Etude médico-économique de vaccins: Vaccination antipneumococcique des adultes

Rapport pour le Haut Conseil de la Santé Publique

Ministère des Affaires sociales, de la Santé et des Droits des femmes

Philippe Beutels, Adriaan Blommaert, Lander Willem

Centre for Health Economics Research and Modelling Infectious Diseases (CHERMID), University of Antwerp, Belgium

Agnès Lepoutre, Daniel Lévy-Bruhl

Direction des maladies infectieuses, Agence nationale de santé publique, France

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1 Introduction

Pneumococcal infection can cause severe invasive (IPD: meningitis and sepsis, pneumonia with bacteraemia) and non-invasive diseases (otitis media, non-invasive pneumonia). Invasive diseases have a high mortality in infants, the elderly and particular risk groups. Currently two vaccines are on the market to prevent the risk of severe pneumococcal disease. The first, a 23-valent polysaccharide vaccine (marketed as Pneumo23, henceforth called PPV23), is weakly immunogenic and provides protection against invasive pneumococcal disease (IPD). Its effectiveness against non-invasive IPD has not been shown conclusively. The 13-valent conjugate pneumococcal vaccine, marketed as Prevenar13 (henceforth called PCV13), is the second vaccine available for pneumococcal disease prevention. It provides protection against 13 serotypes. Previous conjugate vaccines used in childhood vaccination programs contained fewer serotypes (PCV7 and PCV10). PCV13's efficacy against vaccine-type IPD and pneumonia in the elderly has been investigated in the CAPITA study. Herd immunity effects of childhood vaccination with PCV13 may lead to an overall elimination of vaccine type serotypes in the whole population, undermining the future effectiveness and cost-effectiveness of PCV13 use in adults. Therefore childhood vaccination programs are to be considered as an important factor in evaluating adult programs against *S. pneumoniae*.

The current pneumococcal vaccination strategy in France consists of vaccinating all people at high risk of severe pneumococcal disease, irrespective of age, with PPV23, except for infants and immunosuppressed individuals who are administered PCV13 and the combination of PCV13 and PPV23, respectively. Given the increased incidence and case-fatality with age, elderly pneumococcal vaccination programs might reduce the high pneumococcal disease burden. A second reason to investigate additional vaccination programs is the recent evidence from the CAPITA study concerning PCV13 effectiveness against IPD and non-invasive pneumonia in the elderly. Therefore we assess the effectiveness and cost-effectiveness of PPV23 and/or PCV13 vaccination in 18-84 year olds, depending on the vaccine recipients' risk profile. As risk groups we consider:

- **Low Risk (LR):** immunocompetent and at low risk for pneumococcal infection;
- **Medium Risk (MR):** immunocompetent and at high risk for pneumococcal infection;
- **High Risk (HR)**: immunosuppressed and at high risk for pneumococcal infection.

The incidence and disease burden estimates outlined below in this report clarify more how these risk groups are distinguished, and what this means in terms of incidence and severity of pneumococcal infections.

2 Data and Methods

In general, the main methods for health economic evaluation, including the perspective of the analysis is applied as defined in the latest available French guidelines by the "Hautes Autorité de Santé" (ie as stipulated in the guide " Choix méthodologiques pour l'évaluation économique à la HAS").

We developed a static deterministic state-transition model that describes transitions between a set of health states for the entire adult population over time stratified by age and risk group. The model is used to project results for the new strategies that are being considered, as well as for the current situation. Costs (Euros) and health valuation (quality-adjusted life years, QALYs) will be attached to health states in the models, and discounted in accordance with the French guidelines. The incremental results will be calculated by comparing the different strategies, focusing on the Incremental Direct costs per QALY gained ("ICER") as primary outcome measure.

2.1 Vaccination strategies

Table 1 lists the different adult pneumococcal vaccination strategies considered to be practically feasible for implementation by the pneumococcal expert group of the French High Council for Public Health (FHCPH). These strategies can be categorised as (see Table 1):

- Current situation i.e. vaccinating adult risk groups using PPV23 for immunocompetent (MR) and both vaccines for immunosuppressed (HR) individuals (SC0)
- Increasing vaccination coverage for all age groups in the current situation with a designated fixed budget to achieve this (SC11)
- Vaccinating the general elderly population 65-84 years of age irrespective of risk group with PCV13, PPV23 or a combination of both vaccines (SC1-3);
- Targeting all adult (18-84 years) immunocompetent individuals at higher risk for pneumococcal infection (MR) with either PCV13 or the combination of PCV13 and PPV23 (SC4-5);
- A "maximum" strategy: giving both vaccines to adult MR and the general elderly population (SC6);

A number of theoretical strategies were also defined, but are not included in the main analysis, as they are considered not feasible in the current context in France. These included PCV13 containing vaccination strategies targeted at adults at medium risk up to age 64 years (distinguishing ages 18-49 and 50-64), while maintaining the status quo in all other age and risk groups (SC7-SC10). Other theoretical strategies (SC12-13) assumed improved vaccination coverage, but only in part of the age groups targeted under the current situation (i.e. 18-49, 50-64, so not in 65-84y). For a full overview of defined vaccination strategies, including these theoretical options, see Table 11 in section 9.1).

None of the strategies explicitly focus on elderly over 84-years of age since there is no evidence of vaccine effectiveness in that age group for either vaccine, nor for any risk group.

Each change versus the current situation aims to reach 60% vaccination coverage in 3 years by annual steps of 20%. From year 4 onwards, only the age cohort entering an age group is vaccinated. The first 3 years are assumed to require a fixed additional cost. Vaccine strategy implementation is simulated over a 10 year period (2017-2026), during which only vaccine-naïve individuals are assumed to be vaccinated. Revaccination options are not considered. All consequences of vaccination are considered until the last vaccinated person has died.

In addition to comparing practically feasible vaccination strategies (Table 1), the optimal vaccine and age-target choices per risk group are investigated. For each risk group, we then allow a different vaccine choice (no change, PCV13, PPV23 or both) per age group (18-49, 50-64; 65-84 years). This analysis is run by homogeneously vaccinating a complete age group over a 3 year period.

Table 1: Potentially feasible vaccination strategies by vaccine choice per age and risk group combination [1]

Vaccination strategy	Low risk (LR)	Medium risk (MR)	High risk (HR)	Program cost (per catch-up[2] year)
SC0 (Current situation)	no vaccination	2% PPV23 per year in 18-84 year olds	2% (PCV13+PPV23) per year in 18-84 year olds	€0
SC1	**PCV13** 65-84 (catch-up) 65 (after catch-up)	**PCV13** 65-84 (catch-up) 65 (after catch-up)	**PCV13** 65-84 (catch-up) 65 (after catch-up)	€400,000
SC2	**PPV23** 65-84 (catch-up) 65 (after catch-up)	**PPV23** 65-84 (catch-up) 65 (after catch-up)	**PPV23** 65-84 (catch-up) 65 (after catch-up)	€800,000
SC3	**(PCV13+PPV23)** 65-84 (catch-up) 65 (after catch-up)	**(PCV13+PPV23)** 65-84 (catch-up) 65 (after catch-up)	**(PCV13+PPV23)** 65-84 (catch-up) 65 (after catch-up)	€400,000
SC4	no change	**PCV13** 18-84 (catch-up) 18 (after catch-up)	no change	€400,000
SC5	no change	**(PCV13+PPV23)** 18-84 (catch-up) 18 (after catch-up)	no change	€400,000
SC6 (SC3+SC5)	**(PCV13+PPV23)** 65-84 (catch-up) 65 (after catch-up)	**(PCV13+PPV23)** 18-84 (catch-up) 18+65 (after catch-up)	**(PCV13+PPV23)** 65-84 (catch-up) 65 (after catch-up)	€400,000
SC11	no change	**PPV23** 18-84 (catch-up) 18 (after catch-up)	**(PCV13+PPV23)** 18-84 (catch-up) 18 (after catch-up)	**€800,000**

LR: Low Risk, MR: Medium Risk; HR: High Risk group

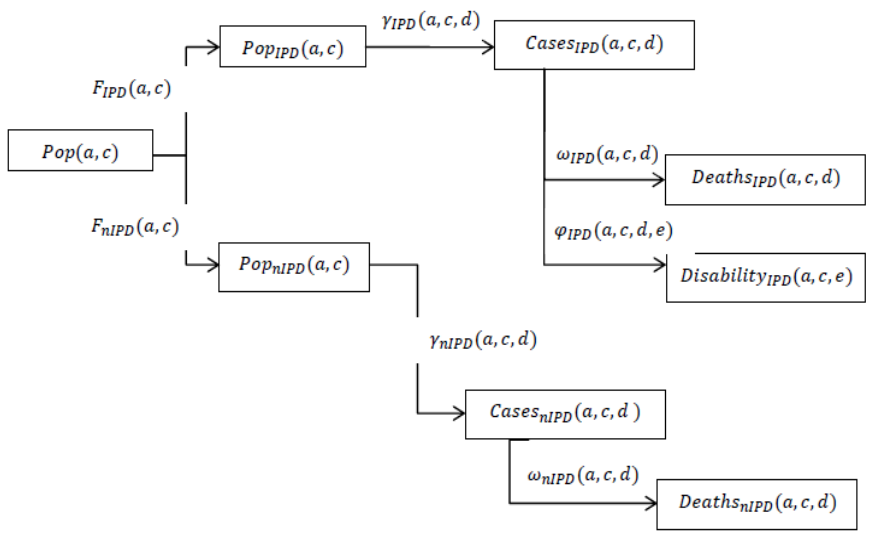
[1] Considered a priori feasible for implementation by the Expert group of French High Council for Public Health (FHCPH), see acknowledgements. In addition to this base list, additional more implausible theoretical strategies were also considered (see Table 11 in section 9.1)

[2] We vaccinate over a 3 year catch-up period (2017-2019) an entire age group homogeneously at 20% per year. Over a 7 year period after the catch up period (2020-2026) we vaccinate only the age cohort entering an age group at an annual coverage of 60%.

2.2 Model structure

We developed and applied an age-structured static multi-cohort model to simulate the costs and effects of adult pneumococcal conjugate vaccination strategies per risk group separately (see Figure 1 and [1]). Single year age cohorts between 18 and 84 years of age are simultaneously followed from the moment of vaccination until death of the last survivor in the youngest cohort. The vaccines (PCV13, PPV23 or both), their uptake and duration of vaccine induced protection determine each cohort's vaccine effectiveness (VE). This VE together with the background serotype-evolution (influenced mainly by the children's PCV13 program), determine the susceptible population at each age, separate for invasive (IPD) and non-invasive (nIPD) pneumococcal disease, and per serotype category (see Box 1). Age specific incidences are then applied to calculate IPD and nIPD (non-invasive CAP: in and out of hospital) cases and their associated costs, deaths and Quality-Adjusted Life Years (QALYs) lost. Long-term consequences of meningitis (hearing loss or other neurological sequelae) are also taken into account. Different risk groups are considered as distinct populations and the same model is run in separate iterations using risk group specific population, vaccine protection, burden of disease and epidemiological inputs (see Table 2 and Table 3). Finally risk group specific outputs are recombined over the years to make up the different vaccination strategies (Table 1), whilst accounting for time preference through discounting of costs and effects in accordance with the French guidelines.

Figure 1: Structure of the model



From left to right: population, population at risk for invasive (IPD) or non-invasive (nIPD) pneumococcal disease, disease cases and disease consequences (fatality or long term consequences).
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 nIPD ($F_{IPD}(a,c)$ or $F_{nIPD}(a,c)$ respectively) to calculate the number of people susceptible for IPD or nIPD disease respectively (see Box 1). $\gamma_{IPD}(a,c,d)$ and $\gamma_{nIPD}(a,c,d)$: yearly rate to develop IPD or nIPD respectively, with d indicating the disease category, i.e. hospitalised pneumonia with bacteremia or meningitis for IPD; in- and outpatient non-invasive CAP for nIPD (impact of otitis media is assumed negligible). $\omega_{IPD}(a,c,d)$ and $\omega_{nIPD}(a,c,d)$: age- and cohort-specific death rates of the different IPD and non-IPD disease categories, respectively. $\varphi_{IPD}(a,c,d,e)$: rate at which meningitis cases develop sequelae of category e (hearing loss or other neurological sequelae). Other disease categories are assumed to have no long term sequelae.

Box 1 – Calculation of the population susceptible to invasive and non-invasive pneumococcal disease

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

with:

- P_{vac} : vaccination coverage, i.e. the proportion of the population at age *a* and belonging to cohort *c* that is vaccinated, τ one of four serotype categories which take values from the set {*OPV23, OPCV13, both, none*}. Here *"OPV23"* 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.
- $A_{IPD,\tau}(a,c)$ the age and cohort dependent serotype coverage of serogroup category τ. This factor can incorporate serotype distribution changes due to the childhood vaccination program and the possible replacement of non-PCV13 types.
- $VE_{(IPD,\tau)}(a,c)$: 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 nIPD disease stages, the initial vaccine efficacy, the duration of vaccine protection and waning of vaccine efficacy over time.
- $Q_{IPD}(a,c)$: the ratio of the incidence (in a susceptible population) of cohort *c* at age *a* and the incidence reference period (pre-vaccine 2001-2002). This factor incorporates the impact of childhood vaccination on total IPD incidence over time.

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

2.3 Model parameters

In this section we present the model parameters, their values and their sources. Table 2 lists a general overview, whereas Table 3 shows disease specific parameters. Details on these burden of disease estimates is also provided in appendices (as indicated in the table references).

Table 2: General model input parameter definitions, values and sources

Parameter	Scale/detail	Value (95% C.I.[a] or distribution) or scenario sensitivity analysis	Reference
Size target group	Per year of age	Age dependent	[2]
Risk group proportions	Per age group	Age dependent	[3-6]; see appendix 4, section 12.1.1

Cost vaccine administration	At year of implementation vaccination program	• €25.7 : general practitioner
		• € 39.9: specialist physician
		• LR category : GP consult needed in 80% of the cases
		• HR and MR risk
		  ○ 50% of cases no additional GP consult needed
		  ○ If a consult needed
		  ▪ 80% of cases a specialist
		  ▪ 20% of cases a general
			[7] and Proposal expert group FHCPH [b]

		practitioner	
Cost of vaccine program implementation	For reaching 60% vaccine uptake	1. €800,000 (PPV23 or current uptake) 2. €400,000 (PCV13 or PCV13+PPV23 program)	Proposal expert group FHCPH
Cost dose PCV13	Per dosage	€55.22 (price reductions of 5%,10%,25% and 50% in sensitivity analysis)	[8]
Cost dose PPV23	Per dosage	€12.46 (price reductions of 5%,10%,25% and 50% in sensitivity analysis)	[8]
Targeted vaccine uptake		• **60% base case** • 50% or 75% sensitivity analysis	Proposal expert group FHCPH
Current vaccine choice and vaccine uptake	Per risk group in the age category 18-84	• LR: no vaccination • MR: 2% PPV23 vaccination • HR: 5% (PPV23 + PCV13) vaccination in 2014 and 2% from 2017 onwards	[9] calculation see Appendix 4
Vaccine efficacy PCV13 (VE)	Vaccine type (per protocol analysis)	• LR & MR: ○ IPD:75.0% (41.4%; 90.8%) ○ Non-Invasive CAP: 45.0% (14.2%; 65.3%) • HR: ○ IPD: 78% of CAPITA ○ Non-invasive CAP: 65% CAPITA ○ In sensitivity analysis: 50% and 100% of CAPITA for IPD and non-invasive CAP	CAPITA: [10] for LR & MR; [11, 12] confirmed by FHCPH expert opinion for HR
Age dependence PCV13 VE	Per protocol	Via the hazard ratio: f_{HR}= 1.067 (1.010; 1.127) The vaccine efficacy ($VE(a)$ in function of age (a) is then: $VE(a) = 1 - exp[\beta_{vac} + \beta_{vac\ X\ age} * (a - a_{ref})]$ With a_{ref} the average age CAPITA 72.8 years, With β_{vac}= $log(1 - VE)$, VE measured in the CAPITA trial; $\beta_{vac\ X\ age} = log(f_{HR})$ For people under 65 we conservatively use the vaccine efficacy at 65. For people above 85 for IPD and above 80 for non-invasive CAP we assume 0% VE (thus avoiding negative values)	[13]
PCV13 waning		4 years of no waning followed by logistic waning until 50% of original vaccine waning is used 13 years after vaccination In sensitity analysis: 4-5 years no waning and 9-15 years to reach 50% of initial VE (see Appendix 3, section 11.1)	Base case is a smoothed version of [11]
PPV23 VE and waning	Per age in years and over time after vaccination	(1) 61% (42; 74) for LR and MR 0-2 years after vaccination, age of vaccination below 85 years (2) 62% (21; 82) for LR 2-5 years after vaccination age of vaccination below 75 years (3) 0% for other age and risk groups	[14] with recalculation of age groups (see Appendix 3, section 11.2)
Serotype coverage by serotype group IPD	Measured in adults in 2014; Percentage (counts)	- 0.54% (3/553 cases); PCV13 only - 30.92% (171/553 cases); PCV13 and PPV23 - 34.54% (191/553 cases); PPV23 only - 34.00% (188/553 cases); no vaccine: simulated from a dirichlet distribution	[15]See calculation Appendix 4
Serotype coverage by serotype group non-invasive CAP	Measured in adults in 2013: Percentage (counts)	(1) 2.13% (4/188 cases); PCV13 only (2) 31.38% (59/188 cases); PCV13 and PPV23 (3) 18.62% (35/188 cases); PPV23 only (4) 47.87% (90/188 cases); no vaccine: simulated from a dirichlet distribution	[15] See calculation Appendix 4

Incidence evolution IPD		- Base case: in years: 2001-2018 linear reduction to: o 60% of 2001-2002 incidence (18-64 years of age) o 50% of 2001-2002 incidence (over 65 years of age) after which it stays constant - Low incidence case: reduction to 30% for all age groups from 2001 to 2018 after which it remains constant - High incidence case 2001-2018 remains constant, increase to 2001-2002 value in the period 2019-2040	Proposal expert group FHCPH, see calculation Appendix 4
Incidence evolution non-invasive CAP		Assumed to stay constant	Proposal FHCPH-expert group
Serotype distribution evolution of IPD and non-invasive CAP		Serotype distribution by 2020 - PCV7 serotypes: o 5% (18-64 year olds) o 3% (over 65 year olds) - In PCV13 and not in PCV7 or PPV23: 0% - In PCV13 and PPV23: to 10% (all ages) Other serotypes are assumed to fill up to 100% proportionally to 2014 serotype coverage. After 2020 it is assumed to stay constant	Proposal expert group FHCPH see calculation Appendix 4
Proportion of long term consequences	Per disease category and age in years	24% (all sequelae) Of which we assume 50% hearing loss cases and 50% other neurological sequelae	Proposal expert group FHCPH based on [16]
Discount rate	Same for cost and effects	4% in base case In sensitivity analysis varied to 2.5%	[17]
Cost of long term consequences of meningitis		€8,000 euro per year for all sequelae during remaining life span	Proposal FHCPH expert group based on [18]
Life expectancy		Age dependent	[19]
Quality of life (utility) outpatient pneumonia		0.508 (0.442; 0.575) to last on average 8.5 days	[20]
Quality of life (utility) meningitis consequences		• 0.635 (0.578 ; 0.691) hearing loss • 0.319 (0.252 ; 0.386) other neurological sequelae Assumed to last life long, Sampled from a normal distribution	[20]
Baseline quality of life (utility) for outpatient CAP and meningitis consequences		Sampled from normal distribution with (mean=0.93,standard error= 0.15/sqrt(753))	[21]
Baseline quality of life by age (utility) to adjust life years gained by their quality		Age dependent	Quality of life by age using EQ5D instrument (Bilcke et. al. in revision).

