trade off' OR 'time trade-off' OR 'tto':ab,ti	1548
	#15	#4 OR #6 OR #7 OR #8 OR #11 OR #12 OR #13 OR #14	352453
	#16	#3 AND #15	41
Note	Updated search performed in March 2016.		

Database		CRD HTA and CRD NHS EED	
Date			20/01/2015
Date covered			No restriction
Search strategy	**#**	**Searches**	**Results**
	1	MeSH DESCRIPTOR Quality of Life EXPLODE ALL TREES IN NHSEED,HTA	1342
	2	MeSH DESCRIPTOR Quality-Adjusted Life Years EXPLODE ALL TREES IN NHSEED,HTA	3116
	3	(health utilit* index OR HUI) IN NHSEED, HTA	144
	4	(EuroQol OR EQ-5D OR EQ5D) IN NHSEED, HTA	753
	5	(short form health survey or SF-36 or SF36 or SF-6D or SF6D) IN NHSEED, HTA	281
	6	(quality-adjusted life year* or quality adjusted life year* or QALY) IN NHSEED, HTA	4917
	7	(quality of life or HRQL) IN NHSEED, HTA	4504
	8	(standard gamble or SG) IN NHSEED, HTA	303
	9	(time-trade off or time trade-off or TTO) IN NHSEED, HTA	368
	10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	7262
	11	MeSH DESCRIPTOR Middle Aged EXPLODE ALL TREES IN NHSEED,HTA	6587
	12	MeSH DESCRIPTOR Aged EXPLODE ALL TREES IN NHSEED,HTA	5479
	13	MeSH DESCRIPTOR Aged, 80 and over EXPLODE ALL TREES IN NHSEED,HTA	1951
	14	#11 OR #12 OR #13	7820
	15	MeSH DESCRIPTOR Pneumococcal Infections EXPLODE ALL TREES IN NHSEED,HTA	124
	16	MeSH DESCRIPTOR Streptococcus pneumoniae EXPLODE ALL TREES IN NHSEED,HTA	16
	17	#15 OR #16	128
	18	#10 AND #14 AND #17	32
Note	Updated search performed in March 2016.		

Appendix 4.2.2. Selection procedures

The electronic searches returned 157 citations in total (84 in Medline(OVID), 0 in PsynINFO(OVID), 0 in Econlit(OVID), 41 in Embase and 32 in CRD HTA & CRD NHS EED). Four publications were further identified via inspection of reference lists. After exclusion of 38 duplicates, 123 unique citations were left. The flow chart of the selection process is presented below.

Figure 26 – Flowchart of literature review process (QoL for pneumococcal outcome)



The updated search performed in March 2016 for studies published in the 2015-early 2016 time window returned 22 additional unique citations. After assessment, one study was retained that was both a cost-utility analysis of pneumococcal vaccination in the elderly and a primary QoL study.[92]

Appendix 4.3. Studies identification - Health utility values for bacterial pneumonia, bacterial meningitis, bacteraemia, empyema and sepsis in adults

Appendix 4.3.1. Search strategies

Database		Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present	
Date			12/02/2015
Date covered			1946 to present
Search strategy	**#**	**Searches**	**Results**
	1	"Quality of Life"/	121955
	2	Quality-Adjusted Life Years/	7269
	3	(health utilit* index or HUI).mp.	1182
	4	(EuroQol or EQ-5D or EQ5D).mp.	4555
	5	(quality-adjusted life year* or quality-adjusted life-year* or quality adjusted life year* or quality adjusted life-year* or QALY).mp.	10755
	6	(standard gamble or SG).mp.	6551
	7	(time-trade off or time trade-off or TTO).mp.	1099
	8	(quality adj1 life).mp.	4146
	9	hrql.mp.	2476
	10	(SF-36 or SF36 or SF-6D or SF6D or SF-12 or SF12).mp.	16854
	11	short form health survey.mp.	3106
	12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	148085
	13	Meningitis, Bacterial/	5477
	14	Bacteremia/	18548
	15	Empyema/	3480
	16	Pneumonia, Bacterial/	8627
	17	Shock, Septic/	18522
	18	13 or 14 or 15 or 16 or 17	53159
	19	"Aged, 80 and over"/ or Aged/ or Middle Aged/	3922687
	20	12 and 18 and 19	36

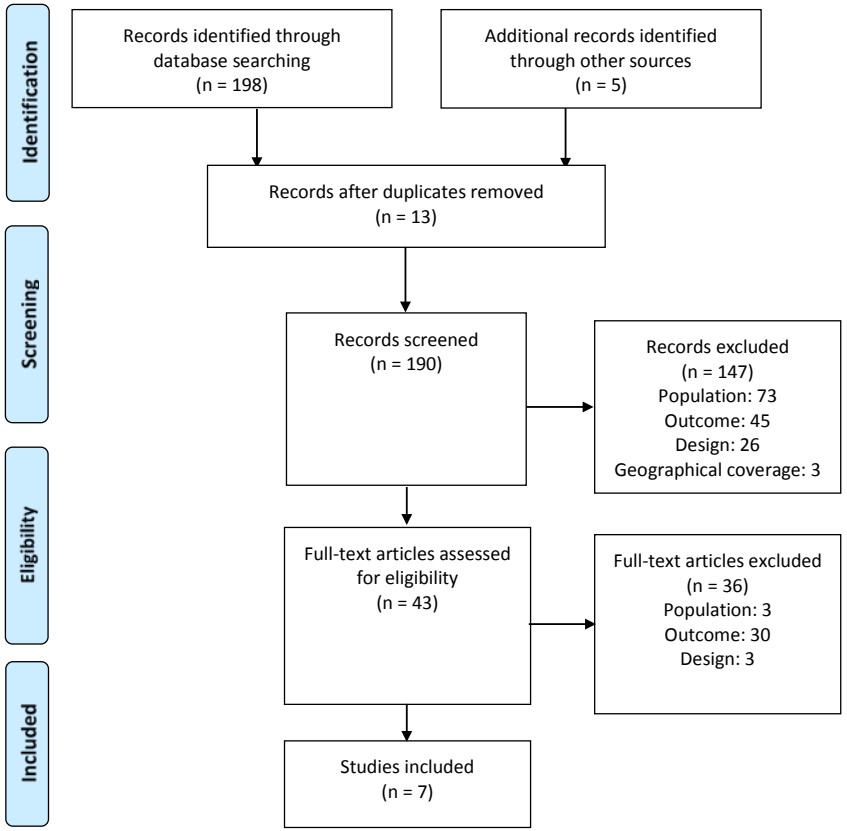
Note	mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier Updated search performed in March 2016.