LR: Low Risk, MR: Medium Risk; HR: High Risk group

Unless mentioned otherwise these percentages were simulated as $exp(1 - lognorm(\mu, \sigma))$, with $lognorm$ representing a draw from the log-normal distribution with μ the log of the proportion estimate and $\sigma = log\left(\frac{1-LL}{1-UL}\right)$ calculated from the lower (LL) and upper (UL) confidence limits, following Briggs et al. [22]

* Expert group of the French High Council for Public Health (FHCPH)

IPD: invasive pneumococcal disease; CAP: community acquired pneumonia

Table 3: Disease specific input parameters: incidence, hospitalisation rates, case-fatality, costs and Quality of Life losses (numbers rounded to 2 decimals)

Parameter and approach to explore uncertainty (either deterministic or probabilistic sensitivity analysis)	**Risk group**	**Value (95% C.I. or distribution) per disease category**				**Ref.**
		IPD pneumonia	**Meningitis**	**Hospitalised non-invasive CAP**	**Outpatient non-invasive CAP**	
Incidence rate $\gamma_{IPD}(a,c,d)$ and $\gamma_{nIPD}(a,c,d)$ per 100,000[(a)] In sensitivity analysis we varied IPD incidences +-15% and non-invasive CAP incidence +-25% suggested by FHCPH-experts	LR	1.95 (18-49 year-olds) 3.30 (50-64 year-olds) 6.73 (65-79 year-olds) 25.93 (80+ year-olds)	0.27 (18-49 year-olds) 0.45 (50-64 year-olds) 0.61 (65-79 year-olds) 1.08 (80+ year-olds)	5.90 (18-49 year-olds) 10.04 (50-64 year-olds) 20.41 (65-79 year-olds) 78.94 (80+ year-olds)	109.65 (18-64 year-olds) 113.72 (65+ year-olds)	(calculation Appendix 4) see references below [(b)]
	MR	17.68 (18-49 year-olds) 16.32 (50-64 year-olds) 16.95 (65-79 year-olds) 45.29 (80+ year-olds)	2.41 (18-49 year-olds) 2.23(50-64 year-olds) 1.54(65-79 year-olds) 1.89 (80+ year-olds)	53.48 (18-49 year-olds) 49.59 (50-64 year-olds) 51.40 (65-79 year-olds) 137.84 (80+ year-olds)	346.25(18-64 year-olds) 352.54(65+ year-olds)	
	HR	167.79 (18-49 year-olds) 274.14 (50-64 year-olds) 257.28 (65-79 year-olds) 247.27 (80+ year-olds)	22.88 (18-49 year-olds) 37.38 (50-64 year-olds) 23.35 (65-79 year-olds) 10.30 (80+ year-olds)	507.61 (18-49 year-olds) 832.93 (50-64 year-olds) 780.15 (65-79 year-olds) 752.61 (80+ year-olds)	702.69(18-64 year-olds) 770.79(65+ year-olds)	
Case fatality ratio $\omega_{IPD}(a,c,d)$ and $\omega_{nIPD}(a,c,d)$ Sensitivity analysis for hospitalised pneumonia: <u>Base case:</u> Only a part of the 6 months mortality after hospitalisation is included Percentage of hospitalisation survivors who are assumed to die of pneumonia in a 6 month period after hospitalisation: Base: 6 month mortality	LR	<u>Base case:</u> 2.90% (18-64 year-olds) 11.48% (65+ year-olds) <u>Min. scenario:</u> 2.90%(18-64 year-olds) 10.5%(65+ year-olds) <u>Max. scenario</u> 6.78%(18-64 year-olds) 15.87%(65+ year-olds)	7% (18-49 year-olds) 17% (50-64 year-olds) 20% (65-79 year-olds) 49% (80+ year-olds)	<u>Base case:</u> 2.29% (18-64 year-olds) 12.91% (65+ year-olds) <u>Min. scenario:</u> 0.67% 6.00% <u>Max. scenario</u> 5.33% 27.02%	0.2% (18-64 year-olds) 0.7% (65+ year-olds)	[23-28]
	MR	<u>Base case:</u> 15.50% (18-64 year-	7% (18-49 year-olds) 17% (50-64 year-olds)	<u>Base case:</u> 2.29% (18-64 year-	0.2% (18-64 year-olds) 0.7% (65+ year-olds)	[23-28]

<table><tr><td></td><td></td><td>(Max. scenario only)</td></tr><tr><td>Non-bacteremic CAP below 18 years</td><td>0%</td><td>4%</td></tr><tr><td>Non-bacteremic CAP; above 18 years</td><td>1.1%</td><td>6%</td></tr><tr><td>IPD pneumonia; below 18 years</td><td>1.3%</td><td>3%</td></tr><tr><td>IPD pneumonia; above 18 years</td><td>4.3%</td><td>11%</td></tr></table> <u>Min. scenario:</u> non-invasive CAP mortality 1.5 times smaller than base case mortality and 6 months after hospitalisation mortality for all pneumonia is not included <u>Max. scenario</u> non-invasive CAP mortality is 2 times larger than base case mortality and 6 months after hospitalisation mortality for all pneumonia is fully included		olds) 24.24% (65+ year-olds) <u>Min. scenario:</u> 15.50% (18-64 year-olds) 23.4% (65+ year-olds) <u>Max. scenario</u> 18.88% (18-64 year-olds) 28.00% (65+ year-olds)	20% (65-79 year-olds) 49% (80+ year-olds)	olds) 12.91% (65+ year-olds) <u>Min. scenario:</u> 0.67% 6.00% <u>Max. scenario</u> 5.33% 27.02%		
	HR	<u>Base case:</u> 15.80% (18-64 year-olds) 17.91% (65+ year-olds) <u>Min. scenario:</u> 15.80% (18-64 year-olds) 17.00% <u>Max. scenario</u> 19.17% (18-64 year-olds) 21.98% (65+ year-olds)	7% (18-49 year-olds) 17% (50-64 year-olds) 20% (65-79 year-olds) 49% (80+ year-olds)	<u>Base case:</u> 2.29% (18-64 year-olds) 12.91% (65+ year-olds) <u>Min. scenario:</u> 0.67% 6.00% <u>Max. scenario</u> 5.33% 27.02%	0.2% (18-64 year-olds) 0.7% (65+ year-olds)	[23-28]
QALY loss average [min; max], uncertainty is explored by bootstrapping from original data	LR	0.0203 [-0.3288;0.5244] (18-64 year-olds) 0.1741[-0.2768;0.671] (65+ year-olds)		0.0491 [-0.3283; 0.9692] (18-64 year-olds) 0.0679[-0.2713; 0.8336] (65+ year-olds)	See Table 2	[29, 30] Caculation see App. 3
	MR	0.031[-0.242;0.7798] (18-64 year-olds) 0.0988[-0.3921;0.7009] (65+ year-olds)		0.0708[-0.2539;0.6936] (18-64 year-olds) 0.0985[-0.3177;0.6936] (65+ year-olds)	See Table 2	[28, 29 see App. 3
	HR	0.0873 [-0.2139; 0.5294] (18-64 year-olds) 0.1788 [-0.1154; 0.523] (65+ year-olds)		0.1366[-0.2139;0.7024] (18-64 year-olds) 0.2128[-0.1788;0.6174] (65+	See Table 2	[28, 29 see App. 3

			year-olds)		
Direct medical cost (€) average (95% interval) of 1,000 bootstrap simulations[(c)] Uncertainty defined by bootstrapping input data	LR	7,457 (6,539; 8,628) (18-64 year-olds) 8,558 (7,173; 10,313) (65-74 year-olds) 7,529 (6,258; 8,824) (75-84 year-olds) 6,592 (5,459; 7,828) (85+ year-olds)	6,490 (5,696; 7,432) (18-64 year-olds) 7,445 (6,258; 8,857) (65-74 year-olds) 6,555 (5,443; 7,766) (75-84 year-olds) 5,740 (4,745; 6,819) (85+ year-olds)	340 (303; 384) (18-64 year-olds) 203 (184; 222) (65-74 year-olds) 200 (181; 221) (75-84) 202 (180; 225) (85+ year-olds)	[30, 31] see App. 3
	MR	9,720 (8,304; 11,536) (18-64 year-olds) 11,146 (9,212; 13,468) (65-74 year-olds) 9,794 (8,367; 11,454) (75-84 year-olds) 8,580 (7,218; 10,130) (85+ year-olds)	8,454 (7,272; 9,777) (18-64 year-olds) 9,692 (8,161; 11,502) (65-74 year-olds) 8,523 (7,304; 9,848) (75-84 year-olds) 7,468 (6,283; 8,787) (85+ year-olds)	340 (303; 384) (18-64 year-olds) 203 (184; 222) (65-74 year-olds) 200 (181; 221) (75-84 year-olds) 202 (180; 225) (85+ year-olds)	[30, 31] see App. 3
	HR	9,397 (7,832; 11,156) 18-64 year-olds) 10,789 (8,594; 13,214) (65-74 year-olds) 9,478 (7,857; 11,255) (75-84 year-olds) 8,304 (6,686; 9,954) (85+ year-olds)	8,176 (6,921; 9,556) (18-64 year-olds) 9,384 (7,651; 11,399) (65-74 year-olds) 8,250 (6,828; 9,839) (75-84 year-olds) 7,229 (5,881; 8,849) (85+ year-olds)	340 (303; 384) (18-64 year-olds) 203 (184; 222) (65-74 year-olds) 200 (181; 221) (75-84 year-olds) 202 (180; 225) (85+ year-olds)	[30, 31] see App. 3

LR: Low Risk, MR: Medium Risk; HR: High Risk group

[(a)] As model input, narrower age groups were used for IPD incidence, see Table 18 in Appendix 3

[(b)] IPD incidence (meningitis and bactereamic pneumonia) [40]; Outpatient CAP incidence [32]; Risk group proportions [5, 12, 33, 34]; Relative risk of pneumococcal disease in risk groups [35]; Proportion of pneumococcal caused outpatient pneumonia and proportion bactermia in hospitalised pneumococcal pneumonia cases [36]

[(c)] Mean cost estimate based on a linear regression model on the log-cost scale (using Duan's smearing estimate [37] to transform to the log scale), separate for hospitalised pneumococcal disease and non-invasive outpatient CAP. The hospitalised pneumococcal disease model includes invasiveness of the disease, risk and age group as predictors; the non-invasive CAP model only includes risk and age group. Uncertainty was taken into account by bootstrapping, which is robust against model misspecification.

2.3.1 Disease burden estimates

Table 3 summarises disease specific parameters per age and risk group. It shows disease incidence to be the main distinghuising factor for risk groups. These risk group differences are based on a combination of risk group specific pneumococcal disease risks [35]. France's specific age-stratified prevalence of risk groups [5, 12, 33, 34] was combined with IPD (bacteremic pneumonia and meningitis [40]) incidence and outpatient non-invasive CAP incidence ([32], as well as the proportion caused by pneumococcus [36]) to estimate risk and age-group specific incidences. The incidence of hospitalised non-invasive pneumonia was derived from the incidence of invasive pneumococcal pneumonia using a literature based ratio of non-invasive pneumonia to invasive pneumonia (irrespective of age and risk group) [36]. More detail on the calculation is provided in Appendix 4.

IPD pneumonia mortality, QALY estimates and direct health care cost estimates are estimated by risk and age group (Table 3). Remaining age-specific life expectancy per year of age and case-fatality ratios, except for those related to invasive pneumonia, are asumed equal across risk groups.

The ongoing childhood vaccination program is assumed to impact adult IPD and non-invasive CAP incidences differently. Whereas non-invasive CAP incidences are assumed to remain constant over time, the IPD incidences are assumed to drop until the year 2018, after which they either remain constant (base case) or relapse to the 2001-2002 incidence by 2040 (max. scenario sensitivity analysis, see Table 2).

The PCV13 serotype coverages of IPD and non-invasive CAP are assumed to converge by 2020 such that still 15% PCV13 coverage in 18-64 year-olds and 13% in over 65-year-olds remains, after which it stays constant. This implies childhood vaccination is assumed to reduce but not eliminate the circulation of PCV13 serotypes in the elderly.

2.3.2 Vaccine efficacy parameters

PCV13 costs more than 4 times what PPV23 costs per dose, has only half the IPD serotype coverage in 2014, but has been shown to be effective against vaccine type CAP, to offer a longer duration of protection and is assumed in this analysis to also offer protection in medium risk and high risk (ie immunocompromised) individuals (Table 2).

PCV13's vaccine efficacy in immunocompetent (LR and MR) individuals was sourced from the only trial in the elderly [10]. In the absence of any specific clinical trail evidence on PCV13's efficacy in immunosuppressed individuals, we follow Mangen et al in assuming immunosuppressed individuals have 22% and 35% lower efficacy against IPD and non-invasive CAP than immunocompetent individuals [11]. PCV13's initial VE is assumed to decline by age at vaccination, as demonstrated by Van Werkhoven et al. [13]. The duration of vaccine protection at baseline was taken to be similar to previous cost-effectiveness analyses ([38, 39]. That is, 5 years without waning followed by logistic waning with 50% of the initial level of protection lost after 13 years, and varied between 6 and 15

years in sensitivity analysis (see Appendix 3). The duration of vaccine protection is considered age and risk group independent.

In a large observational study, Andrews et al provide risk group specific PPV23 efficacy information, which is used to inform PPV23 efficacy parameters against IPD ([14], See Appendix 3). It shows PPV23 to be ineffective in immunosuppressed individuals (HR), whereas immunocompetent individuals benefit from 5 years of vaccine protection when they are vaccinated under 74 years of age and do not suffer from underlying comorbidities (LR). For other PPV23 vaccine recipients we assume 2 years of vaccine protection (MR all ages and LR 75-84 years of age, see Appendix 3). In contrast to VE against IPD, current evidence of PPV23 VE against non-invasive CAP is inconclusive. Therefore all analyses are done, assuming - based on the FHCPH-expert judgements informed by the literature - either 0% or 30% for PPV23 efficacy against non-invasive CAP. The same duration of protection per age and risk group is assumed for IPD and non-IPD.

The combined use of PCV13 and PPV23 is assumed to yield the per-serotype best protection of the two vaccines.

Adverse effects from these vaccines were assumed to be negligible.

2.4 Incremental cost-effectiveness analysis under uncertainty

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

We use cost-effectiveness acceptability frontiers (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 expected net benefit (when a QALY is valued at the WTP level shown) [41].

Not all parameter uncertainty could be captured by probability distributions therefore pneumococcal incidence (varied +-25% for non-invasive CAP, +-15% for IPD), future incidence evolution, case-fatality ratio of pneumococcal pneumonia and PCV13 vaccine characteristics (protection in high risk groups: 50-100% of CAPITA, duration of protection and vaccine price per dose) were defined as separate senarios varied in univariate and multivariate sensitivity analysis together with other factors such as discount rate, and targeted vaccine coverage (see Table 2 and Table 3).

Since the assumed PPV23 efficacy against non-invasive CAP is central in choosing between PCV13 and PPV23, all univariate sensitivity analysis were performed twice, once with 0% and once with 30% PPV23 efficacy against non-invasive CAP.

In multivariate sensitivity analysis we explored the extreme (minimum- maximum) scenarios of vaccine protection (PPV23 non-invasive CAP protection, PCV13 duration of protection and protection in the HR group) and epidemiological parameters (incidence and pneumonia mortality) together with the current PCV13 price and 5%, 10% ,25% and 50% price reductions to anticipate price negociations.

In the results section below we discuss the baseline analysis in detail and highlight a few notable results from the univariate (or one way) sensitivity analyses and multivariate analysis, a complete overview of results can be found in the appendices.