Database		**Embase**	
Date			12/02/2015
Date covered			No restriction
Search strategy	**#**	**Searches**	**Results**
	#2	'bacteremia'/exp	34368
	#3	'bacterial meningitis'/exp	14126
	#4	'community acquired pneumonia'/exp	8707
	#5	'bacterial pneumonia'/exp	9961
	#6	'empyema'/exp	12463
	#7	'septic shock'/exp	33975
	#8	'bacteremia'/exp OR 'bacterial meningitis'/exp OR 'community acquired pneumonia'/exp OR 'bacterial pneumonia'/exp OR 'empyema'/exp OR 'septic shock'/exp	106839
	#9	'middle aged'/exp OR 'aged'/exp OR 'young adult'/exp	2731120
	#10	'quality of life'/exp OR 'cost utility analysis'/exp	290921
	#11	'health utility index' OR 'hui':ab,ti	2074
	#12	'short form health survey' OR 'sf-36' OR 'sf36' OR 'sf-12' OR 'sf12' OR 'sf-6d' OR 'sf6d':ab,ti	27705
	#13	'euroqol' OR 'eq-5d' OR 'eq5d':ab,ti	8140
	#14	'quality-adjusted life year' OR 'quality adjusted life year' OR 'qaly':ab,ti	16564
	#15	'quality of life' OR 'hrql':ab,ti	322235
	#16	'standard gamble' OR 'sg':ab,ti	8704
	#17	'time-trade off' OR 'time trade-off' OR 'tto':ab,ti	1564
	#18	('quality of life'/exp OR 'cost utility analysis'/exp) OR ('health utility index' OR 'hui':ab,ti) OR ('short form health survey' OR 'sf-36' OR 'sf36' OR 'sf-12' OR 'sf12' OR 'sf-6d' OR 'sf6d':ab,ti) OR ('euroqol' OR 'eq-5d' OR 'eq5d':ab,ti) OR ('quality-adjusted life year' OR 'quality adjusted life year' OR 'qaly':ab,ti) OR ('quality of life' OR 'hrql':ab,ti) OR ('standard gamble' OR 'sg':ab,ti) OR ('time-trade off' OR 'time trade-off' OR 'tto':ab,ti)	357222
	#19	('bacteremia'/exp OR 'bacterial meningitis'/exp OR 'community acquired pneumonia'/exp OR 'bacterial pneumonia'/exp OR 'empyema'/exp OR 'septic shock'/exp) AND ('middle aged'/exp OR 'aged'/exp OR 'young adult'/exp) AND (('quality of life'/exp OR 'cost utility analysis'/exp) OR ('health utility index' OR 'hui':ab,ti) OR ('short form health survey' OR 'sf-36' OR 'sf36' OR 'sf-12' OR 'sf12' OR 'sf-6d' OR 'sf6d':ab,ti) OR ('euroqol' OR 'eq-5d' OR 'eq5d':ab,ti) OR ('quality-adjusted life year' OR 'quality adjusted life year' OR 'qaly':ab,ti) OR ('quality of life' OR 'hrql':ab,ti) OR ('standard gamble' OR 'sg':ab,ti) OR ('time-trade off' OR 'time trade-off' OR 'tto':ab,ti))	162
Note	Updated search performed in March 2016.		

Appendix 4.3.2. Selection procedures

The electronic searches returned 198 citations in total (36 in Medline(OVID) and 162 in Embase). Five publications were further identified via inspection of reference lists. After exclusion of 13 duplicates, 190 unique citations were left. The flow chart of the selection process is presented below.

Figure 27 – Flowchart of literature review process (QoL for any bacterial outcome)



The updated search performed in March 2016 for studies published in the 2015-early 2016 time window returned 28 additional unique citations. After assessment, one study was retained and included in our review of primary QoL studies.[91]

Appendix 4.3.3. Utility review results

Utility scores used in economic evaluations of adult pneumococcal vaccination

The utility scores used in the 24 economic evaluations of adult pneumococcal vaccination are presented inTable 61. The review highlighted the paucity of documented quality of life data available for the economic evaluation of interventions against pneumococcal diseases in adults. Virtually all studies relied on the same two data sources.

The majority of the studies (16 out of 24) used the quality adjusted life weight attributed by Sisk for bacteraemia (with or without focus, thus including bacteraemic pneumonia), elicited from the 1990 National Health Interview Survey in the United States.[98, 160] On the basis of a specified level of activity limitation and of perceived health attributed by patients having suffered the condition “unspecified septicemia”, a weight of 0.2 was derived. Sisk assumed that patients would remain 34 days in this health state, after which they would return to their average age-specific health-related quality of life. In subsequent cost-utility studies, this weight and assumed duration was extended to other health states, and applied to all invasive pneumococcal diseases (meningitis, bacteraemia with our without focus, bacteraemic pneumonia) and to hospitalised non-bacteraemic pneumonia. Nearly all studies that modelled the long-term consequences of meningitis sequelae and the vaccine adverse-events relied on the same weights, i.e. 0.4 lifelong and 0.9 during 3 days respectively, although these were pure assumptions.[161]

The other group of studies used the weights identified through literature review by Melegaro et al.[162] in their economic evaluation of the 7-valent vaccine in children. In this study, QALY losses for bacteraemia (-0.0079) and meningitis (-0.0232) were obtained from Bennett et al.[163] who asked parents of 3-36 month old children to value 8 outcomes of occult bacteraemia with a standard gamble technique. As there is evidence that the type and evolution of clinical syndrome associated with invasive pneumococcal infections differ between children and adults,[164] applying weights derived for children to adults may not be appropriate. Melegaro et al.[162] further estimated the QALY losses for hospitalised non-bacteraemic pneumonia (-0.006) and outpatient pneumonia (-0.004) from the theoretical weights assumed in Vold Pepper et al.[165] for adult pneumococcal vaccination.

Table 61 – Utility scores used in the published cost-utility analyses of adult pneumococcal vaccination

Author, year, country	Vaccine	Baseline – reference population	Invasive pneumococcal diseases				NBPP hospitalised	NBPP non-hospitalised	Long-term disability post meningitis	Vaccine adverse event	Sources
			All IPD	Meningitis	Bacteraemia ***	Bacteraemic pneumonia					
Mangen et al., The Netherlands[92]	PCV13	Healthy and high-risk populations* Age-dependent (18-85+ years)	-0.0709				-0.0709	-0.0045			CHO-CAP[166] for NBB IP, GRACE[167] for NBB OP, assumption for IPD
Chen, 2014, USA[168]	PCV13	Healthy and high-risk populations* Age-dependent (50-85+ years)	0.2 during 34 days				0.2 during 34 days	-0.004 (-0.209 during 7 days)	0.4 lifelong	-0.1 during 3 days	Smith, 2012[169] Siddiqui, 2008[170] (= Melegaro, 2004[162]) for NBPP OP
Boccalini, 2013, Italy[171]	PCV13	Healthy population Age-dependent (65-85+ years)		0.2 during 34 days		0.2 during 34 days	0.2 during 11 days				Sisk, 2003[98] Assumption for NBPP IP
Cho, 2013, USA[172]	PCV13	None		-0.0232 (reduction from 1)	-0.0079 (reduction from 1)	-0.0079 (reduction from 1)	-0.006 (reduction from 1)	-0.004 (reduction from 1)			Rubin, 2010[173] (= Melegaro, 2004[162])
Lin, 2013, USA[174]	PPV23	Population aged 65+ years (uniform +/- 0.05)	0.2 (uniform 0.1-0.5) during 34 days						0.4 (uniform 0.2-0.6) lifelong	0.9 (uniform 0.80-0.99) during 3 days	Sisk, 2003[98] Assumption for LT disability and VAE
Michaelidis, 2013, USA[175]	PPV23	Healthy population Age-dependent (65-85+ years) (uniform +/-0.05)	0.2 (uniform 0.15-0.25) Duration not reported						0.4 (uniform 0.2-0.6) lifelong	0.9 (uniform 0.80-0.99) Duration not reported	Sisk, 2003[98] Assumption for LT disability and VAE
Smith, 2013, USA[176] (immuno-comp)	PCV13	High-risk population* Age-dependent (50-85+ years) (uniform +/-0.05)	0.2 (uniform 0.1-0.5) during 34 days				0.2 uniform 0.1-0.5) during 34 days		0.4 (uniform 0.2-0.6) lifelong	0.9 (uniform 0.80-0.99) during 3 days	Sisk, 2003[98] Assumption for NBPP IP, LT disability and VAE
Smith, 2013, USA[177]	PCV13	Healthy and high-risk* populations Age-dependent (65-85+ years) (uniform +/-0.05)	0.2 (uniform 0.1-0.5) during 34 days				0.2 uniform 0.1-0.5) during 34 days		0.4 (uniform 0.2-0.6)	0.9 (uniform 0.80-0.99) during 3 days	Sisk, 2003[98] Assumption for NBPP IP, LT disability and VAE