3 Results

3.1 Model prediction of the pneumococcal disease burden in 2017

The annual pneumococcal disease and economic burden is expected to amount to 320 meningitis cases, 71,242 pneumonia cases treated in ambulatory care and 14,743 pneumonia hospitalisations, leading to about 1,607 deaths and 24,700 QALYs lost in the French population between 18 and 84 years of age (48 million people), costing about €151 million (discounted) in treatment (see Table 4). A substantial part of this burden is in the MR group between 65 and 84 years of age where we expect 3190 hospitalisations, 573 deaths and 5179 QALYs lost in a population of 3.6 million people.

Table 4: Model based estimate of the 2017 disease and cost burden related to *S. pneumoniae* in adults 18-84 (average of 1000 simulations, rounded to the nearest unit).

LOW RISK (immunocompetent, not at higher risk) (LR)				
Age	**18-49 years**	**50-64 years**	**65-84 years**	**18-84 years**
Age-risk group size	24,796,563	10,179,754	6,261,628	41,237,946
Meningitis cases	55	38	32	126
Hearing loss cases	6	4	3	13
Neurological sequelae cases	6	4	3	13
Pneumococcal pneumonia hospitalisations	1,865	1,302	2,294	5,461
Outpatient pneumococcal pneumonia cases	27,181	11,159	7,118	45,459
Deaths meningitis	4	7	8	19
Pneumonia deaths	99	54	340	493
Total deaths	103	60	348	512
Undiscounted quality adjusted life years lost[§]	4,652	1,502	3,320	9,474
Discounted quality adjusted life years lost[§]	2,396	1,021	2,658	6,074
Total life years lost undiscounted	4,922	1,649	4,604	11,174
Total life years lost discounted	2,245	1,027	3,576	6,849
Direct health care costs discounted (€)[§]	24,275,277	13,844,528	18,603,177	56,722,982
MEDIUM RISK (immunocompetent, at higher risk) (MR)				
Age	**18-49 years**	**50-64 years**	**65-84 years**	**18-84 years**
Age-risk group size	833,326	2,056,104	3,565,384	6,454,814
Meningitis cases	17	38	43	98
Hearing loss cases	2	4	4	10
Neurological sequelae cases	2	4	4	10
Pneumococcal pneumonia hospitalisations	568	1,300	3,147	5,015
Outpatient pneumococcal pneumonia cases	2,884	7,117	12,565	22,566
Deaths meningitis	1	7	11	19
Pneumonia deaths	35	81	562	678
Total deaths	36	88	573	697
Undiscounted quality adjusted life years lost[§]	1,433	1,982	5,179	8,593
Discounted quality adjusted life years lost[§]	747	1,336	4,180	6,263
Total life years lost undiscounted	1,587	2,320	7,280	11,187
Total life years lost discounted	762	1,465	5,715	7,943
Direct health care costs discounted (€)[§]	6,746,650	15,197,256	32,766,081	54,709,987
HIGH RISK (immunosuppressed at higher risk) (HR)				
Age	**18-49 years**	**50-64 years**	**65-84 years**	**18-84 years**
Age-risk group size	108,765	143,560	186,410	438,735
Meningitis cases	21	45	30	96
Hearing loss cases	2	4	3	10
Neurological sequelae cases	2	4	3	10
Pneumococcal pneumonia hospitalisations	706	1,531	1,810	4,047
Outpatient pneumococcal pneumonia cases	767	1,012	1,439	3,218
Deaths meningitis	1	8	7	16

Pneumonia deaths	38	82	262	382
Total deaths	40	90	269	398
Undiscounted quality adjusted life years lost[§]	1,600	2,103	2,930	6,633
Discounted quality adjusted life years lost[§]	850	1,427	2,352	4,629
Total life years lost undiscounted	1,732	2,391	3,825	7,948
Total life years lost discounted	837	1,503	2,935	5,276
Direct health care costs discounted (€)[§]	7,197,190	14,872,871	17,656,190	39,726,252
In all risk groups combined (LR+MR+HR)				
Age	**18-49 years**	**50-64 years**	**65-84 years**	**18-84 years**
Age-risk group size	25,738,654	12,379,418	10,013,423	48,131,495
Meningitis cases	92	122	106	320
Hearing loss cases	10	12	10	32
Neurological sequelae cases	10	12	10	32
Pneumococcal pneumonia hospitalisations	3,139	4,134	7,250	14,523
Outpatient pneumococcal pneumonia cases	30,833	19,288	21,122	71,242
Deaths meningitis	6	21	26	54
Pneumonia deaths	173	217	1,164	1,553
Total deaths	179	238	1,190	1,607
Undiscounted quality adjusted life years lost[§]	7,685	5,587	11,429	24,700
Discounted quality adjusted life years lost[§]	3,992	3,784	9,190	16,965
Total life years lost undiscounted	8,240	6,361	15,709	30,309
Total life years lost discounted	3,845	3,995	12,227	20,067
Direct health care costs discounted (€)[§]	38,219,117	43,914,655	69,025,448	151,159,220

[§]The costs and QALYs lost due to long term consequences (hearing loss or neurological sequelae) following a meningitis episode in 2017 are fully included even though these outcomes did not necessarily occur in 2017.

3.2 Cost-effectiveness of vaccination strategies

3.2.1 Base case-analysis

in , strategies are more cost-effective if they are depicted more to the right (more effective) and lower (less costly) versus the origin. In the origin the current situation, SC0, is placed. Improving the coverage of the current situation (SC11) dominates SC2 and SC4 (this is irrespective of the assumed PPV23 efficacy against non-invasive CAP - not shown in). Indeed, SC11 is more effective and less costly than SC2 and SC4. Furthermore SC5, SC1, SC3 are more effective and more costly than SC11, but these three strategies are dominated (by extended dominance) by SC6, because in comparison to SC11, SC6 is both more effective and more cost-effective (lower inclination line) than SC5, SC1 and SC3 in relation to SC11. So the efficiency frontier runs from SC0 over SC11 to SC6. SC6 consists of giving both vaccines to all elderly individuals (65-84 years) and in addition to the adult MR-group (18-64 years). Over a period of 10 years, this strategy entails a vaccination investment of €1,546 million which would avoid 10,312 hospitalisations, 1,562 deaths and 23,732 life years lost at a price of €140,386 per QALY (95% CI: 109,710; 179,464).

So Improving vaccination coverage of the current strategy, i.e. vaccinating 18-84-year-old risk groups with PPV23 for medium risk (MR) and the combination of both vaccines for high risk (immunosuppressed) individuals (HR), is the most cost-effective strategy (see SC11 in Table 1). It costs €30,659 (95% C.I: €24,938-€38,185) per QALY gained, when PPV23 would offer no protection against non-invasive CAP. Although this is a priori considered practically unfeasible to implement, it is of interest to note that limiting this strategy to those younger than 65 years, would be less effective, but more cost-effective (ICER <€20,000/QALY see SC12 and SC13 in Table 12 and Table 14).

Even though increasing the uptake of the current strategy (SC11) is the most cost-effective option that was initially considered, after careful deliberation the FHCPH-expert group considered it unrealistic to substantially increase PPV23 uptake given the current uptake has been low for a long period of time (see Table 2).

In view of this, the analysis needs to refocus after excluding SC11 (as well as the other theoretical strategies such as SC11 and SC12 only shown in appendices). In that case the efficiency frontier runs from SC0 over SC4 and SC5 to SC6 (see).

This is also illustrated in Figure 3 and Table 5, LR: Low Risk, MR: Medium Risk; HR: High Risk group; *fixed vaccine program costs and per-dose administration and purchasing costs

Table 6, Table 7 and Table 8. That is, targeting the adult MR-group with either PCV13 (SC4) or a combination of both vaccines (SC5) is more cost-effective than the other options at a willingness to pay (WTP) of €80,000 per QALY and more, regardless of the assumed PPV23 efficacy against non-invasive CAP. This efficacy only influences the level of WTP at which there is a switch in most beneficial strategy (see Figure 3). When PPV23 ‘s non-invasive CAP efficacy is increased from 0% to 30%, the required WTP to add PPV23 (ie to go from SC4 to SC5) declines from about €150,000 to about €100,000 per QALY.

Even though PPV23 vaccination in 65-84 year-olds across all risk groups (SC2) is dominated by PCV13 vaccination of the MR-group across all age groups (18-84 years) (SC4), the cost-effectiveness ratios

versus the current situation are similar when we assume PPV23 protects against non-invasive CAP. (SC2: €87,681/QALY and SC4: €87,100/QALY).

3.2.2 Uncertainty and sensitivity analysis

When we inspect the CEAFs in Figure 3, Figure 4, Figure 5, Figure 6, Figure 7, Figure 8 and Figure 9, a common feature 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. Yet at higher WTP, the certainty by which alternative options become the most beneficial is relatively high as well.

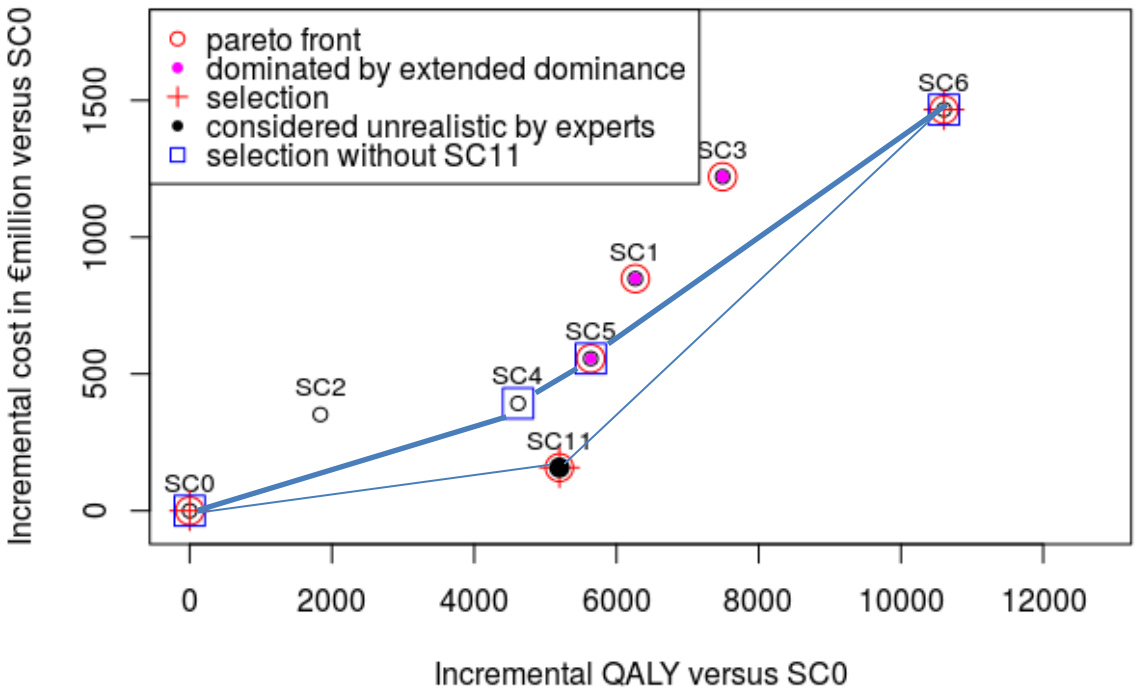
Focussing on practically feasible scenarios only (Table 1, but excluding SC11), targeting the adult MR-group (18-84 years) with either PCV13 (SC4) or a combination of both vaccines (SC5) dominates the other vaccination options throughout these sensitivity analyses, when the WTP range is €70,000-€100,000 per QALY gained.

The WTP can only be reduced to below €50,000 per QALY if PCV13's price is reduced by 50% combined with a longer duration of protection than in base case and/or with maximum disease burden assumptions (See Figure 8 and Figure 9, and input parameter section disease burden Table 3)

Vaccinating the general elderly population (65-84y, all risk groups) with PPV23 might be the most beneficial strategy when PPV23 protects against non-invasive CAP and (1) PCV13 is less effective in the 18-64 year old MR-group, PCV13's VE is assumed age independent, future pneumococcal incidences are low due to childhood vaccination or especially when PCV13's VE wanes quickly after 4 to 10 years after vaccination or (2) hospitalised pneumonia mortality is 2 times higher than under base case assumptions and 6 months of hospital mortality can be attributed to the pneumonia episode (see Figure 4), or (3) PPV23 's price is reduced by 25% (not shown in the plots).

For PCV13 vaccination of the general elderly population to become the most beneficial choice, we require 0% PPV23 efficacy against non-invasive CAP, a 50% PCV13 price reduction or maximum disease burden assumptions and a WTP around €100,000/QALY (Figure 8 and Figure 9).

Figure 2: Cost-effectiveness plane of scenarios 0, 1, 2, 3, 4, 5, 6 and 11, assuming no PPV23 efficacy against non-invasive pneumonia



SC0: Current situation

SC1: PCV13 in 65-84
SC2: PPV23 in 65-84
SC3: (PCV13 + PPV23) in 65-84
SC4: PCV13 in MR 18-84
SC5: (PCV13 + PPV23) in MR 18-84
SC6: (PCV13 + PPV23) in 65-84 & (PCV13 + PPV23) in MR 18-64

SC11: PPV23 in MR. 18-84 & PCV13+PPV23 in HR 18-84 (current situation at higher uptake)

Table 5: Avoided burden and cost-effectiveness of the different vaccination strategies versus the current situation, assuming **0% PPV23 efficacy** against non-invasive CAP: (mean(median) [95% interval] based on 1000 simulations, rounded to the nearest unit)

Avoided:	SC1: PCV13 in 65-84	SC2: PPV23 in 65-84	SC3: (PCV13 + PPV23) in 65-84	SC4: PCV13 in MR 18-84	SC5: (PCV13 + PPV23) in MR 18-84	SC6: (PCV13 + PPV23) in 65-84 & (PCV13 + PPV23) in MR 18-64
Meningitis cases	140(144) [76;182]	97(97) [71;117]	208(211) [153;250]	115(117) [72;143]	161(163) [122;191]	307(310) [233;363]
Pneumococcal CAP hospitalisations	6,502(6,532) [3,857;8,840]	1,389(1,397) [1,085;1,651]	7,415(7,404) [5,180;9,648]	4,347(4,378) [2,774;5,763]	4,855(4,859) [3,448;6,235]	10,005(10,025) [7,180;12,816]
Outpatient pneumococcal CAP cases	17,804(17,828) [8,840;25,402]	159(157) [89;228]	17,893(17,832) [9,812;25,402]	18,841(18,925) [10,816;26,030]	18,891(18,925) [11,272;26,030]	30,194(30,239) [17,995;41,615]
Meningitis deaths	37(39) [17;51]	23(23) [17;28]	53(54) [36;66]	24(25) [12;31]	33(34) [23;40]	68(69) [48;83]
Pneumonia deaths	1,068(1,076) [658;1,435]	231(232) [179;274]	1,221(1,220) [875;1,572]	614(620) [404;808]	720(722) [539;903]	1,494(1,495) [1,103;1,890]
Total deaths	1,105(1,113) [693;1,478]	254(255) [196;301]	1,274(1,274) [926;1,632]	638(644) [422;836]	753(756) [561;941]	1,562(1,562) [1,171;1,965]
Undiscounted life years lost	14,128(14,207) [9,523;18,447]	3,560(3,586) [2,778;4,240]	16,463(16,522) [12,260;20,634]	10,505(10,570) [7,660;13,140]	12,535(12,564) [10,037;15,057]	23,732(23,824) [18,420;28,938]
Discounted life years lost	8,347(8,389) [5,495;10,983]	2,383(2,399) [1,841;2,844]	9,947(9,983) [7,352;12,492]	5,816(5,850) [4,153;7,382]	7,132(7,151) [5,642;8,614]	13,537(13,580) [10,445;16,650]
Undiscounted QALYs lost	10,248(10,259) [6,931;13,468]	2,678(2,689) [2,079;3,198]	11,999(11,944) [9,098;15,246]	8,109(8,106) [6,070;10,193]	9,682(9,688) [7,769;11,720]	18,021(18,023) [14,120;22,231]
Discounted QALYs lost	6,266(6,251) [4,153;8,350]	1,837(1,848) [1,416;2,203]	7,493(7,464) [5,600;9,566]	4,617(4,612) [3,368;5,875]	5,639(5,629) [4,456;6,860]	10,606(10,583) [8,249;13,182]
Direct health care costs undiscounted (€)	62,886,524(63,310,308) [38,596,222;85,549,064]	15,859,952(15,895,923) [12,061,113;19,520,315]	73,332,520(73,216,127) [53,009,209;95,732,686]	50,237,878(50,445,836) [33,615,561;65,339,038]	57,586,603(57,674,344) [41,866,824;72,749,679]	106,772,526(106,863,958) [79,582,355;134,656,319]
Direct health care costs discounted (€)	46,230,231(46,481,240) [27,610,993;63,419,992]	13,263,769(13,277,772) [10,060,653;16,365,670]	55,173,488(55,087,154) [39,841,153;71,906,573]	38,390,508(38,484,150) [25,319,181;50,286,829]	44,722,395(44,774,994) [32,344,288;56,607,940]	80,394,744(80,481,901) [59,177,870;101,772,715]
Direct vaccination costs* undiscounted (€)	-958,659,852	-389,969,119	-1,368,876,796	-441,157,114	-615,572,505	-1,645,906,183
Direct vaccination costs* discounted (€)	-894,655,107	-365,044,135	-1,276,494,557	-430,920,617	-601,016,164	-1,546,611,356
ICER undiscounted(€)	90,124(87,274) [64,926;132,657]	141,709(139,173) [115,897;182,012]	110,038(108,489) [83,705;144,546]	49,256(48,140) [36,852;66,787]	58,390(57,559) [46,447;73,661]	86,657(85,429) [68,078;110,747]
ICER discounted(€)	140,038(135,406) [100,088;208,785]	194,357(190,388) [158,443;250,604]	166,207(163,784) [126,213;219,900]	87,100(84,941) [64,623;120,059]	100,026(98,787) [79,675;127,382]	140,386(138,464) [109,710;179,464]
Incremental cost per life year gained (€, undiscounted)	65,427(63,033) [47,439;96,852]	106,521(104,360) [87,663;135,833]	80,227(78,473) [61,762;107,238]	38,075(36,938) [28,525;52,997]	45,128(44,384) [36,168;56,927]	65,843(64,558) [52,097;85,051]
Incremental cost per life year gained (€, discounted)	105,223(101,022) [75,867;157,472]	149,760(146,633) [123,086;192,632]	125,218(122,401) [96,670;167,789]	69,254(66,977) [51,651;97,721]	79,115(77,766) [63,049;100,759]	110,024(108,087) [86,903;142,514]