Author, year, country	Vaccine	Baseline – reference population	Invasive pneumococcal diseases				NBPP hospitalised	NBPP non-hospitalised	Long-term disability post meningitis	Vaccine adverse event	Sources
			All IPD	Meningitis	Bacteraemia ***	Bacteraemic pneumonia					
Grzesiowski, 2012, Poland[178]	PPV23	Hungarian average population		-0.71 (-0.57 to -0.86) during 17.5 (14-21) days		-0.71 (-0.57 to -0.86) during 12 (9.6-14.4) days	-0.71 (-0.57 to -0.86) during 8.5 (6.8-10.2) days	-0.28 (-0.23 to -0.34) during 8.5 (6.8-10.2) days	-0.34 to -0.51		Sisk, 2003[98] Smith,2008[161] Smith,2002[179] Assumptions (not clear)
Jiang, 2012, Germany[180]	PPV23	Healthy and high-risk* populations Age-dependent (18-85+ years) (triangular +/- 0.05)		0.2 (triangular 0.16-0.24) during 34 days		0.2 (triangular 0.16-0.24) during 34 days	No decrement	No decrement	Hearing loss: 0.8 (triangular 0.6-1) Neurologic: 0.6 (triangular 0.45-0.75)		Sisk, 2003[98] Assumption for NBPP DeWals, 2003[181] for LT disability (infant)
Rozenbaum, 2012, UK[182]	PCV13	None		-0.0232 (beta, se 0.031)	-0.0079 (beta, se 0.083)	-0.0079 (beta, se 0.083)	-0.006 (normal, se 0.0015)		Deaf: 0.81 Mild hearing loss: 0.91 Seizure: 0.83 Hydrocephalus: 0.62 Paresis/palsy: 0.67		Bennett, 2000[163] for IPD, Melegaro, 2004[162] for NBPP, Oostenbrink, 2002[183] for LT disability (infant)
Smith, 2012, USA[169]	PCV13	Healthy and high-risk* populations Age-dependent (50-85+ years) (uniform +/-0.05)	0.2 (uniform 0.1-0.5) during 34 days				0.2 (uniform 0.1-0.5) during 34 days		0.4 (uniform 0.2-0.6) lifelong	0.9 (uniform 0.8-0.99) during 3 days (0.1 loss)	Sisk, 2003[98] Assumption for NBPP IP, LT disability and VAE
Dhankhar, 2010, USA[184]	PPV23	None	-0.006 (triangular +/-15%)				-0.006 (triangular +/-15%)	-0.004 (triangular +/- 15%)		-0.1 (triangular, -0.2 to -0.01)	Siddiqui, 2008[170] (= Melegaro, 2004[162]) Smith, 2010[185] for VAE
Rozenbaum, 2010, The Netherlands[186]	PCV13	Healthy and high-risk* populations Age-dependent (65-85+ years)		0.2 during hospital stay	0.2 during hospital stay	0.2 during hospital stay					Sisk, 2003[98]
Smith, 2010, USA[185] **(HCW)**	PPV23	Healthy population Age-dependent (18-74 years)	0.2 (uniform 0.1-0.6) for 34 days						0.4 (uniform 0.2-0.6) lifelong	0.9 (uniform 0.8-0.99) for 3 days	Sisk, 2003[98] Assumption for VAE and LT disability
Smith, 2010, USA[187]	PPV23	Healthy population Age-dependent (50+ years)	0.2 (uniform 0.1-0.5) for 34 days						0.4 (uniform 0.2-0.6) lifelong	0.9 (uniform 0.8-0.99) for 3 days	Sisk, 2003[98] Assumption for VAE and LT disability

Author, year, country	Vaccine	Baseline – reference population	Invasive pneumococcal diseases				NBPP hospitalised	NBPP non-hospitalised	Long-term disability post meningitis	Vaccine adverse event	Sources
			All IPD	Meningitis	Bacteraemia ***	Bacteraemic pneumonia					
Smith, 2009, USA[188]	PPV23	Healthy and high-risk* populations Age-dependent (65-85+ years) (uniform +/-0.05)	0.2 (uniform 0.1-0.5) for 34 days						0.4 (uniform 0.2-0.6) lifelong	0.9 (uniform 0.8-0.99) for 3 days	Sisk, 2003[98] Assumption for VAE and LT disability
Middleton, 2008, USA[189]	PPV23	Healthy population Age-dependent (50-85+ years) (uniform +/-0.05)	0.2 (uniform 0.1-0.5) during hospital stay								Sisk, 2003[98]
Smith, 2008, USA[161]	PPV23	Healthy and high-risk* populations Age-dependent (50 -85+ years) (uniform +/-0.05)	0.2 (uniform 0.1-0.5) during 34 days						0.4 (uniform 0.2-0.6) lifelong	0.9 (uniform 0.8-0.99) during 3 days	Sisk, 2003[98] Assumption for VAE and LT disability
Sisk, 2003, USA[98]	PPV23	Healthy and high-risk** populations Age-dependant (50-85+ years) (triangular +/-0.05)	0.2 (triangular 0.15-0.25) during 34 days (at hospital or at home)								Erickson, 1995[190] Assumption for duration
Vold Pepper, 2000, USA[165]	PPV23	None					0.85 duration not clear	0.9 duration not clear		0.9 duration not clear	Assumption
Sisk, 1997, USA[160]	PPV23	Healthy population Age-dependant (65-85+ years)			0.2 during 34 days	0.2 during 34 days					Erickson, 1995[190] Assumption for duration
Sisk, 1986, USA[191]	PPV23	None				0.4 duration not reported	0.4 duration not reported	0.6 duration not reported			Sisk, 1980[192]
Sisk, 1980, USA[192]	PPV14	None				0.4 duration not reported	0.4 duration not reported	0.6 duration not reported		Systemic reaction: 0.4 during 3 days	Bush, 1973[193]

*NBPP IP: non-bacteraemic pneumococcal pneumonia hospitalised; NBPP OP: non-bacteraemic pneumococcal pneumonia ambulatory; VAE: vaccine adverse event, SE: standard error. * High-risk population defined as immunocompetent with comorbidities and immunocompromised. ** High-risk population defined as immunocompetent people with congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, chronic renal failure, cirrhosis or chronic alcoholism. *** Bacteraemia without focus or bacteraemia with focus (other than pneumonia). Note: the negative sign in the table refers to loss in quality of life.*

Primary QoL studies relevant for adult pneumococcal diseases

An overview of the methods and results of the 11 studies reporting utility weights for health states relevant to adult pneumococcal diseases are presented in the tables below.

Methods

In most studies (9 out of 11) the health states descriptions/valuations were performed by the patients themselves. In two studies respondents were not patients but healthy adults (lay-people or health care professionals) assessing hypothetical scenarios describing the condition of interest without specifying the age of the hypothetical patient.[94, 101]

The majority of the studies (9 out of 11) used the generic EQ-5D instrument to describe the health states. The two other studies elicited their utility indexes directly with the person trade-off technique[101] or indirectly with the Health and Activity Limitation index.[98]

Only two studies reported the quality of life impact for health states explicitly related to *Streptococcus pneumoniae*.[92, 94] In Galante et al. utility weights (EQ-5D) were derived for the acute phase of a pneumococcal pneumonia (both hospitalised and not hospitalised), for pneumococcal sepsis, pneumococcal meningitis, and neurologic and auditive sequelae.[94] In Mangen et al.,[92] QALY losses (EQ-5D) for an hospitalised (non-IPD) CAP were derived from the preliminary results (n= 147 cases) of the CHO-CAP study, a case-control study nested within CAPITA aimed at prospectively collecting QoL data from an expected 600 elderly persons (>65 year) hospitalised with pneumococcal CAP in The Netherlands.[166] The full results of this study were still unpublished at the time of the current review.

Seven studies explored the long-term impact (i.e. from 6 months to 2 years after hospital discharge) on the quality of life of survivors of severe sepsis or septic shock, without specifying the origin or the causative pathogen.

The two remaining studies reported the quality of life impact of permanent sequelae following serogroup C meningococcal infection (amputations)[99] and following bacterial meningitis (locomotor and cognitive impairments).[101] In this last study values for an acute episode of all-cause pneumonia lasting 2 weeks then followed by complete recovery were also reported.

The review did not identify studies exploring the QoL impact of empyema.

Values

EQ-5D utility weights reported for survivors of severe sepsis and septic shock were rather consistent and ranged from 0.68[93] to 0.84[97] six-months after hospital discharge. Dabrinsky et al.[100] report EQ-5D scores at different time intervals after severe sepsis. Survivors of severe sepsis were found to experience a continual improvement towards population-based normal levels in their health utility scores over a 6-month period. The average utility weights were 0.53 at one month, 0.62 at two months, 0.68 at three months and 0.69 at six months after sever sepsis.[100] By contrast to this QoL improvement over time,[100] Karlsson et al.[95] found that severe sepsis or septic shock patients remained at a lower QoL (0.75) compared to the QoL of the age- and sex-adjusted general population in Finland (0.86), even 1.5 year after the disease. They report however that the QoL of sepsis patients before this critical illness was already lower than that of the general population (0.81 versus 0.86).

Much lower weights were reported by the two studies assessing the QoL of patients with an acute sepsis. Sisk et al.[98] reported a 0.2 HALex score for an acute unspecified septicemia while Galante et al.[94] found a negative utility weight of -0.295 for an acute pneumococcal sepsis. In both studies the assumed duration of the acute disease was 3 to 4 weeks.

Two papers elicited utilities for permanent neurological sequelae (broadly defined as mental retardation and behaviour problems) from scenarios describing an hypothetical patient having suffered from bacterial[101] or pneumococcal[94] meningitis. Although both papers used different methods, namely the EQ-5D[94] and the PTO,[101] the resulting scores were rather comparable: 0.24 in Stouthard et al.[101] and 0.32 in Galante et al.[94]

Table 62 – Quality of life studies relevant to pneumococcal diseases in adults: summary of methods

Studies	Method	Respondent	Number	Age (years)	Disease period	Follow-up period	Disease
Mangen, 2015, The Netherlands[92]	EQ-5D	Patients	147	65+ years	10/2008 to spring 2014	12 months	Hospitalised pneumococcal CAP
Honselmann, 2015, Germany[91]	EQ-5D	Patients	73	Median 67 years (IQR 58-75)	02/2008 to 01/2009	12 months	Severe sepsis, septic shock
Orwelius, 2013, Portugal[93]	EQ-5D VAS	Patients	91	Median 60 years (IQR 50-70)	01/2005 to 06/2005	6 months	Community acquired sepsis, severe sepsis, septic shock
Galante, 2011, Argentina/UK[94]	EQ-5D VAS	Proxy (convenience sample of adults assessing hypothetical scenarios)	73	Mean 31 years (range 22-58)	Not applicable	Not applicable	Pneumococcal diseases
Karlsson, 2009, Finland[95]	EQ-5D	Patients or proxy (next of kin)	98	Mean 60.4 years (SD 10.3) at disease onset	11/2004 to 02/2005	17 months on average (range 12-20 months)	Severe sepsis, septic shock
Korosec Jagodic, 2006,Slovenia[96]	EQ-5D	Patients or proxy (family member)	10	Mean 45 years (SD 19.8) at disease onset	01/2003 to 12/2003	2 years	Severe sepsis, septic shock
Granja, 2004, Portugal[97]	EQ-5D VAS	Patients	104	Median 52 years (IQR 38-66)	03/1997 to 03/2001	6 months	Severe sepsis, septic shock
Sisk, 2003, USA[98]	HALex	Patients	Not stated	All ages	1987-1992	Not applicable	Septicemia
De Wals, 2002, Canada[99]	EQ-5D	Patients or proxy (parents or researcher)	Not stated	All ages	1990-1994	Not stated	Sequelae after serogroup C meningococci
Drabinsky, 2001, USA[100]	EQ-5D VAS	Patients	93	Mean 60 years (SD 17) at disease onset	Not stated	1, 2, 3 and 6 months	Severe sepsis
Stouthard, 1997, The Netherlands[101]	PTO	Proxy (health care professionals assessing hypothetical scenarios)	38	All ages	Not applicable	Not applicable	All-cause pneumonia and sequelae after bacterial meningitis

EQ-5D: EuroQol 5 dimensions; VAS: visual analogue scale; HALex: Health and Activity Limitation Index; PTO: person trade-off; IQR: interquartile range; SD: standard deviation; CAP: community-acquired pneumonia.