LR: Low Risk, MR: Medium Risk; HR: High Risk group; *fixed vaccine program costs and per-dose administration and purchasing costs

Table 6: Incremental avoided burden and incremental cost-effectiveness along the cost-effectiveness frontier*, assuming **0% PPV23 efficacy** against non-invasive CAP: (mean(median) [95% interval] based on 1000 simulations, rounded to the nearest unit)

Avoided	SC4: PCV13 in MR 18-84 Versus SC0	SC5: (PCV13 + PPV23) in MR 18-84 versus SC4	SC6: (PCV13 + PPV23) in 65-84 & (PCV13 + PPV23) MR 18-64, versus SC5
Meningitis cases	115(117)[72;143]	47(46)[32;61]	146(147)[110;174]
Pneumococcal CAP hospitalisations	4,347(4,378)[2,774;5,763]	508(497)[331;747]	5,151(5,161)[3,702;6,588]
Outpatient pneumococcal CAP cases	18,841(18,925)[10,816;26,030]	50(0)[0;568]	11,303(11,325)[6,724;15,585]
Deaths meningitis	24(25)[12;31]	9(9)[6;13]	35(36)[25;43]
Pneumonia deaths	614(620)[404;808]	106(104)[69;149]	773(774)[557;989]
Total deaths	638(644)[422;836]	115(113)[75;160]	808(810)[590;1,028]
Undiscounted total life years lost	10,505(10,570)[7,660;13,140]	2,030(2,023)[1,363;2,670]	11,197(11,197)[8,410;13,958]
Discounted total life years lost	5,816(5,850)[4,153;7,382]	1,316(1,309)[879;1,735]	6,405(6,416)[4,791;8,010]
Undiscounted QALY lost	8,109(8,106)[6,070;10,193]	1,573(1,571)[1,072;2,050]	8,338(8,299)[6,371;10,490]
Discounted QALY lost	4,617(4,612)[3,368;5,875]	1,022(1,017)[695;1,342]	4,966(4,944)[3,736;6,294]
Direct health care costs undiscounted (€)	50,237,878(50,445,836)[33,615,561;65,339,038]	7,348,725(7,321,829)[4,898,258;10,147,049]	49,185,923(48,969,699)[36,159,477;63,233,321]
Direct health care costs discounted (€)	38,390,508(38,484,150)[25,319,181;50,286,829]	6,331,886(6,305,517)[4,198,062;8,758,906]	35,672,349(35,555,248)[26,160,247;45,859,154]
Direct vaccination costs (vaccine program, administration and purchase) undiscounted	-441,157,114	-174,415,391	-1,030,333,678(-1,030,333,678)
Direct vaccination costs (vaccine program, administration and purchase) discounted	-430,920,617	-170,095,547	-945,595,193
ICER undiscounted	49,256(48,140)[36,852;66,787]	109,509(106,422)[80,317;157,865]	119,739(118,327)[92,408;156,025]
ICER discounted	87,100(84,941)[64,623;120,059]	165,348(161,085)[120,258;238,347]	186,597(184,341)[143,044;244,428]
Incremental cost per life year gained (undiscounted)	38,075(36,938)[28,525;52,997]	84,963(82,599)[61,609;124,552]	89,206(87,606)[69,318;118,041]
Incremental cost per life year gained (discounted)	69,254(66,977)[51,651;97,721]	128,606(125,106)[92,931;188,844]	144,701(141,616)[112,207;191,630]

LR: Low Risk, MR: Medium Risk; HR: High Risk group

* Cost-effectiveness frontier: here we only present the options that are considered practically feasible and are not dominated by other options (see Figure 2).

Table 7: Avoided burden and cost-effectiveness versus the current situation, assuming **30% PPV23 efficacy** against non-invasive CAP: (mean(median) [95% interval] based on 1000 simulations, rounded to the nearest unit)

Avoided:	SC1: PCV13 in 65-84	SC2: PPV23 in 65-84	SC3: (PCV13 + PPV23) in 65-84	SC4: PCV13 in MR 18-84	SC5: (PCV13 + PPV23) in MR 18-84	SC6: (PCV13 + PPV23) in 65-84 & (PCV13 + PPV23) in MR 18-64
Pneumococcal CAP hospitalisations	6,502(6,532) [3,857;8,840]	3,111(3,117) [2,669;3,534]	8,667(8,680) [6,535;10,905]	4,347(4,378) [2,774;5,763]	5,546(5,546) [4,233;6,890]	11,459(11,478) [8,777;14,211]
Outpatient pneumococcal CAP cases	17,804(17,828) [8,840;25,402]	8,568(8,568) [7,123;10,064]	23,505(23,491) [16,055;30,887]	18,841(18,925) [10,816;26,030]	22,372(22,383) [15,309;29,294]	37,180(37,180) [25,879;48,147]
Pneumonia deaths	1,068(1,076) [658;1,435]	512(513) [437;578]	1,422(1,423) [1,091;1,765]	614(620) [404;808]	806(807 [634;986]	1,703(1,706) [1,324;2,093]
Total deaths	1,105(1,113) [693;1,478]	535(536) [456;606]	1,475(1,476) [1,137;1,824]	638(644) [422;836]	840(841) [659;1,025]	1,771(1,775) [1,390;2,170]
Undiscounted total life years lost	14,128(14,207) [9,523;18,447]	7,641(7,661) [6,516;8,663]	19,205(19,248) [15,298;23,274]	10,505(10,570) [7,660;13,140]	13,669(13,684) [11,190;16,188]	26,727(26,748) [21,800;31,906]
Discounted total life years lost	8,347(8,389) [5,495;10,983]	5,135(5,146) [4,368;5,828]	11,823(11,852) [9,473;14,282]	5,816(5,850) [4,153;7,382]	7,950(7,964) [6,505;9,425]	15,552(15,591) [12,721;18,580]
Undiscounted QALY lost	10,248(10,259) [6,931;13,468]	5,615(5,625) [4,766;6,436]	13,960(13,929) [10,916;17,111]	8,109(8,106) [6,070;10,193]	10,530(10,519) [8,619;12,555]	20,206(20,139) [16,309;24,272]
Discounted QALY lost	6,266(6,251) [4,153;8,350]	3,879(3,886) [3,259;4,459]	8,874(8,858) [6,923;10,822]	4,617(4,612) [3,368;5,875]	6,272(6,267) [5,115;7,508]	12,123(12,092) [9,692;14,551]
Direct health care costs undiscounted (€)	62,886,524(63,310,308) [38,596,222;85,549,064]	31,242,037(31,287,805) [25,903,375;36,427,424]	84,345,580(84,360,103) [64,078,078;106,086,007]	50,237,878(50,445,836) [33,615,561;65,339,038]	64,502,436(64,395,276) [49,111,225;79,690,708]	119,964,838(119,953,391) [92,519,674;147,976,748]
Direct health care costs discounted (€)	46,230,231(46,481,240) [27,610,993;63,419,992]	27,112,457(27,129,095)[2 2,462,327;31,632,667]	65,140,343(65,154,500) [49,605,993;81,748,062]	38,390,508(38,484,150) [25,319,181;50,286,829]	51,340,349(51,239,610) [39,110,553;63,329,055]	92,437,603(92,481,919) [71,248,341;113,910,217]
ICER undiscounted	90,124(87,274) [64,926;132,657]	64,290(63,736) [55,053;76,367]	93,248(92,165) [73,814;119,696]	49,256(48,140) [36,852;66,787]	52,896(52,355) [42,986;65,585]	76,359(75,710) [61,593;95,153]
ICER discounted	140,038(135,406)[100,08 8;208,785]	87,681(86,927) [74,766;104,840]	138,331(136,768) [110,204;177,229]	87,100(84,941) [64,623;120,059]	88,591(87,815) [72,023;109,928]	121,313(120,310) [98,472;152,002]
Incremental cost per life year gained (undiscounted)	65,427(63,033) [47,439;96,852]	47,215(46,773) [40,945;55,711]	67,778(66,730) [54,268;85,115]	38,075(36,938) [28,525;52,997]	40,761(40,292) [33,142;50,509]	57,743(57,037) [46,893;71,235]
Incremental cost per life year gained (discounted)	105,223(101,022)[75,867 ;157,472]	66,187(65,604) [57,399;78,253]	103,781(102,133) [83,568;129,490]	69,254(66,977) [51,651;97,721]	69,887(69,134) [57,120;86,544]	94,555(93,204) [77,246;115,956]

LR: Low Risk, MR: Medium Risk; HR: High Risk group

Table 8: Incremental avoided burden and incremental cost-effectiveness along the cost-effectivenes frontier*, assuming **30% PPV23 efficacy** against non-invasive CAP: (mean(median) [95% interval] based on 1000 simulations, rounded to the nearest unit)

Avoided:	SC4: PCV13 in MR 18-84 versus SC0	SC5: (PCV13 + PPV23) MR 18-84 versus SC4	SC6: (PCV13 + PPV23) in 65-84 & (PCV13 + PPV23) MR 18-64 versus SC5
Pneumococcal CAP hospitalisations	4,347(4,378)[2,774;5,763]	1,200(1,188)[954;1,501]	5,913(5,909)[4,525;7,347]
Outpatient pneumococcal CAP cases	18,841(18,925)[10,816;26,030]	3,530(3,487)[2,611;4,700]	14,808(14,816)[10,581;18,966]
Pneumonia deaths	614(620)[404;808]	192(191)[150;242]	896(897)[691;1,112]
Total deaths	638(644)[422;836]	201(200)[157;253]	931(933)[720;1,149]
Undiscounted total life years lost	10,505(10,570)[7,660;13,140]	3,164(3,160)[2,422;3,878]	13,058(13,061)[10,376;15,835]
Discounted total life years lost	5,816(5,850)[4,153;7,382]	2,134(2,128)[1,643;2,610]	7,602(7,607)[6,046;9,192]
Undiscounted QALY lost	8,109(8,106)[6,070;10,193]	2,421(2,417)[1,873;2,952]	9,677(9,657)[7,629;11,800]
Discounted QALY lost	4,617(4,612)[3,368;5,875]	1,655(1,652)[1,282;2,026]	5,851(5,845)[4,586;7,217]
Direct health care costs undiscounted (€)	50,237,878(50,445,836)[33,615,561;65,339,038]	14,264,558(14,207,115)[11,028,233;17,974,354]	55,462,402(55,481,231)[42,248,397;69,592,317]
Direct health care costs discounted (€)	38,390,508(38,484,150)[25,319,181;50,286,829]	12,949,840(12,897,576)[10,029,243;16,129,171]	41,097,254(41,071,778)[31,410,310;51,675,011]
ICER undiscounted	49,256(48,140)[36,852;66,787]	67,216(66,183)[52,989;86,827]	102,015(101,059)[81,491;129,313]
ICER discounted	87,100(84,941)[64,623;120,059]	96,464(95,105)[75,989;124,203]	156,580(154,845)[124,541;199,341]
Incremental cost per life year gained (undiscounted)	38,075(36,938)[28,525;52,997]	51,435(50,663)[40,587;67,115]	75,587(74,617)[60,753;94,981]
Incremental cost per life year gained (discounted)	69,254(66,977)[51,651;97,721]	74,797(73,830)[59,017;96,911]	120,457(118,810)[97,289;150,879]

LR: Low Risk, MR: Medium Risk; HR: High Risk group

* Cost-effectiveness frontier: here we only present the options that are considered practically feasible and are not dominated by other options (see Figure 2).

Figure 3: Cost-effectiveness acceptability frontier for practically feasible vaccination strategies (SC0-6), comparing 0% PPV23 efficacy (left panel) and 30% PPV23 efficacy against non-invasive CAP (right panel)

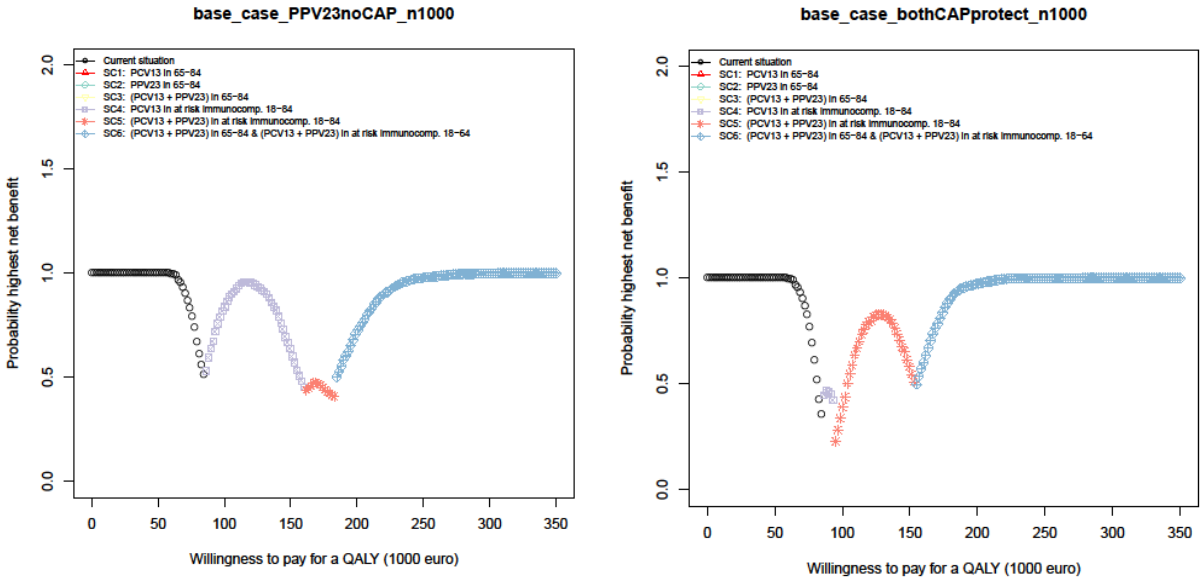


Figure 4: Cost-effectiveness acceptability frontier for practically feasible vaccination strategies (SC1-6) showing PPV23 containing strategies to be the most beneficial when PPV23 has 30% VE against vaccine type non-invasive CAP. Top left: PCV13 efficacy assumed age independent; Top right: Minimal scenario for future vaccine type incidence; Bottom left: Minimal scenario for duration of PCV13 efficacy; Bottom right: maximum scenario for hospitalised pneumonia mortality

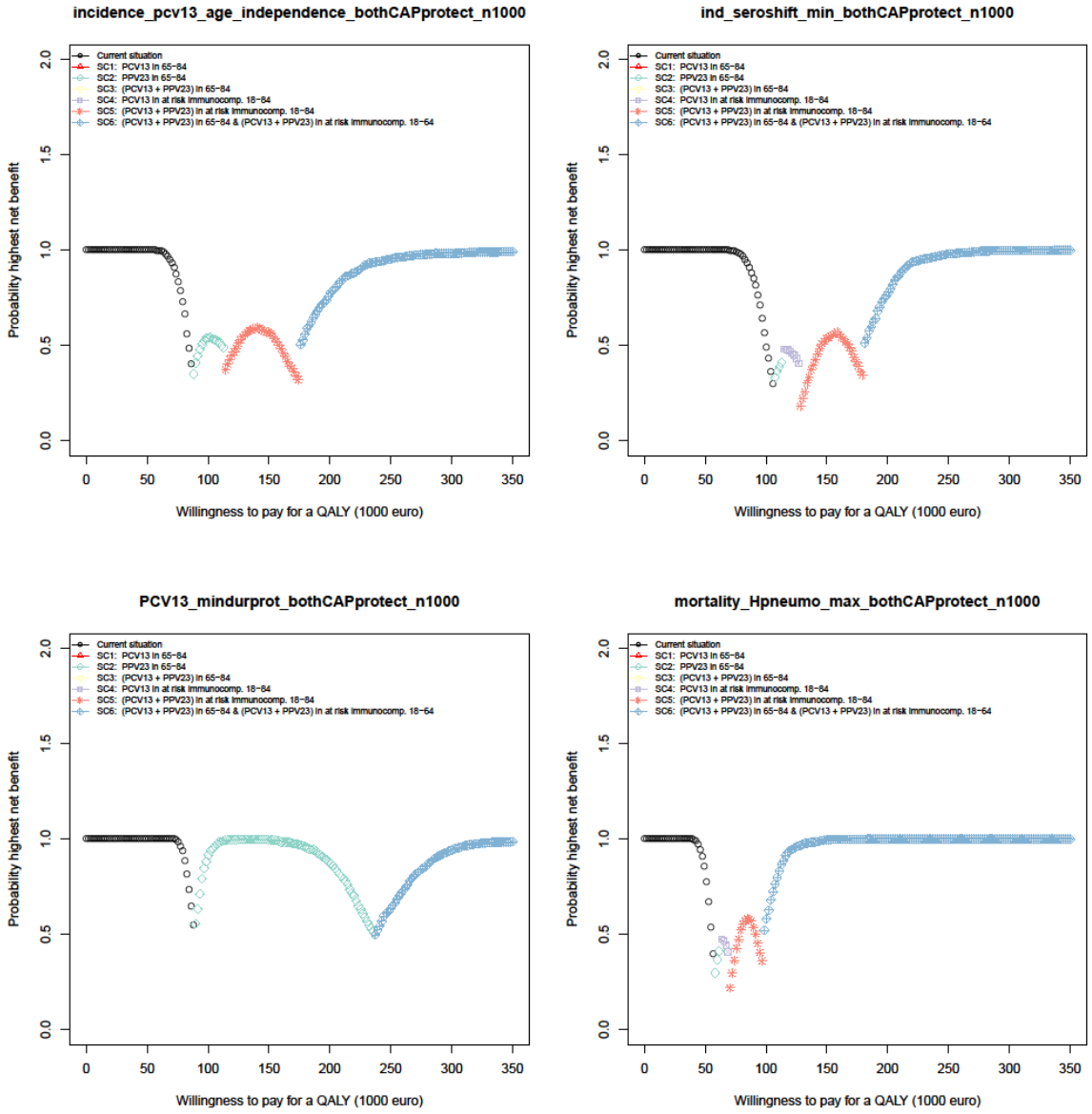


Figure 5: Cost-effectiveness acceptability frontier for practically feasible vaccination strategies (SC1-6) under decreasing PCV13 vaccine price (from left to right: 10%, 25% and 50% PCV13 price reduction) assuming 0% PPV23 efficacy against non-invasive CAP.