Appendix 4.4. Summary of the studies reporting utility values relevant to pneumococcal disease in adults

Mangen et al., 2015[92]		
Method description	CAPiTA is a placebo-controlled double-blind RCT evaluating the effectiveness of a 13-valent conjugated pneumococcal vaccine in preventing vaccine-type pneumococcal CAP in 84 496 elderly in the Netherlands. Participants of CAPiTA, who consented and provided information on health status (EQ-5D) and socio-demographic background at the time of vaccination, constitute the source population of CHO-CAP[166] and are eligible for the nested matched cohort study. CHO-CAP patients hospitalized with CAP form the "diseased" cohort and the "non-diseased" cohort consists of unaffected persons (i.e. no CAP). Observations in the diseased cohort and in matched controls from the non-diseased cohort are used to determine QoL changes attributable to CAP. Based on an estimated 2 000 CAPiTA participants being hospitalized with CAP and an assumed CHO-CAP participation rate of 30% of all CAPiTA participants, 600 CAP episodes are expected among CHO-CAP participants (the "diseased" cohort). For each patient with CAP, two non-diseased CHO-CAP subjects will be selected from the CHO-CAP cohort, with matching for age, gender and EQ-5D baseline-score. Data on quality-of-life (using EQ-5D and SF-36 questionnaires) will be collected at 0, 1, 6 and 12 months after hospitalization for CAP. Mangen et al.[92] report the preliminary EQ-5D results using data from one-third of all participants (i.e. 147 confirmed CAP cases). The descriptive EQ-5D-3L five-digit numbers were converted into utilities by using preference weights (e.g. tariffs) from the Dutch population.	
Respondent	Patients	
n	147	
Age group	65 years and older at CAPiTA enrolment	
Disease period	October 2008 to spring 2014	
Follow-up period	12 months	
Reference population	Age-, sex- and EQ-5D baseline-score-matched subjects from the non-diseased cohort	
Disease	Hospitalised pneumococcal community-acquired pneumonia (CAP)	
Method/instrument	EQ-5D	
Results	**Health status**	**Mean EQ-5D (SE)**
	QALY loss for an hospitalised pneumococcal CAP	0.0709 (0.02)

Honselmann et al., 2015[91]			
Method description	This study analysed all adults admitted between February 2008 to January 2009 to the intensive care unit (ICU) of a German university hospital Finland to identify patients with severe sepsis or septic shock, according to the criteria defined by the American College of Chest Physicians / Society of Critical Care Medicine. One year after ICU discharge, survivors were contacted and QoL was determined either by mail or through telephone interview using the EQ-5D questionnaire.		
Respondent	Patients		
n	73		
Age group	At 1 year post ICU discharge: median age 67 (IQR 58 to 75)		
Disease period	February 2008 to January 2009		
Follow-up period	1 year		
Reference population	Age- and sex-matched control group with similar comorbidities		
Disease	Severe sepsis or septic shock (causative pathogen not reported)		
Method/instrument	EQ-5D and VAS		
Results	**Health status**	**Median EQ-5D (IQR)**	**Median VAS (IQR)**
	Severe sepsis or septic shock survivors	50 (25 – 75)	0.8 (0.3 – 0.9)
	Reference population	70 (50 – 90)	1 (0.9 – 1)

Orwelius et al., 2013[93]			
Method description	During the period January to June 2005, adult (aged 18+ years) patients with admission diagnoses of community-acquired sepsis, severe sepsis or septic shock were identified from 9 intensive care units (ICU) in Portugal. Health status of the surviving patients was assessed 6 months after ICU discharge, using the EQ-5D questionnaire. Patients received the questionnaire by post for self-completion. The diagnostic categories for ICU admissions were: medical non-coronary (76%), medical coronary (1%), trauma (3%), non-schedule surgery (20%).		
Respondent	Patients		
n	91		
Age group	Median age is 60 years (Interquartile range, IQR: 50-70) at follow-up		
Disease period	January 2005 – June 2005		
Follow-up period	6 months		
Reference population	None		
Disease	Community-acquired sepsis, severe sepsis or septic shock (causative pathogen not reported)		
Method/instrument	EQ-5D and VAS		
Results	**Health status**	**Median EQ-5D (IQR)**	**Median VAS (IQR)**
	Survivors of community-acquired sepsis, severe sepsis or septic shock	0.68 (0.50-0.91)	70 (50-80)

Galante et al. 2011[94]					
Method description	Between July and August 2009, a convenience sample of Argentinian adults (73 subjects, mean age 31 years, range 22-58) was interviewed and asked to classify 8 hypothetical health states related to pneumococcal diseases with the generic EQ-5D-3L questionnaire. Each health state was described with a half-page vignette presenting the disease as close to clinical reality as possible. The vignettes were developed in collaboration with clinicians treating patients suffering from the disease of interest and were pilot tested with members of the general population. To evaluate and control for sequence or order effects, three sets of questionnaires in which the health states were ordered in different ways were used and randomly administered to each third of the sample. The descriptive EQ-5D-3L five-digit number of each health state were converted into utilities by using preference weights (e.g. tariffs) from the general reference UK population.[194] These weights were derived from data of the York "Measurement and Valuation of Health" study, in which 42 composite EQ-5D health states were empirically valued by 2997 persons using time trade-off as the valuation method. Measures for the other health states were interpolated form the direct valuations of the 42 health states through regression analyses. Quality weights yielded can range from -0.543 (the worst imaginable health state) to 1. Anchor points are "Healthy" (valued as "1") and "Dead" (valued as "0").[194] The description of the health states "acute otitis media" and "acute otitis media with myringotomy" were presented for a hypothetical child. The descriptions for the health states "meningitis", "sepsis", "pneumonia", "neurologic sequelae" and "auditive sequelae" did not specify the age of the hypothetical patient, assuming the respondents would relate their answers to their current age. The description of the health states "auditive sequelae" and "neurological sequelae" implied that the condition started during childhood and lasted lifelong. The symptoms of the health states meningitis, sepsis and hospitalised pneumonia were described to last at least 3 weeks (including 7-15 hospitalisation days for meningitis and sepsis, and 4-10 hospitalisation days for pneumonia). The symptoms for non-hospitalised pneumonia were described to last 7-10 days.				
Respondent	Proxy (lay adults)				
n	73				
Age group	Acute otitis media: Hypothetical child Meningitis, sepsis, pneumonia, neurologic and auditive sequelae: Hypothetical adult (Mean age is 31.66 years, SD: 9.34, range 22-58. This corresponds to the average age of the respondents as these were asked to rate hypothetical scenarios at their current age).				
Disease period	NA (Hypothetical scenarios)				
Follow-up period	NA (Hypothetical scenarios)				
Reference population	None				
Disease	Pneumococcal diseases				
Method/instrument	EQ-5D-3L and VAS				
Results	**Health status**	**EQ-5D**		**VAS**	
		Mean (95% CI)	**Median (IQR)**	**Mean (95% CI)**	**Median (IQR)**
	Meningitis	-0.330 (-0.394; -0.265)	-0.429 (-0.484; -0.221)	34.2 (30.5 – 37.9)	30 (25.5 – 50)
	Sepsis	-0.295 (-0.359; -0.231)	-0.331 (-0.484; -0.166)	31.7 (27.8 – 35.6)	30 (20 – 40)
	Hospitalised pneumonia	0.035 (-0.048; 0.118)	-0.056 (-0.239; 0.258)	46.4 (42.6 – 50.1)	45 (39.5 – 60)
	Ambulatory pneumonia	0.508 (0.442 – 0.575)	0.673 (0.346 – 0.708)	58.4 (55.1 – 61.7)	60 (50 – 70)
	Acute otitis media	0.391 (0.310 – 0.473)	0.516 (0.088 – 0.691)	63.4 (60.1 – 66.8)	62 (57.5 – 70)
	Acute otitis media with meringotomy	0.073 (-0.029; 0.174)	-0.008 (-0.261; 0.585)	50.6 (46.7 – 54.6)	50 (40 – 60)
	Auditive sequelae	0.635 (0.578 – 0.691)	0.725 (0.378 – 0.812)	60.1 (56.7 – 63.5)	60.5 (52 – 70)
	Neurologic sequelae	0.319 (0.252 – 0.386)	0.205 (0.082 – 0.603)	43.4 (40 – 46.8)	40 (30.5 – 51)

Karlsson et al., 2009[95]			
Method description	During the period from 1 November 2004 to 28 February 2005, adult (aged 18+ years) admissions and stays in 24 intensive care units (ICU) in Finland were screened to identify patients with severe sepsis or septic shock, according to the criteria defined by the American College of Chest Physicians / Society of Critical Care Medicine. At study entry, participating patients were asked to fill in the EQ-5D questionnaire concerning their quality of life before the acute critical illness. If the patient was unable to answer, the next of kin filled in the questionnaire on behalf of the patient. All survivors received a second, mailed EQ-5D questionnaire for self-completion, at the end of April 2006 (i.e. on average 17 months after ICU discharge).		
Respondent	Patient or proxy (closest relative)		
n	98		
Age group	At disease onset: mean age 60.4 years (standard deviation 10.3). At follow-up: mean age 53.4 (standard deviation 14.0)		
Disease period	From 1 November 2004 to 28 February 2005		
Follow-up period	17 months (range 12-20 months, IQR 16-18 months)		
Reference population	Age- and sex-matched reference values from the general Finnish population		
Disease	Severe sepsis or septic shock (causative pathogen not reported)		
Method/instrument	EQ-5D and VAS		
Results	**Health status**	**Median EQ-5D (IQR)**	**Median VAS (IQR)**
	Severe sepsis or septic shock survivors		
	- Before disease onset	0.81 (0.62 – 0.90)	65 (40 – 80)
	- At follow-up	0.75 (0.56 – 0.94)	68 (51 – 80)
	Reference population		
	- Before disease onset	0.86 (0.81 – 0.88)	70 (68 – 77)
	- At follow-up	0.86 (0.83 – 0.88)	70 (68 – 77)

Korosec Jagodic et al., 2006[96]			
Method description	Over a one-year period (January 2003 to December 2003), adult patients (aged 18+ years) with admission diagnoses of severe sepsis or septic shock were identified from an intensive care unit (ICU) in Slovenia. Two years following ICU admission, the quality of life of surviving patients was assessed during a telephone interview using the EQ-5D questionnaire. Patients or family members of patients discharged alive were contacted to determine their willingness to participate in the study and were asked to complete the questionnaire by phone. The origin of the severe sepsis or septic shock in survivors was mostly abdominal sepsis.		
Respondent	Patients or proxy (family member)		
n	10		
Age group	Mean age is 45 years (standard deviation, SD: 19.8) at disease onset		
Disease period	January 2003 – December 2003		
Follow-up period	2 years		
Reference population	None		
Disease	Severe sepsis or septic shock		
Method/instrument	EQ-5D		
Results	**Health status**		**Mean EQ-5D (SD)**
	Survivor of severe sepsis or septic shock		0.72 (0.24)

Granja et al., 2004[97]			
Method description	During the period from March 1997 to March 2001, adult patients (aged 18+ years) with admission diagnoses of severe sepsis or septic shock were identified from an intensive care unit (ICU) in Portugal. Severe sepsis or septic shock were defined according to the 2001 International Sepsis Definitions Conference criteria. Patients exhibiting non severe sepsis on admission were excluded, as well as patients developing non severe sepsis or sever sepsis/septic shock after admission. Health status of the surviving patients was assessed during a follow-up consultation 6 months after ICU discharge, using the EQ-5D questionnaire. The origin of the severe sepsis or septic shock in survivors was mostly respiratory.		
Respondent	Patients		
n	104		
Age group	Median age is 52 years (Interquartile range, IQR: 38-66) at follow-up		
Disease period	March 1997 - March 2001		
Follow-up period	6 months		
Reference population	None		
Disease	Severe sepsis or septic shock		
Method/instrument	EQ-5D and VAS		
Results	**Health status**	**Median EQ-5D (IQR)**	**Median VAS (IQR)**
	Survivor of severe sepsis or septic shock	0.84 (0.58 – 1)	75 (50 – 80)

Sisk et al. 2003[98] (based on Erickson et al. 1995[190] and Gold et al. 1998[195])		
Method description	The US National Health Interview Survey (NHIS) collects information about the activity limitation and the perceived health (Health and Activity Limitation Index, HALex) from a national sample of about 50 000 households. The six levels of activity limitation and the 5 levels of perceived health define 30 health states plus the dead state, with 1 as the best health state and 0 as dead or the worst. Correspondence analysis and a multi-attribute utility model were then used to assign weights (HALex scores) to each of the 30 health states. During the years 1987 to 1992, respondents surveyed in the NHIS were asked about the presence of a specific set of conditions, including an "unspecified septicemia" condition. For each "unspecified septicemia" individual condition report, the respondent's levels of activity limitation and perceived health were used to obtain the HALex score associated with that condition in that individual. Data were then aggregated by condition.	
Respondent	Patients	
n	Not reported	
Age group	All ages	
Disease period	1987-1992	
Follow-up period	NA (a duration of 34 days of restricted-activity or bed days (in hospital or at home) is assumed based on bacteraemia)	
Reference population	None	
Disease	Unspecified septicemia (not detail on the causal pathogen)	
Method/instrument	Health and Activity Limitation Index with correspondence analysis and multi-attribute utility model	
Results	**Health status**	**Mean (range)**
	Unspecified septicemia	0.2 (0.15 – 0.25)

De Wals et al., 2002[99]		
Method description	All meningococcal serogroup C disease survivors identified in Quebec in the 1990-1994 period were sent the EQ-5D for completion if physical sequelae were noted in the medical records or if incomplete recovery was reported by the patient or parent. Most sequelae were complications of septicemia, mainly skin scars and amputations. When the individual could not be contacted of was unable to complete the questionnaire, this was done either by a parent or by a researcher using medical notes.	
Respondent	Patients or proxy (parents or researcher)	
n	Not stated	
Age group	All ages	
Disease period	1990-1994	
Follow-up period	Not stated	
Reference population	Not stated	
Disease	Serogroup C meningococcal disease with physical sequelae or incomplete recovery.	
Method/instrument	EQ-5D	
Results	**Health status**	**QoL reduction**
	Survivor with sequelae (mainly skin scar and amputation)	0.282

Drabinsky et al., 2001[100] (Abstract only)			
Method description	Patients with severe sepsis of presumed infectious origin were identified from 53 US hospitals. Patients' health status was assessed at day 30, 60, 90 and180 using EuroQoL-5D and a visual analog scale. Instruments were completed by the patient while in hospital and follow-up assessments were performed by telephone interview.		
Respondent	Patients		
n	93		
Age group	Mean age is 60 years (Standard deviation, SD: 17 years) at disease onset		
Disease period	Not stated		
Follow-up period	6 months		
Reference population	Not stated		
Disease	Survivors with severe sepsis of presumed infectious origin		
Method/instrument	EQ-5D and VAS		
Results	**Health status**	**Mean – EQ-5D**	**Mean – VAS**
	Severe sepsis – day 30	0.53	0.61
	Severe sepsis – day 60	0.62	0.68
	Severe sepsis – day 90	0.68	0.71
	Severe sepsis – day 180	0.69	0.72