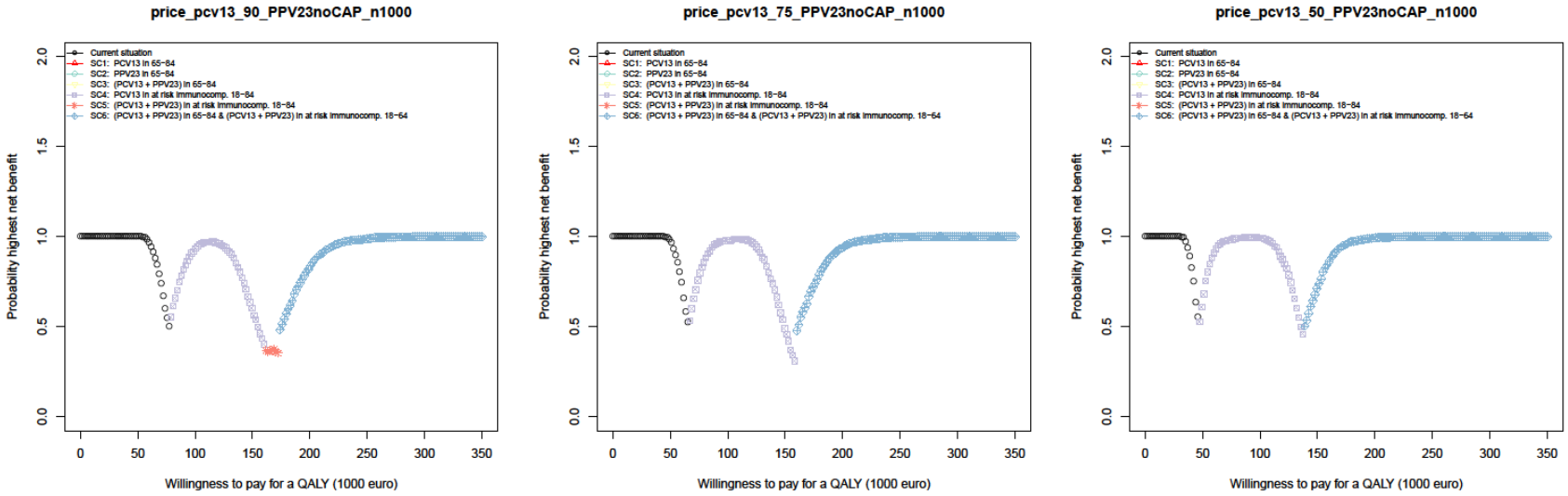


Figure 6: Cost-effectiveness acceptability frontier for practically feasible vaccination strategies (SC1-6) when varying PCV13 duration of protection and PPV23 efficacy against CAP. Top row: assuming 0% PPV23 efficacy against non-invasive CAP; Bottom row: assuming 30% PPV23 efficacy against non-invasive CAP; left side: minimal scenario of PCV13 duration of protection; Right side: maximal scenario of PCV13 duration of protection

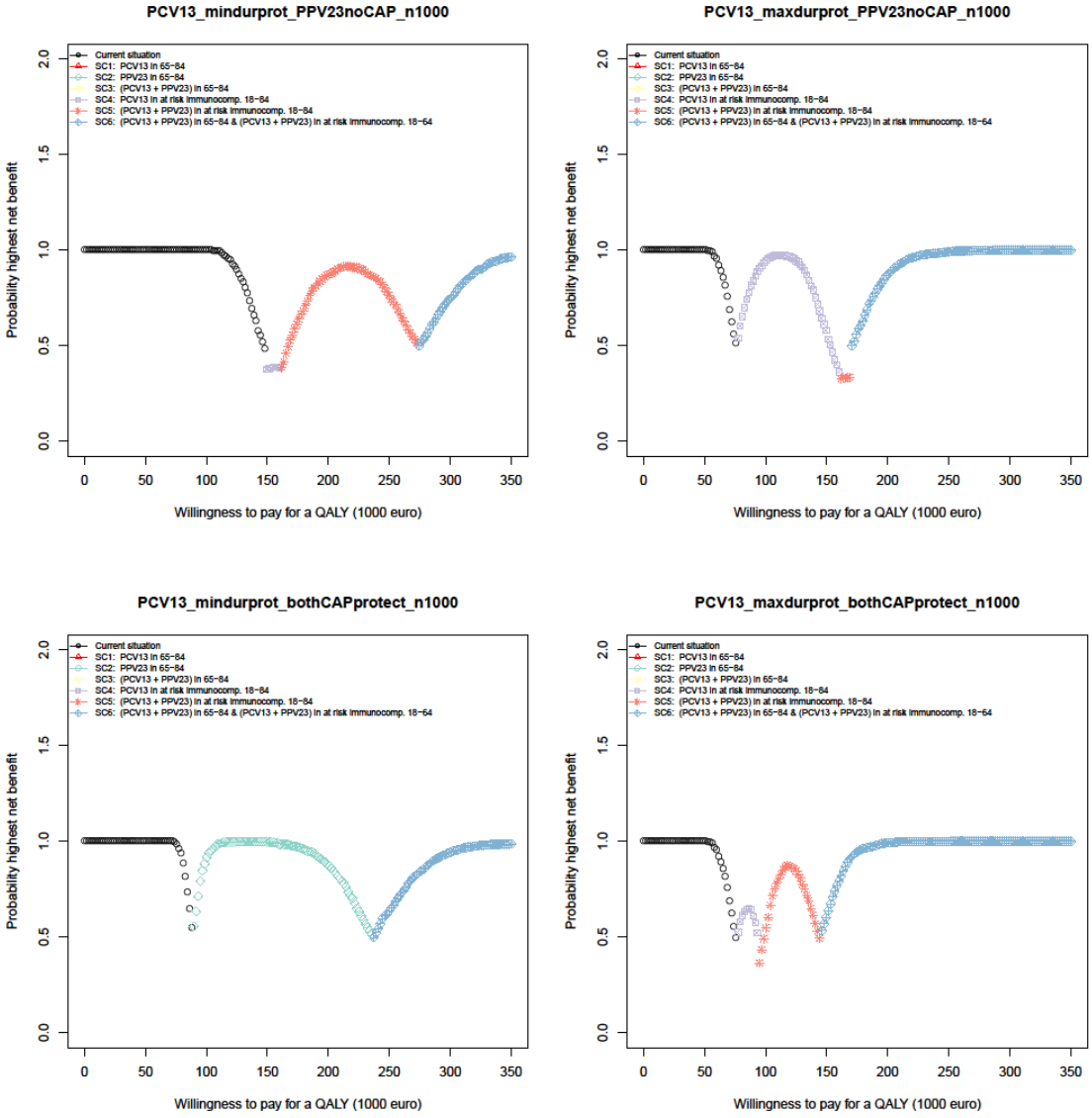


Figure 7: Cost-effectiveness acceptability frontier for practically feasible vaccination strategies (SC1-6) when varying the evolution of future incidence. Top row: assuming 0% PPV23 efficacy against non-invasive vaccine type CAP; Bottom row: assuming 30% PPV23 efficacy against non-invasive vaccine type CAP; left side: minimal scenario of the decrease in vaccine type serotype coverage; Right side: maximal scenario of the decrease in vaccine type serotype coverage

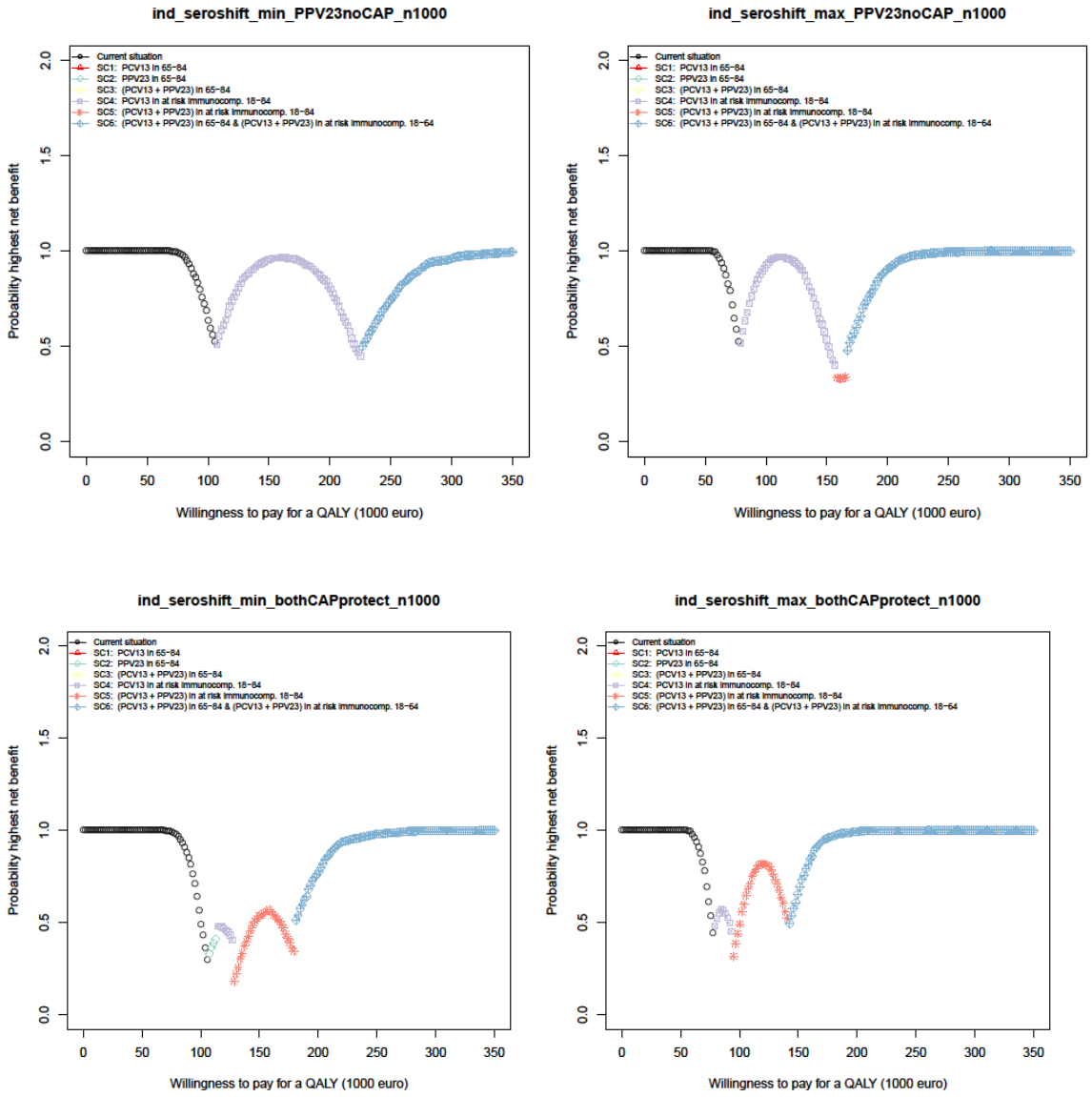
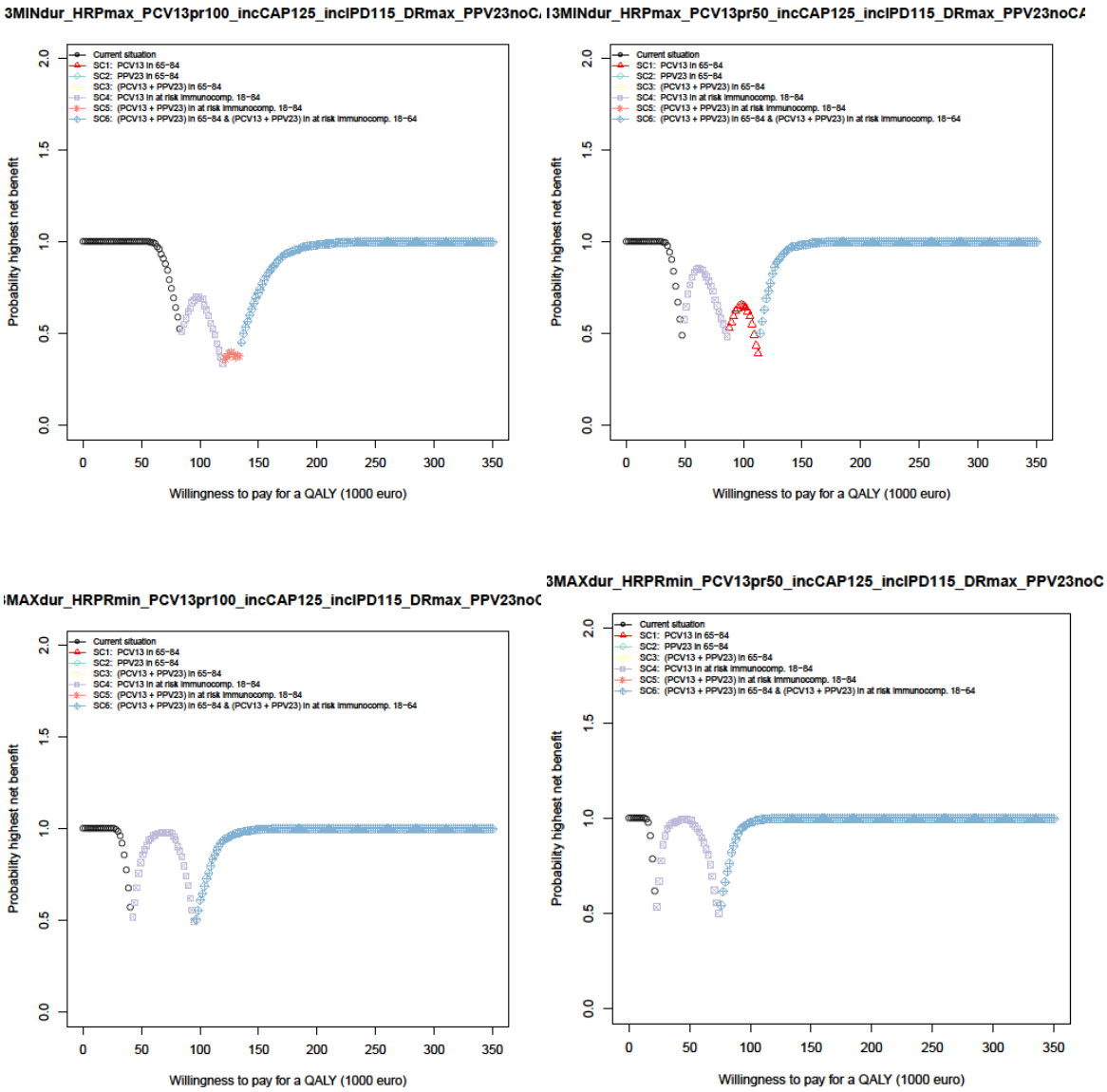


Figure 8: Cost-effectiveness acceptability frontier for practically feasible vaccination strategies (SC1-6) when varying PCV13 duration of protection: (min.[(a)] top; max.[(b)] bottom); PCV13 price: (current price left; 50% price reduction right); **0% PPV23 efficacy** against non-invasive CAP and disease burden and PCV13 in immunocompetent in favor of general elderly population vaccination[(c)].