Stouthard, 1997[101]		
Method description	38 Dutch doctors (mean age 47.7 years, SD 9.2 years) in a series of panel sessions were asked to attribute utilities to 52 disease groups and 175 disease stages using the person trade-off (PTO) and interpolation methods. Average PTO valuations were first calculated for 16 selected disease stages (=indicator conditions). All other remaining disease stages were then interpolated by the panel members. Members were asked to value a random set of 30 new disease stages each by placing each disease stage separately on the scale of two indicator conditions. Each disease stage was defined with a standardised description: first a description of the disease group and its stages, then a generic health status description of the disease stage to be valued (EQ-5D+ classification). The duration of the disease stages was universally defined as 1 year. For acute disease stages characterised by a short episode of a few weeks of illness (e.g. 2 weeks for pneumonia) followed by complete recovery, the states were described and valued as “a short episode in an otherwise healthy year”. The process was repeated with a panel of 15 lay individuals (mean age 39 years, range 24-64) - little difference was found between the results elicited by the doctors or the lay panel.	
Respondent	Proxy (health care professionals)	
n	38	
Age group	All ages (no specific age mentioned in the description of the disease stages)	
Disease period	Not applicable (hypothetical scenarios)	
Follow-up period	Not applicable (hypothetical scenarios)	
Reference population	Not applicable	
Disease	Pneumonia (causative pathogen not reported), sequelae after bacterial meningitis	
Method/instrument	PTO and interpolation	
Results	**Health status**	**Mean (95% confidence interval)**
	Pneumonia (duration 2 weeks)	0.90 (0.809 – 0.984)
	Bacterial meningitis sequelae - Permanent locomotor impairment	0.83 (0.702 – 0.964)
	Bacterial meningitis sequelae - Permanent cognitive impairment	0.75 (0.616 – 0.881)
	Bacterial meningitis sequelae - Permanent locomotor and cognitive impairment	0.24 (0.139 – 0.348)

APPENDIX 5. FURTHER DATA ON LITERATURE REVIEWS ON PCV13 AND PPV23 EFFICACY AND EFFECTIVENESS

Appendix 1.5. PCV13 data from CAPITA

Appendix 1.5.1. Efficacy against specific vaccine serotype

Efficacy against specific vaccine serotypes was evaluated in a post-hoc analysis. VE against IPD was not significant due to low number of cases (≤1 case of each vaccine serotype) and is described in Table 63.[86] Efficacy against pneumococcal CAP due to specific vaccine serotypes but was significant only for serotype 7F (77%, p=0.0015, Table 63.[86] In serotype-specific analyses, only efficacy against 7F was significant at 85% (p=0.0074), Table 63.[86]

Table 63 – CAPITA PCV13 efficacy against serotypes or serotype groups in 65+, by clinical group

Study and country	Pnc CAP	IPD-CAP	NB CAP
CAPITA, Netherlands[86]			
7F	77% (SS)	NS	85% (SS)
3	56% (NS)	NS	58% (NS)
19A	56% (NS)	NS	57% (NS)

CAP: community acquired pneumonia; NB: non bacteraemic; IPD: Invasive pneumococcal disease; Pnc: pneumococcal.

APPENDIX 6. COMPARISON OF RECENT ECONOMIC ANALYSES OF PCV13 VACCINATION IN ELDERLY

This short literature review focused on economic analyses performed after CAPITA data were published.

Table 64 – Review of the five most recent cost-effectiveness studies of PCV13: vaccine parameters

Author, year, country	Target population	VE PCV13 against vaccine types	PCV13 waning	VE PPV23 against vaccine types	PPV23 waning	Coverage of vaccine serotypes and % of CAP due to pneumoc.	How is indirect effect modeled, including replacement
Van Hoek, England[152]	≥65 years immune-competent Not stratified by risk group	CAPITA in 65+: IPD: 75% in all ages CAP: 45.6% <75 yrs: 52.4% 75-84 yrs: 46.4% 85+: 0% SA:	Stable 9 yrs, waning every 5 years, IPD/CAP: Yrs 1-9: 75% / 45% Yrs 10-14: 43% / 26% Yrs 15-19: 9% / 5% Yrs 20+: 5% / 3%	None (not modelled)	None (not modelled)	Waight et al, i.e. Rodrigo et al, i.e.	- PCV7 IPD in equilibrium in 2013/14. - Additional 6 PCV13 type IPD have similar reduction as PCV7-types: IRR PCV7 pre/post PCV7 applied to pre-PCV13 PCV13non7 (2007–2011). Similar steady state as for PCV7. - PCV13-VT CAP follow similar trend as IPD, using a ratio CAP/IPD from UK (age specific). - Serotype replacement not included.
Mangen et al., The Netherlands [92]	All adults High risk Medium risk (immunocompetent) Low risk	CAPITA by age: - High-risk: VE against IPD and CAP 22% and 35% lower than VE low/medium-risk OPD CAP = inpatient SA:	Stable 5 yrs, waning/yr: 5% in yrs 6–10 10% in yrs 11–15 No efficacy assumed from yr 16	None (not modelled)	None (not modelled)	PCV13 IPD: 65-74 yrs: 43% 75-84 yrs: 37.8% 85+: 46.3% All CAP: 10% inpatient VT (CAPITA placebo arm). Same assumed for outpatient CAP.	No net indirect effects of infant PCV10 vaccination taken into account, as no indirect of PCV10 is observed in the Netherlands up to 2013.
Boccalini, 2013, Italy[171]	All 65 years All 65 and 70 years All 65, 70 and 75 yrs	CAP: 88% (BP and NBP) PM: 94%, as for PCV7 in kids	Constant during 5 years	IPD: 70% NBPP: 0%	Constant during 5 years	- PCV13: IPD: 69%, CAP: 73.5% - PPV23: IPD: 83% 40% CAP due to Sp	Not included due to lack of data In SA, 10% reduction incidence to account for it.

		Reduced by 10% in SA					
Stoecker, 2016, US	65 years healthy and medium risk (not immunocompromised)	CAPITA at 65 years: IPD: 75% NBPP: 45%	Decline by 10% every 5 years of age, linearly within each 5 years	From Moberley: IPD: 74% NBPP: 0%	Linear waning to: - 50% of initial VE after 5 years - 30% of initial VE over next 5 years - 0% in the next 5 yrs	- PCV13: IPD: 21-25% Outpatient NBP: 10% , CAP: 73.5% - PPV23: IPD: 60-62%	PCV7 indirect effect in US applied to project PCV13 indirect effect - 86.6% in 6 add. types in 2013-2019. Linear increase each year then stabilize. +17% in PPV23 unique types in 6 years starting in 2019
Chen, 2014, USA[168]	Adults 50+ with risk Healthy ≥65 years	- Healthy 65+, 1st year: IPD: 72.5%; NBPP: 60.5% - Medium risk: IPD: 61% (85% healthy) NBPP: 49.8% (82%) - High risk: IPD: 48%; NBPP: 6%	Expert panel. Linear decline on 15 years	- Healthy, 1st year: IPD: 74% in 65-79 60% in 80+ NBPP: 36.5% in all 65+ - Medium risk: IPD: 63% and 51% NBPP: 27% in 65+ - High risk: 16/13% for IPD, 0% for NBPP	Linear decline on 10 yrs	Same assumed for IPD and NBPP PCV13: 50% PPV23: 65%	No indirect effect in the base case SA: PCV7 indirect effect in US (Pilishvili 2012) used to project PCV13 when full effect in 65+: No change in PCV7 -90% for 6 add. PCV13 +21% for nonPCV13 (unique to PPV23 or not)
Smith, 2013, USA[177]	All 65 years All 65 and 70 years	IPD: 85% in healthy 65 yrs, 50% in high risk, 79% in healthy 75 yrs NBPP: 70-75% of IPD VE values (64%, 35%, 59%)	Expert panel, IPD, 65 healthy: Yr 1: 85% Yr 3: 80% Yr 5: 70% Yr 10: 50% Yr 15+: 33%	IPD: 80% in healthy 65 yrs, 0% in high risk 67% in healthy 75 yrs NBPP: 0%	Expert panel IPD, 65 healthy: Yr 1: 80% Yr 3: 73% Yr 5: 58% Yr 7: 33% Yr 10+: 0%	NBPP same as IPD - PCV13: 41-49% age dependent - PPV23: 63-74% age dependent 30% all CAP due to Sp Outpatient CAP excluded	PCV7 indirect effect in US applied to project PCV13 indirect effect: - Decrease in 4 carried serotypes (3, 6A, 7F, 19A) - Increase in nonPCV13

Medium risk: immunocompetent with comorbidities; High risk: immunocompromised; VT: vaccine types; Sp: Streptococcus pneumoniae; IPD: invasive pneumococcal disease; NBPP; non-bacteraemic pneumococcal pneumonia; PM: pneumococcal meningitis.

Table 65 – Review of the five most recent cost-effectiveness studies of PCV13: other study characteristics and main results

Author, country	Interventions compared	Model, horizon, perspective	QALY loss per episode	PCV13 costs	ICER	Most influential parameters
Van Hoek, England[152]	PCV13+PPV23 vs PPV23	Static Markov Health care payer	IPD: 0.13-0.01 according to age CAP: 0.006	49.10£ vaccine + 1 extra GP visit (for PPV23)	Base PCV13: 257,771£/QALY Lowest in SA: 169,638£ (no waning)	CFR Waning IPD incidence
Mangen et al., The Netherlands[92]	PCV13 vs nothing (no PPV23) Base: all 65-74 years Various scenario by age and risk group	Static Markov Societal?	Inpatient CAP or IPD: 0.0709 (CHO-CAP) Outpatient CAP: 0.0045 (Grace study)	68.56€ vaccine + 10.63€ administration	Base PCV13: 8,650€/QALY VE in high risk at 0: 16,000€/QALY All SA <30,000€/QALY Note: very high burden in high risk	Vaccine cost Waning VE in high risk VE against IPD CFR
Boccalini, 2013, Italy[171]	PCV13 and PCV13 + PPV23 vs no vaccination	Static, 5 years, only medical costs (health care payer)	Inpatient CAP/IPD: 0.2 IPD: 0.02 (34 days) CAP: 0.01 (11 days)	42.5€ per dose + 3-6€ for delivery	Base PCV13: 17,000-22,00€/QALY PCV13 + PPV23: 21,500-27,900€/QALY	Not described; SA included small variations in input (e.g. -10% VE/incidence)
Stoecker, 2016, US[155]	PCV13 + PPV23 PCV13 only at 65 y	Static, life expectancy, societal	QALY decrement: IPD: 0.009 (27 days) NBP inpatient: 0.006 (27 days) NBP outpatient: 0.004 (18 days)	85$/dose Admin. Cost: 17$	Add PCV13 to PPV23 at 65 yrs: 62,065$/QALY PCV13 vs PPV23 at 65 yrs: 46,396$/QALY	PCV13 vaccine price Herd immunity VE of PPV23 against NBP
Chen, 2014, USA[168]	Many, by risk group Always PPV23 +/- PCV13	Static, 50 years, only medical costs (health care payer)	IPD and inpatient CAP: 0.074 (0.8*34 days) Outpatient CAP: 0.004 (0.21*7 days)	120.95$ per dose + 15$ administration	ACIP recommendations (mix PCV13/PPV23) + PCV13+PPV23 for immunocompromised at 65 years: 23,416$/QALY Others >100,000$/QALY	Herd immunity: not CE if PCV13 disease is reduced by >50% VE
Smith, 2013, USA[177]	Many, in 65 and 75 years. PCV13 only, PPV23 only or both	Static Markov, by risk. Lifetime. Societal	IPD and inpatient CAP: utility weight 0.2	128$ per dose and administration	PPV23 always dominated by PCV13 PCV13 at 65 yr: 11,300$/QALY PCV13 at 75 yr: 62,800$/QALY PCV13 re-vaccination >83,000$/QALY	Herd immunity: not CE PCV13 and PPV23 VE against NBPP Costs PCV13

APPENDIX 7. COSTS OF OUTPATIENT PNEUMONIA

Whenever possible the lowest alternative price was used (Generic price).

Table 66 – Unique medication names for Belgian outpatient pneumonia cases

Medication	Price (Euro)	Remarks/assumptions
Acatar	6.08	
Acetylcysteine Topgen	6.13	10x600g verpakking sandoz
Actifed siroop	7.36	200 ml sanofi: Tusso Rhinathiol
Actived siroop	7.36	
Dafalgan Codeïne	6.35	Paracetamol 500mg+30 mg codeine
Dafalgan Forte	7.42	30*1g sandoz
Lysomucil	7.72	30*600mg harde capsules Sandoz
Paracodeïne	6.35	assumed paracecetamol+ codeine
Proflox	29.23	Moxifloxacine assume 14 doseges (14x400mg sandoz)
QVAR 100 autohaler	24.01	200dos 100µg/dos UCB
Sedergine	2.58	20x325 mg Bristol-Myers Squibb
Sekin hoestsiroop	6.5	
Seritide	30.72	Seretide 120 dosises GSK; 25µg salmeterorl/dos; 205g propionaat
Strepsils	7.45	36x (Reckitt Benckiser)
Ventolin	6.75	Tabletten 100x 2mg GSK
Ventoline	6.75	Tabletten 100x 2mg GSK
acetylcysteine	7.72	30x600 mg bruistabletten Sandoz
actifed	7.36	
amoxicilline	11.88	30x500 mg Sandoz Tabletten
augmentin 875/125	14.34	Clavulaanzuur 875 amoxiclillin +125g clavulaanzuur 20 filmomulde tabletten GSK
clamoxyl	11.88	zie amoxicillin
dextrometorfaan siroop 10	7.36	zie actifed
lysomucil	7.72	30*600mg harde capsules Sandoz
paracodine	7.42	30*1g sandoz
proflox	29.23	Moxifloxacine assume 14 dosages (14x400mg sandoz)
proflox 400mg	29.23	Moxifloxacine assume 14 dosages (14x400mg sandoz)
pulmicort 200	12.27	Budesonide 200µg 120 capsules (Novartis Pharma)
sedergine	2.58	Bristol Myers Squibb bruistablet 20x325mg

Table 67 – Cost estimates for identified pneumonia cases in the Grace WP9 project, using medicine prices from Table 66 and assuming 1 GP consult per pneumonia case in absence of a reported number of GP visits

Patient number	Medication cost (euro)	Cost for a GP visit (euro)	Total cost (euro)
1	135.81	23.32	159.13
2	139.64	23.32	162.96
3	38.54	23.32	61.86
4	22.18	23.32	45.5
5	11.88	23.32	35.2
6	20.42	23.32	43.74
7	25.68	23.32	49
8	66.24	23.32	89.56
Mean			80.9

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