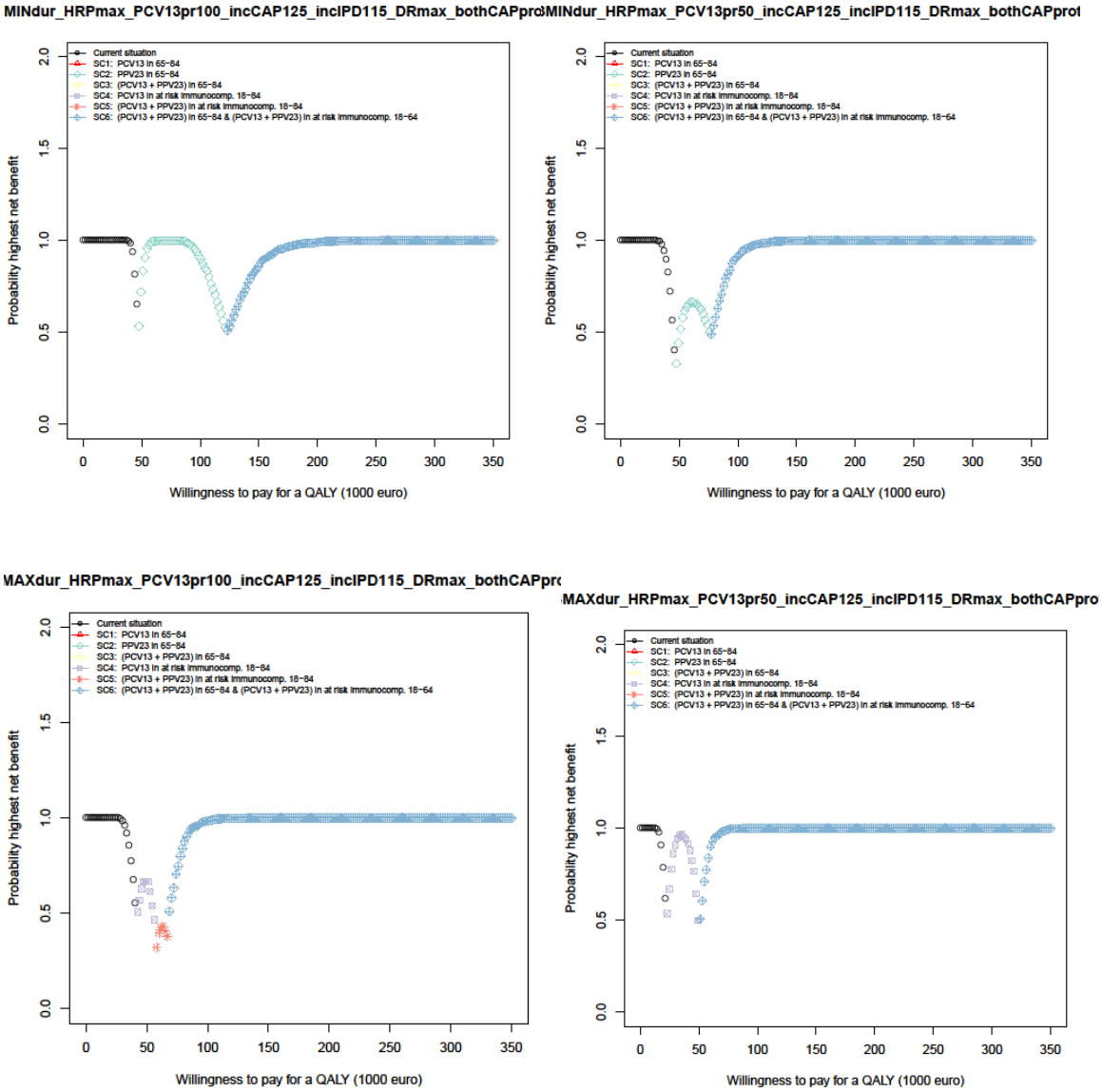


(a) 4 years without waning followed by rapid waning until no protection at 10 years after vaccination

(b) 9 years without waning followed by waning until no protection at 20 years after vaccination

(c) Maximal disease burden: 115% of base case IPD incidence, 125% of base case non-invasive CAP incidence; non-invasive CAP mortality is doubled compared to base case mortality, and includes all pneumonia mortality for 6 months post-hospitalisation; assuming the same PCV13 VE across risk groups

Figure 9: Cost-effectiveness acceptability frontier for practically feasible vaccination strategies (SC1-6) varying PCV13 duration of protection: (min.[(a)] top; max.[(b)] bottom); PCV13 price: (current price left; 50% price reduction right); **30% PPV23 efficacy** against non-invasive CAP and disease burden and PCV13 in immunocompetent in favor of general elderly population vaccination[(c)].



[(a)] 4 years without waning followed by rapid waning until no protection at 10 years after vaccination

[(b)] 9 years without waning followed by waning until no protection at 20 years after vaccination

[(c)] High disease burden: 115% of base case IPD incidence, 125% of base case non-invasive CAP incidence; non-invasive CAP mortality is doubled compared to base case mortality, and includes all pneumonia mortality for 6 months post-hospitalisation; assuming the same PCV13 VE across risk groups

3.3 Optimal vaccine and age-target choice per risk group

In addition to the 13 theoretical (of which 7 feasible) strategies, we also considered which would be the most optimal choices in terms of vaccine (PPV23, PCV13 or both) and age range, given one of the three risk groups are targeted (see for instance Figure 10 for the medium risk (MR) group).

Vaccinating the LR-group is not beneficial at a WTP below €150,000 per QALY under base case assumptions. From €150,000 per QALY onwards, PPV23 in 65-84-year-olds in the LR group becomes beneficial only if the vaccine protects against non-invasive CAP. Vaccinating the complete adult HR group between 18 and 84 years of age with PCV13, in contrast, is already beneficial at a WTP below €10,000/QALY, regardless of assumptions on uncertain parameters (other than the driving key assumption here, namely that PCV13 is efficacious in HR individuals, albeit at a lower efficacy than what the CAPITA trial reported for LR individuals).

The most beneficial choice in the MR-group depends on the assumed PPV23 efficacy against non-invasive CAP and other uncertain parameters. Under baseline assumptions, PCV13 in 18 to 49-year-olds at MR at a WTP of €50,000-€70,000 per QALY gained expands to 18 to 64 year olds at a WTP 70,000-110,000 as the most beneficial choice if PPV23 does not protect against non-invasive CAP. Otherwise, PPV23 in 18-49 or 18-49 and 65-84 (WTP €50,000-€60,000) is preferred and only above a WTP of €60,000 PCV13 vaccination in 18-64 year olds (combined with PPV23 in over 65-year-olds) becomes the most beneficial choice. The choice for PPV23 is strengthened when PCV13 does not depend on age or has a duration of protection below 10 years. A PCV13 price reduction of 10-25% secures a PCV13 choice even if PPV23 protects against non-invasive CAP.

3.4 Sensitivity analysis at a willingness to pay of €50,000 per QALY

We also illustrate our results in multivariate sensitivity analysis using net benefit box plots, while focusing on a single WTP value of €50000 per QALY gained (see Figure 11 and Figure 12). When the net benefits are positive (>0 in the graphs), that means that it is cost-saving versus the current situation (assuming a QALY is worth €50000 to a policy maker). 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 then that means the strategy and scenario it represents is on average or completely more beneficial.

Vaccinating the LR-group with PCV13 or PPV23 is cost-ineffective, even assuming a maximal pneumococcal disease burden, 50% PCV13 price reduction and 30% PPV23 efficacy against non-invasive CAP (Figure 11).

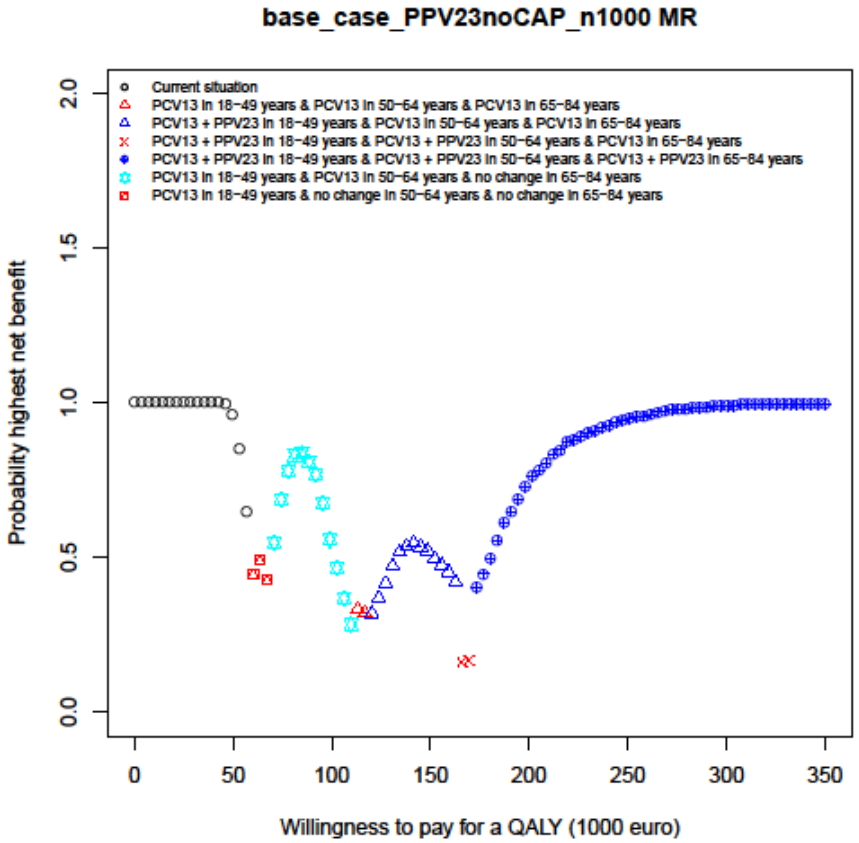
PPV23 is only borderline cost-effective in the MR-group between 18 and 49 years of age, under maximal disease burden assumptions. For those aged over 50 years, it should also be effective against non-invasive CAP (Figure 12). Under maximal disease burden assumptions, PCV13 is more beneficial (with each QALY valued at €50,000) in 18-64-year-olds, but only if it offers a longer than baseline duration of vaccine protection. In 65-84 year olds, PCV13 requires a long duration of

protection and a 25% price reduction to achieve positive net benefits and a 50% price reduction to be more beneficial than PPV23.

When the assumed disease burden is minimal, PCV13 can only be cost-effective in 18-49 when it offers a long duration of protection and its price is halved.

Vaccinating the HR- group with PCV13 is generally highly cost-effective and even cost-saving depending on price and risk group (see also appendices).

Figure 10: Cost-effectiveness acceptability frontier in the medium risk group, for choices between vaccines (no change, PCV13 and/or PPV23) and age category (18-49 years |50-64 years |65-84 years)



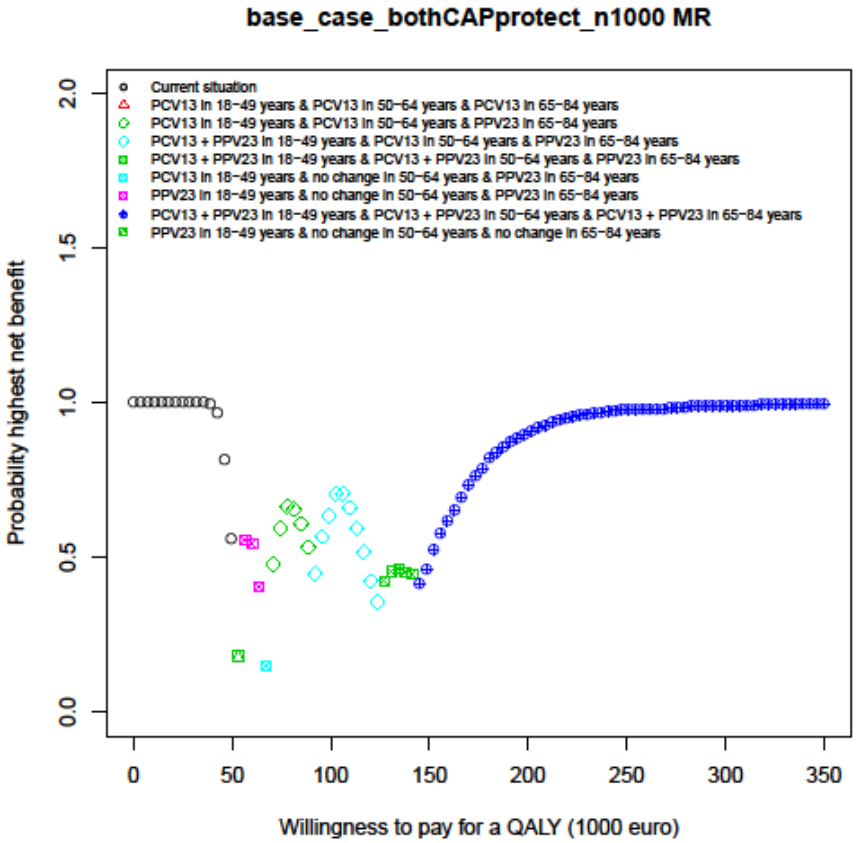
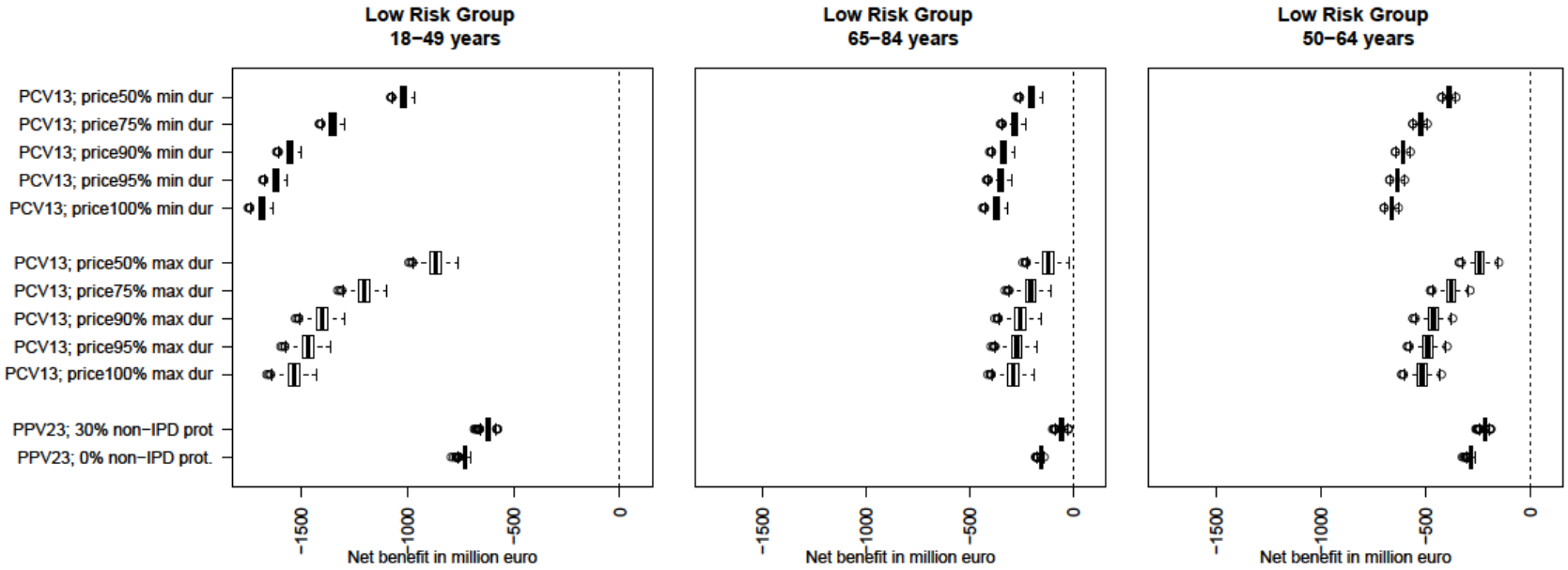


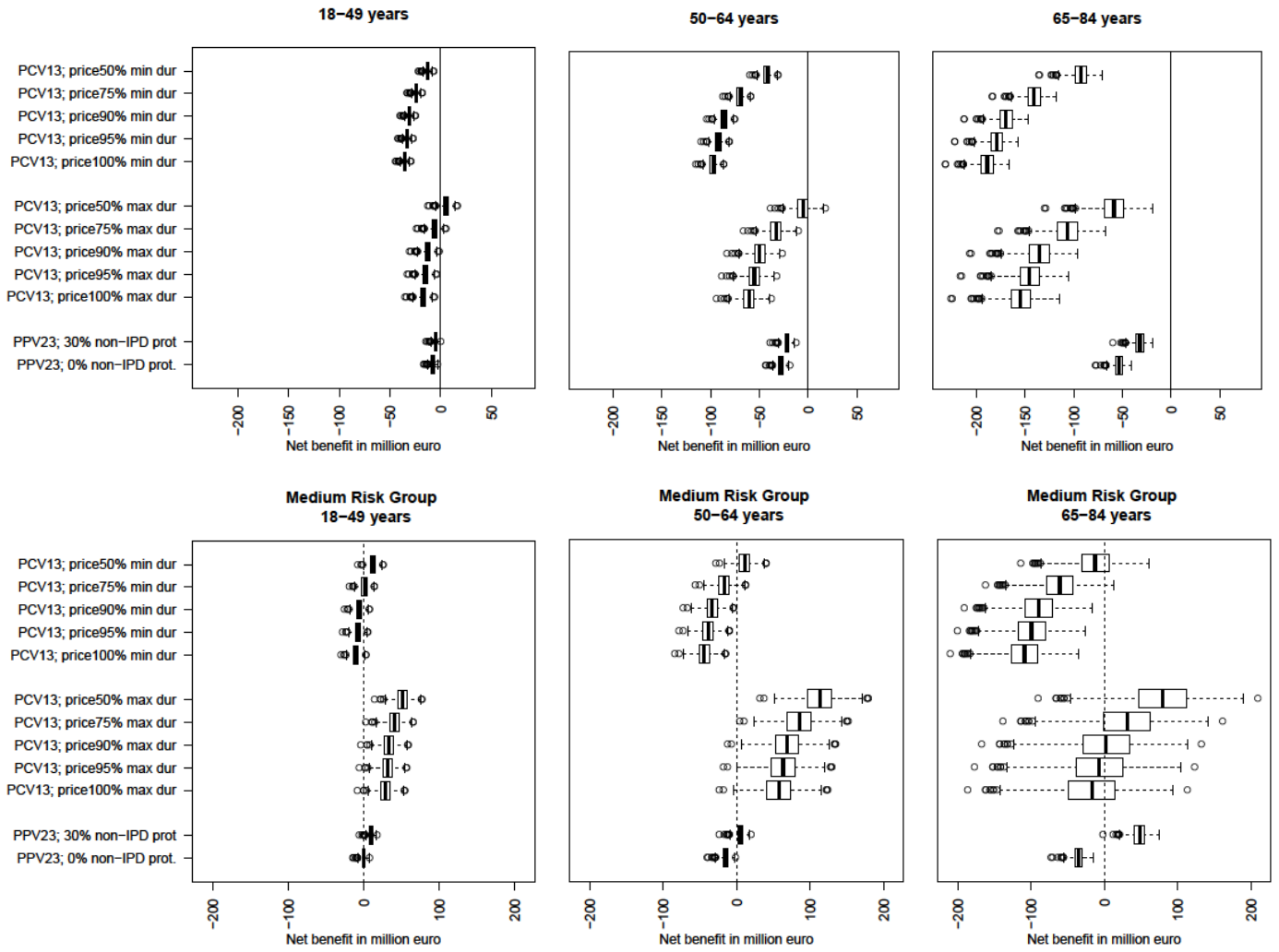
Figure 11: Net benefit box plots of PPV23 use and PCV13 use in the low risk (LR)-group per age group, versus the current situation assuming a willingness to pay of 50,000 euro per QALY gained and high disease burden assumptions [(a)]



LR: immunocompetent, not at higher risk for pneumococcal infection; Price 100% is the current price; Price 90% is 90% of the current PCV13 price etc; non-IPD prot. = no PPV23 efficacy against non-invasive CAP

[(a)] Maximal disease burden: 115% of base case IPD incidence, 125% of base case non-invasive CAP incidence; non-invasive CAP mortality is doubled compared to base case mortality, and includes all pneumonia mortality for 6 months post-hospitalisation; assuming the same PCV13 VE across risk groups

Figure 12: Net benefit box plots of PPV23 use and PCV13 use in MR-group per age group, versus the current situation assuming a willingness to pay of 50,000 euro per QALY gained comparing minimal[(a)] (top) and maximal[(b)] (bottom) disease burden assumptions



MR immunocompetent, at higher risk for pneumococcal infection; Price 100% is the current price; Price 90% is 90% of the current PCV13 price etc; non-IPD prot. = no PPV23 efficacy against non-invasive CAP;

[(a)] Minimal disease burden: 85% of base case IPD incidence, 75% of base case non-invasive CAP incidence; Minimum hospitalised pneumonia mortality non-invasive CAP mortality is reduced by one third (-1/3) compared to base case mortality and excludes all pneumonia mortality for 6 months post-hospitalisation;

[(b)] Maximal disease burden: 115% of base case IPD incidence, 125% of base case non-invasive CAP incidence; non-invasive CAP mortality is doubled compared to base case mortality, and includes all pneumonia mortality for 6 months post-hospitalisation.

3.5 Budget impact analysis

We also present a budget-impact analysis of the various vaccination strategies, as shown in Table 9 (assuming 0% PPV23 vaccine efficacy against vaccine type non-invasive CAP) and

Table 10 (assuming 30% PPV23 vaccine efficacy against vaccine type non-invasive CAP).

Table 9: Vaccination costs, treatment costs avoided, return on investment and direct net benefits over 5 and 10 year periods implementing different vaccination strategies versus the current situation assuming **0% PPV23 efficacy** against non-invasive CAP. Result of 1,000 simulation summarised as mean (median)[95% interval]

Vaccination strategy	Medical costs over 5 years	Medical costs over 10 years	Vaccination costs over 5 years	Vaccination costs over 10 years	Return on Investment over 5 years	Return on Investment over 10 years	Direct net benefits over 5 years	Direct net benefits over 10 years
SC1: PCV13 in 65-84	16,635,821	32,262,588	-770,143,515	-894,655,107	2.2	3.6	-753,507,695	-862,392,519
SC2: PPV23 in 65-84	21,158,078	25,620,608	-317,574,563	-365,044,135	6.7	7.0	-296,416,484	-339,423,527
SC3: (PCV13 + PPV23) in 65-84	32,046,929	50,543,555	-1,095,894,908	-1,276,494,557	2.9	4.0	-1,063,847,978	-1,225,951,002
SC4: PCV13 in MR 18-84	18,139,251	30,884,449	-429,961,470	-430,920,617	4.2	7.2	-411,822,219	-400,036,167
SC5: (PCV13 + PPV23) in MR 18-84	30,964,517	43,811,781	-599,035,956	-601,016,164	5.2	7.3	-568,071,438	-557,204,383
SC6: (PCV13 + PPV23) in 65-84 & (PCV13 + PPV23) in MR 18-64	47,499,969	73,494,104	-1,364,031,499	-1,546,611,356	3.5	4.8	-1,316,531,530	-1,473,117,252
SC11: PPV23 in MR 18-84 & PCV13+PPV23 in HR 18-84	32,987,315	43,457,973	-199,184,122	-197,899,141	16.6	22.0	-166,196,806	-154,441,168

It shows that the vaccination costs are high and by far outweigh the benefits in terms of avoided treatment costs to the extent that the return on investment is for all feasible strategies lower than 10% (the exception is strategy 11, SC11, shown here only for illustration). The net benefits are negative (ie net costs) and amount to roughly €300 million to €1.5 billion, depending on the strategy more than on the length of the time horizon considered over which benefits accrue. Also the influence of assuming PPV23 protects against non-invasive CAP is secondary to the sheer magnitude of the vaccination effort, when it comes to estimating this purely monetary budgetary impact.

Table 10: Vaccination costs, treatment costs avoided, return on investment and direct net benefits over 5 and 10 year periods implementing different vaccination strategies versus the current situation assuming **30% PPV23 efficacy** against non-invasive CAP. Result of 1,000 simulations (only mean shown)

scenario	Medical costs over 5 years	Medical costs over 10 years	Vaccination costs over 5 years	Vaccination costs over 10 years	Return on Investment over 5 years	Return on Investment over 10 years	Direct net benefits over 5 years	Direct net benefits over 10 years
SC1: PCV13 in 65-84	16,635,821	32,262,588	-770,143,515	-894,655,107	2.2	3.6	-753,507,695	-862,392,519
SC2: PPV23 in 65-84	9,827,791	12,235,923	-317,574,563	-365,044,135	3.1	3.4	-307,746,771	-352,808,212
SC3: (PCV13 + PPV23) in 65-84	23,721,542	40,878,865	-1,095,894,908	-1,276,494,557	2.2	3.2	-1,072,173,365	-1,235,615,691
SC4: PCV13 in MR 18-84	18,139,251	30,884,450	-429,961,470	-430,920,617	4.2	7.2	-411,822,219	-400,036,167
SC5: (PCV13 + PPV23) in MR 18-84	24,380,401	37,196,585	-599,035,956	-601,016,164	4.1	6.2	-574,655,554	-563,819,579
SC6: (PCV13 + PPV23) in 65-84 & (PCV13 + PPV23) in MR 18-64	37,132,416	61,756,169	-1,364,031,499	-1,546,611,356	2.7	4.0	-1,326,899,083	-1,484,855,187
SC11: PPV23 in MR 18-84 & PCV13+PPV23 in HR 18-84	23,208,804	33,628,725	-199,184,122	-197,899,141	11.7	17.0	-175,975,318	-164,270,416

4 Executive summary

Pneumococcal infection can cause severe invasive (IPD: meningitis and sepsis, pneumonia with bacteraemia) and non-invasive diseases (otitis media, non-invasive pneumonia). Invasive diseases have a high mortality in infants, the elderly and particular risk groups. Currently two vaccines are on the market in France to prevent the risk of severe pneumococcal disease. The first, a 23-valent polysaccharide vaccine (marketed as Pneumo23, henceforth called PPV23), is weakly immunogenic and provides protection against invasive pneumococcal disease (IPD). Its effectiveness against non-invasive IPD has not been shown conclusively. The 13-valent conjugate pneumococcal vaccine, marketed as Prevenar13 (henceforth called PCV13), is the second vaccine available for pneumococcal disease prevention. It provides protection against 13 serotypes. The previous conjugate vaccines used in the childhood vaccination program in France contained fewer serotypes (PCV7). PCV13's efficacy against vaccine-type IPD and pneumonia in the elderly has been investigated in the CAPITA study.

We developed a static deterministic state-transition model that describes transitions over time between relevant pneumococcal health states for the entire adult population in France, stratified by age and risk group until the last vaccinated age cohort has died. The model was used to project results for new vaccination strategies that are being considered, as well as for the current situation.

The current pneumococcal vaccination strategy in France consists of vaccinating all people at high risk of severe pneumococcal disease, irrespective of age, with PPV23, except for infants and immunosuppressed individuals who are administered PCV13 and the combination of PCV13 and PPV23, respectively. Given the increased incidence and case-fatality with age, elderly pneumococcal vaccination programs might reduce the high pneumococcal disease burden.

In this report, we assess the effectiveness and cost-effectiveness of PPV23 and/or PCV13 vaccination in 18-84 year olds, depending on the vaccine recipients' risk profile. In the absence of data showing protection from either of these vaccines in elderly people 85 years of age or older, this oldest age group was not considered as a possible target for vaccination. We considered the following risk groups:

- Low Risk (LR): immunocompetent and at low risk for pneumococcal infection;
- Medium Risk (MR): immunocompetent and at high risk for pneumococcal infection;
- High Risk (HR): immunosuppressed and at high risk for pneumococcal infection.

The following strategies were considered feasible and acceptable in the current context:

1. Current situation, i.e. vaccinating (at relatively low coverage) adult risk groups aged 18-84 years using PPV23 for immunocompetent (MR) and both PCV13 and PPV23 for immunosuppressed (HR) individuals at risk (SC0)
2. Vaccinating the elderly 65-84 years of age irrespective of risk group with PCV13 (SC1)
3. Vaccinating the elderly 65-84 years of age irrespective of risk group with PPV23 (SC2)

4. Vaccinating the elderly 65-84 years of age irrespective of risk group with the combination of PCV13 and PPV23 (SC3)
5. Vaccinating all adult (18-84 years) MR individuals with PCV13 (SC4)
6. Vaccinating all adult (18-84 years) MR individuals with the combination of PCV13 and PPV23 (SC5)
7. Vaccinating all adult (18-84 years) MR individuals and the elderly 65-84 years of age irrespective of risk group, with the combination of PCV13 and PPV23 (SC6)

Each of these strategies was modelled building up from the current situation. That is, changes were modelled in the risk and age groups as defined by the strategies, but in age and risk groups where a strategy was not specifically different from the current situation, the current situation was assumed to be maintained (SC0). Furthermore, in the first 3 years, we modelled for each of these strategies a catch-up phase during which the uptake increases linearly to 60% in an entire age group, after which the uptake was modelled to remain at 60% for the cohorts ageing into an age group (in other words: catch-up vaccination was assumed to last for three years, after which only new vaccine recipients at the lowest end of an age group would receive the vaccine).

The annual pneumococcal disease and cost burden is expected to amount in 2017 to 320 meningitis cases, 71,242 pneumonia cases treated in ambulatory care and 14,743 pneumonia hospitalisations, leading to about 1,607 deaths and 24,700 Quality Adjusted Life Years (QALYs) lost in the French population between 18 and 84 years of age (48 million people), costing about €151 million (discounted) in treatment. A substantial part of this burden occurs in the MR group between 65 and 84 years of age where we expect 3190 hospitalisations, 573 deaths and 5179 QALYs lost in a population of 3.6 million people.

The current recommendation was found to be the most cost-effective strategy. If it would be feasible to increase the coverage of the current vaccines in the currently targeted age and risk groups, that would be the most cost-effective option.

However, since substantial improvements in coverage were not considered feasible without additional changes to recommendations, the identification of the most efficient option focuses on the other options depends largely on the assumed PPV23 efficacy against non-invasive CAP, and the duration of protection offered by PCV13:

- **If PPV23 has 0% vaccine efficacy against vaccine type non-invasive CAP:** Strategies SC1, SC2 and SC3 are not cost-effective, as they are dominated by more effective and more cost-effective strategies. Strategy SC4 (PCV13 in MR: 18-84y) seems relatively cost-effective at about €80000 per QALY gained, and adding PPV23 in this MR group 18-84y (SC5) seems expensive relative to the additional health gains (ca €165000 per QALY gained). At €186000 per QALY gained, the maximum strategy SC6 (PCV13+PPV23 in all 65-84, and in MR 18-64) has a cost-effectiveness that is comparable to that of SC5.
- **If PPV23 has 30% vaccine efficacy against vaccine type non-invasive CAP:** Strategies SC1, SC2 and SC3 are still not cost-effective, as they remain dominated by more effective and more cost-effective strategies. Strategy SC4 remains the the same as above, but SC5 becomes more acceptable at €96000 per QALY gained, and the gap between SC5 and SC6 is now much wider (ca €156000 per QALY gained)

These strategies require many people to be vaccinated, particularly during the catch-up phase, which makes them expensive already early in the programme: SC4 is expected to cost (net costs, so accounting for avoided treatment costs) about €412 million, SC5 €568 million, and SC6 €1326 million over the next 5 years. This amount is especially high early in the program (catch-up), and the difference, in terms of net costs and return on Investment, between a 5 year and 10 year time horizon or between PPV23 having 0% or 30% effectiveness against non-invasive CAP, remain relatively limited

We also investigated the potential cost-effectiveness looking at each risk group as a separate potential target, while assuming that the willingness to pay amounts to €50,000 per QALY gained:

- Vaccinating the **LR-group** with PCV13 or PPV23 is cost-**in**effective, even when assuming a high ("maximal") pneumococcal disease burden, 50% PCV13 price reduction and 30% PPV23 efficacy against non-invasive CAP.
- PPV23 is only borderline cost-effective in the **MR-group** between 18 and 49 years of age, under maximal disease burden assumptions. For those aged over 50 years, it should also be effective against non-invasive CAP for it to be beneficial. Under maximal disease burden assumptions, PCV13 is more beneficial (with each QALY valued at €50,000) in 18-64-year-olds, but only if it offers a longer than baseline PCV13 duration of vaccine protection. In 65-84 year olds, PCV13 requires a long duration of protection and a 25% price reduction to achieve positive net benefits and a 50% price reduction to be more beneficial than PPV23. When the assumed disease burden is minimal, PCV13 can only be cost-effective in 18-49 when it offers a long duration of protection and its price is halved.
- Vaccinating the **HR- group** with PCV13 is generally highly cost-effective and even cost-saving depending on price and risk group.

As shown in extensive sensitivity analyses, the key influential drivers of our analyses are:

- PCV13 duration of protection, which is as yet uncertain as the period of follow-up in the CAPITA study was limited to about 4 years.
- PPV23 non-invasive CAP protection for which there is some evidence
- The pivotal assumption of PCV13 protection in the HR group, which is as yet undemonstrated in clinical trials.

The disease burden is also influential for the results, but the choice between both vaccines, depends in the first place on the three assumptions listed above. For instance, a 25% increase in the incidence of non-invasive pneumonia does not change the overall conclusions, although it makes PCV13 containing strategies more attractive if PPV23 is assumed not to protect against non-invasive pneumonia (and vice versa), while the prioritisation between the vaccines depends also heavily on the other two key assumptions listed above.

These and many other input data and assumptions are extensively tested in sensitivity analyses shown in three supplementary files accompanying this report.

A strength of our analysis, is that we take risk group differences into account and explore many different vaccination options, in consultation with French experts in vaccinology, immunology, pneumology, epidemiology and public health.

Nonetheless, as with any model, there are a number of limitations of the analytical approach: we do not model switching between risk groups over time. So the risk group membership does not change over time. This assumption may underestimate the benefits of vaccinating LR group members, who transition over time to the MR or HR group, while the vaccine still protects. Another conservative assumption is that we use a static model, and therefore ignore the indirect risk reduction in unvaccinated close contacts of vaccine recipients. Since adults, and especially elderly adults are not core transmitters of pneumococcus (they have drier mucus, and tend to have fewer and less intensive social contacts than children), the impact of this simplifying assumption is likely small, given the relatively moderate uptake (although catch-up vaccination was assumed to reach a large part of the adult population). Both these assumptions affect PCV13 more than PPV23. Pneumococcal conjugate vaccines, including PCV13, have been shown to induce herd immunity through high coverage childhood vaccination, whereas polysaccharide vaccines, such as PPV23 do not impact nasopharyngal carriage of pneumococci, and therefore are likely to result in lower indirect effects (only through a reduction in infectivity via symptom reduction, not through a reduction in carriage). Furthermore PCV13 induces a longer duration of protection than PPV23 (which was accounted for), and thus PCV13 may benefit vaccine recipients who switch to a higher risk group over time more than PPV23. This latter aspect was however, to some extent explored in sensitivity analyses by increasing the pneumococcal disease burden.

The reason why PCV13 containing strategies can be cost-effective is determined by the pivotal assumption that PCV13 protects vaccine recipients of the HR group. Yet to date there is no direct empirical evidence to this effect, and the magnitude of the effectiveness of PCV13 in this group was an assumption considered intuitively plausible by the expert group. This assumption is highly influential throughout the analyses of any strategy that contains a component of HR group vaccination. Another related important consideration is that waning of efficacy over time since vaccination, is assumed independent of the risk group. Yet it seems plausible that waning evolves more quickly in vaccine recipients belonging to higher risk groups.

A final assumption that affects the results for both vaccines (and particularly may overestimate the benefits of PCV13), is that we project the evolution of vaccine serotype coverage to saturate to a minimum but not to decline to zero. That is, the PCV13 vaccine types are assumed to remain at a low level throughout time, and are not assumed to disappear completely under the influence of the ongoing PCV13 childhood programme. This is the more influential the longer the assumed duration of protection for PCV13.

In sum, expanding the current recommendation, especially with vaccination strategies aimed at MR and HR groups can be cost-effective given pivotal assumptions on effectiveness hold, and that policy makers are willing to pay €50,000 to €150,000 for a QALY. The likelihood of a cost-effective decision is heavily influenced by the price paid for PCV13 and PPV23. Potential price reductions are important drivers for an attractive cost-effectiveness of both vaccines, and the price difference between them also affects the optimal choice of vaccine. The duration of protection of PCV13 and the evolution of

the serotype circulation among adults in France need to be carefully followed-up, and may change these conclusions, for better or for worse.

5 Acknowledgements

We thank the pneumococcal working group of “le Haut Conseil de la Santé Publique” for stimulating discussions and thoughtful guidance for these analyses.

We are indebted to Prof Gérard de Pouvourville (ESSEC), Drs Serge Gilbert and Henry Partouche (Faculté de Médecine Paris Descartes) for giving us access to unpublished data on incidence and cost data for community acquired pneumonia and quality of life and cost data for hospitalized pneumococcal patients in France.

We thank the Flemish Supercomputer Center (VSC), funded by the Research Foundation - Flanders (FWO) and the Flemish Government (department EWI) to provide computational resources and services. Dr Lander Willem is supported by the FWO, project G043815N.

6 Potential conflicts of interest

A university chair in Philippe Beutels’ centre at the University of Antwerp was supported in 2009-2016 by a gift from Pfizer. There is no connection between either Pfizer or the research of the chair holder (Niel Hens) and this report.

7 Overview of supplementary material

Supplement 1: Univariate sensitivity analyses: cost-effectiveness frontiers and cost-effectiveness acceptability frontiers.

Supplement 2: Multivariate sensitivity analyses: cost-effectiveness frontiers and cost-effectiveness acceptability frontiers.

Supplement 3: Multivariate sensitivity analyses: net benefit boxplots

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9 Appendix 1: Vaccination strategies, including theoretical options

9.1 Specification of all vaccination strategies, including theoretical, implausible ones

Table 11:Theoretical and plausible vaccination strategies defined by vaccine choice per age and risk group combination

Vaccination strategy	LR	MR	HR	Fixed vaccination program cost (per catch-up[1] year)
SC0 (reference strategy)	no vaccination	2% PPV23 per year in 18-84 year olds	2% (PCV13+PPV23) per year in 18-84 year olds	€0
SC1	**PCV13** 65-84 (catch-up) 65 (after catch-up)	**PCV13** 65-84 (catch-up 3) 65 (after catch-up)	**PCV13** 65-84 (catch-up) 65 (after catch-up)	€400,000
SC2	**PPV23** 65-84 (catch-up) 65 (after catch-up)	**PPV23** 65-84 (catch-up) 65 (after catch-up)	**PPV23** 65-84 (catch-up) 65 (after catch-up)	**€800,000**
SC3	**(PCV13+PPV23)** 65-84 (catch-up) 65 (after catch-up)	**(PCV13+PPV23)** 65-84 (catch-up) 65 (after catch-up)	**(PCV13+PPV23)** 65-84 (catch-up) 65 (after catch-up)	€400,000
SC4	no change vs SC0	**PCV13** 18-84 (catch-up) 18 (after catch-up)	no change vs SC0	€400,000
SC5	no change vs SC0	**(PCV13+PPV23)** 18-84 (catch-up) 18 (after catch-up)	no change vs SC0	€400,000
SC6 (=SC3+SC5)	**(PCV13+PPV23)** 65-84 (catch-up) 65 (after catch-up)	**(PCV13+PPV23)** 18-84 (catch-up) 18+65 (after catch-up)	**(PCV13+PPV23)** 65-84 (catch-up) 65 (after catch-up)	€400,000
SC7	no change vs SC0	**PCV13**	no change vs SC0	€400,000

		18-49 (catch-up) 18 (after catch-up)		
SC8	no change vs SC0	**PCV13** 50-64 (catch-up) 50 (after catch-up)	no change vs SC0	€400,000
SC9	no change vs SC0	**(PCV13+PPV23)** 18-49 (catch-up) 18 (after catch-up)	no change vs SC0	€400,000
SC10	no change vs SC0	**(PCV13+PPV23)** 50-64 (catch-up) 50 (after catch-up)	no change vs SC0	€400,000
SC11	no change vs SC0	**PPV23** 18-84 (catch-up) 18 (after catch-up)	**(PCV13+PPV23)** 18-84 (catch-up) 18 (after catch-up)	**€800,000**
SC12	no change vs SC0	**PPV23** 18-49 (catch-up) 18 (after catch-up)	**(PCV13+PPV23)** 18-49 (catch-up) 18 (after catch-up)	**€800,000**
SC13	no change	**PPV23** 50-64 (catch-up) 50 (after catch-up)	**(PCV13+PPV23)** 50-64 (catch-up) 50 (after catch-up)	**€800,000**

LR: immunocompetent, not at higher risk for pneumococcal infection;
MR immunocompetent, at higher risk for pneumococcal infection
HR: immunosuppressed, at higher risk

[1]Catch-up years (2017-2019): we vaccinate over 3 years a whole age interval at 20% per year; after the catch up period (2020-2026) we vaccinate only people coming into the cohort at a baseline coverage of 60%.

[3] No change with respect to the current situation for that risk group

9.2 Results including theoretical vaccination strategies

Table 12: Avoided burden and cost-effectiveness of all plausible and implausible (theoretical) vaccination strategies versus the current situation, assuming **0% PPV23 efficacy** against non-invasive CAP: (mean(median) [95% interval] based on 1000 simulations, rounded to the nearest unit)

Avoided:	SC1: PCV13 in 65-84	SC2: PPV23 in 65-84	SC3: (PCV13 + PPV23) in 65-84	SC4: PCV13 in at risk immuno comp. 18-84	SC5: (PCV13 + PPV23) in at risk immuno comp. 18-84	SC6: (PCV13 + PPV23) in 65-84 & (PCV13 + PPV23) in at risk immunocomp. 18-64	SC7: PCV13 in at risk immuno comp. 18-49	SC8: PCV13 in at risk immuno comp. 50-64	SC9: (PCV13 + PPV23) in at risk immuno comp. 18-49	SC10: (PCV13 + PPV23) in at risk immuno comp. 50-64	SC11: PPV23 in at risk immunocomp. 18-84 & PCV13+PPV23 in at risk immmunodepr. 18-84	SC12: PPV23 in at risk immunocomp. 18-49 & PCV13+PPV23 in at risk immmunosuppr. 18-49	SC13: PPV23 in at risk immunocomp. 50-64 & PCV13+PPV23 in at risk immmunosuppr. 50-64
Meningitis cases	140(144)[76;182]	97(97)[71;117]	208(211)[153;250]	115(117)[72;143]	161(163)[122;191]	307(310)[233;363]	28(29)[21;34]	56(57)[41;67]	36(37)[29;42]	78(78)[62;90]	186(187)[148;218]	56(56)[45;65]	109(109)[88;126]
Pneumococcal CAP hospitalisations	6,502(6,532)[3,857;8,840]	1,389(1,397)[1,085;1,651]	7,415(7,404)[5,180;9,648]	4,347(4,378)[2,774;5,763]	4,855(4,859)[3,448;6,235]	10,005(10,025)[7,180;12,816]	814(813)[614;1,012]	1,907(1,905)[1,435;2,378]	873(872)[674;1,071]	2,068(2,070)[1,592;2,538]	4,621(4,637)[3,680;5,567]	1,398(1,397)[1,110;1,688]	2,696(2,695)[2,152;3,241]
Outpatient pneumococcal CAP cases	17,804(17,828)[8,840;25,402]	159(157)[89;228]	17,893(17,832)[9,812;25,402]	18,841(18,925)[10,816;26,030]	18,891(18,925)[11,272;26,030]	30,194(30,239)[17,995;41,615]	4,014(4,019)[2,699;5,282]	9,945(9,956)[6,687;13,087]	4,014(4,019)[2,699;5,282]	9,945(9,956)[6,687;13,087]	2,875(2,872)[1,990;3,786]	1,117(1,115)[801;1,446]	1,629(1,625)[1,166;2,108]
Deaths meningitis	37(39)[17;51]	23(23)[17;28]	53(54)[36;66]	24(25)[12;31]	33(34)[23;40]	68(69)[48;83]	3(3)[2;3]	10(10)[7;12]	3(3)[3;4]	14(14)[11;16]	33(33)[26;39]	6(6)[5;7]	19(19)[15;22]
Pneumonia deaths	1,068(1,076)[658;1,435]	231(232)[179;274]	1,221(1,220)[875;1,572]	614(620)[404;808]	720(722)[539;903]	1,494(1,495)[1,103;1,890]	54(55)[44;64]	211(211)[166;256]	64(64)[53;73]	237(237)[192;280]	508(509)[420;590]	90(90)[76;103]	244(245)[204;280]
Total deaths	1,105(1,113)[693;1,478]	254(255)[196;301]	1,274(1,274)[926;1,632]	638(644)[422;836]	753(756)[561;941]	1,562(1,562)[1,171;1,965]	57(58)[46;68]	221(222)[175;267]	67(67)[56;77]	251(251)[205;295]	541(543)[447;627]	96(96)[81;109]	263(264)[221;301]
Undiscounted total life years lost	14,128(14,207)[9,523;18,447]	3,560(3,586)[2,778;4,240]	16,463(16,522)[12,260;20,634]	10,505(10,570)[7,660;13,140]	12,535(12,564)[10,037;15,057]	23,732(23,824)[18,420;28,938]	2,293(2,304)[1,841;2,707]	4,612(4,619)[3,669;5,538]	2,723(2,737)[2,271;3,112]	5,407(5,421)[4,469;6,294]	11,163(11,186)[9,396;12,751]	3,621(3,636)[3,044;4,127]	5,985(5,995)[5,087;6,802]
Discounted total life years	8,347(8,389)[5,49	2,383(2,399)[1,84	9,947(9,983)[7,352;1	5,816(5,850)[4,15	7,132(7,151)[5,64	13,537(13,580)[10,445;16,	901(906)[724;1,	2,387(2,390)[1,89	1,097(1,103)[920	2,842(2,846)[2,35	6,091(6,107)[5,073;6,968]	1,478(1,484)[1,246;1,681]	3,073(3,077)[2,614;3,488]

lost	5;10,983]	1;2,844]	2,492]	3;7,382]	2;8,614]	650]	063]	8;2,868]	;1,250]	3;3,303]				
Undiscounted QALY lost	10,248(10,259)[6,931;13,468]	2,678(2,689)[2,079;3,198]	11,999(11,944)[9,098;15,246]	8,109(8,106)[6,070;10,193]	9,682(9,688)[7,769;11,720]	18,021(18,023)[14,120;22,231]	2,049(2,064)[1,641;2,417]	3,659(3,664)[2,921;4,412]	2,438(2,455)[2,035;2,792]	4,316(4,321)[3,578;5,057]	9,202(9,220)[7,748;10,647]	3,280(3,296)[2,763;3,761]	4,980(4,983)[4,227;5,754]
Discounted QALY lost	6,266(6,251)[4,153;8,350]	1,837(1,848)[1,416;2,203]	7,493(7,464)[5,600;9,566]	4,617(4,612)[3,368;5,875]	5,639(5,629)[4,456;6,860]	10,606(10,583)[8,249;13,182]	866(872)[693;1,031]	1,991(1,987)[1,588;2,416]	1,050(1,056)[878;1,209]	2,377(2,383)[1,967;2,796]	5,198(5,196)[4,332;6,054]	1,443(1,449)[1,195;1,676]	2,701(2,700)[2,276;3,138]
Direct health care costs undiscounted (€)	62,886,524(63,310,308)[38,596,222;85,549,064]	15,859,952(15,895,923)[12,061,113;19,520,315]	73,332,520(73,216,127)[53,009,209;95,732,686]	50,237,878(50,445,836)[33,615,561;65,339,038]	57,586,603(57,674,344)[41,866,824;72,749,679]	106,772,526(106,863,958)[79,582,355;134,656,319]	10,821,458(10,842,533)[8,291,869;13,358,429]	23,149,839(23,143,727)[17,431,808;28,818,305]	12,110,401(12,130,844)[9,563,345;14,600,407]	25,879,720(25,847,802)[20,123,218;31,828,924]	52,112,252(51,911,901)[41,721,543;63,061,791]	16,628,897(16,627,460)[13,515,707;20,171,670]	29,843,036(29,829,676)[24,071,229;36,269,046]
Direct health care costs discounted (€)	46,230,231(46,481,240)[27,610,993;63,419,992]	13,263,769(13,277,772)[10,060,653;16,365,670]	55,173,488(55,087,154)[39,841,153;71,906,573]	38,390,508(38,484,150)[25,319,181;50,286,829]	44,722,395(44,774,994)[32,344,288;56,607,940]	80,394,744(80,481,901)[59,177,870;101,772,715]	7,640,541(7,649,766)[5,768,143;9,561,514]	17,264,589(17,238,438)[12,872,614;21,635,517]	8,550,464(8,560,906)[6,618,046;10,513,197]	19,448,212(19,416,636)[14,999,296;24,012,383]	40,036,252(39,829,045)[31,891,737;48,690,970]	11,344,115(11,312,105)[9,099,006;13,943,151]	21,798,765(21,784,067)[17,508,583;26,572,444]
Direct vaccination costs (vaccine program, administration and purchase) undiscounted	-958,659,852(-958,659,852)[-958,659,852;-958,659,852]	-389,969,119(-389,969,119)[-389,969,119;-389,969,119]	-1,368,876,796(-1,368,876,796)[-1,368,876,796;-1,368,876,796]	-441,157,114(-441,157,114)[-441,157,114;-441,157,114]	-615,572,505(-615,572,505)[-615,572,505;-615,572,505]	-1,645,906,183(-1,645,906,183)[-1,645,906,183;-1,645,906,183]	-59,535,651(-59,535,651)[-59,535,651;-59,535,651]	-161,228,777(-161,228,777)[-161,228,777;-161,228,777]	-83,688,667(-83,688,667)[-83,688,667;-83,688,667]	-227,013,545(-227,013,545)[-227,013,545;-227,013,545]	-201,903,442(-201,903,442)[-201,903,442;-201,903,442]	-30,812,055(-30,812,055)[-30,812,055;-30,812,055]	-71,982,033(-71,982,033)[-71,982,033;-71,982,033]
Direct vaccination costs (vaccine program, administration and purchase) discounted	-894,655,107(-894,655,107)[-894,655,107;-894,655,107]	-365,044,135(-365,044,135)[-365,044,135;-365,044,135]	-1,276,494,557(-1,276,494,557)[-1,276,494,557;-1,276,494,557]	-430,920,617(-430,920,617)[-430,920,617;-430,920,617]	-601,016,164(-601,016,164)[-601,016,164;-601,016,164]	-1,546,611,356(-1,546,611,356)[-1,546,611,356;-1,546,611,356]	-57,855,972(-57,855,972)[-57,855,972;-57,855,972]	-153,815,665(-153,815,665)[-153,815,665;-153,815,665]	-81,112,281(-81,112,281)[-81,112,281;-81,112,281]	-216,104,868(-216,104,868)[-216,104,868;-216,104,868]	-197,899,140(-197,899,140)[-197,899,140;-197,899,140]	-30,539,539(-30,539,539)[-30,539,539;-30,539,539]	-69,457,984(-69,457,984)[-69,457,984;-69,457,984]

ICER undiscounted	90,124(87,274)[64,926;132,657]	141,709(139,173)[115,897;182,012]	110,038(108,489)[83,705;144,546]	49,256(48,140)[36,852;66,787]	58,390(57,559)[46,447;73,661]	86,657(85,429)[68,078;110,747]	24,067(23,644)[19,273;31,085]	38,246(37,657)[30,041;49,309]	29,603(29,173)[24,767;36,365]	47,034(46,439)[38,653;57,747]	16,433(16,266)[13,306;20,565]	4,384(4,294)[2,9115;6,114]	8,558(8,428)[6,395;11,249]
ICER discounted	140,038(135,406)[100,088;208,785]	194,357(190,388)[158,443;250,604]	166,207(163,784)[126,213;219,900]	87,100(84,941)[64,623;120,059]	100,026(98,787)[79,675;127,382]	140,386(138,464)[109,710;179,464]	58,704(57,709)[47,060;74,444]	69,515(68,558)[54,813;89,093]	69,687(68,855)[58,466;85,063]	83,500(82,493)[68,727;102,105]	30,659(30,384)[24,938;38,185]	13,448(13,187)[10,244;17,389]	17,826(17,630)[13,968;22,680]
Incremental cost per life year gained (undiscounted)	65,427(63,033)[47,439;96,852]	106,521(104,360)[87,663;135,833]	80,227(78,473)[61,762;107,238]	38,075(36,938)[28,525;52,997]	45,128(44,384)[36,168;56,927]	65,843(64,558)[52,097;85,051]	21,507(21,118)[17,196;27,778]	30,341(29,867)[23,946;39,179]	26,500(26,257)[22,217;32,458]	37,544(37,041)[31,187;46,356]	13,540(13,403)[10,992;16,888]	3,968(3,894)[2,648;5,543]	7,115(7,007)[5,339;9,294]
Incremental cost per life year gained (discounted)	105,223(101,022)[75,867;157,472]	149,760(146,633)[123,086;192,632]	125,218(122,401)[96,670;167,789]	69,254(66,977)[51,651;97,721]	79,115(77,766)[63,049;100,759]	110,024(108,087)[86,903;142,514]	56,372(55,442)[45,804;71,790]	57,944(57,081)[46,205;74,146]	66,653(66,011)[56,728;80,430]	69,802(69,050)[58,460;85,457]	26,139(25,862)[21,548;32,055]	13,106(12,881)[10,111;16,777]	15,647(15,470)[12,486;19,716]

LR: immunocompetent, not at higher risk for pneumococcal infection;

MR immunocompetent, at higher risk for pneumococcal infection

HR: immunosuppressed, at higher risk

Table 13: Incremental avoided burden and incremental cost-effectiveness along the cost-effectivenes frontier*, assuming **0% PPV23 efficacy** against non-invasive CAP: (mean(median) [95% interval] based on 1000 simulations, rounded to the nearest unit)

Avoided	SC12: PPV23 in at risk immunocomp. 18-49 & PCV13+PPV23 in at risk immmunosuppr. 18-49 versus current	SC13: PPV23 in at risk immunocomp. 50-64 & PCV13+PPV23 in at risk immmunosuppr. 50-64 versus SC12	SC11: PPV23 in at risk immunocomp. 18-84 & PCV13+PPV23 in at risk immmunodepr. 18-84 versus SC13	SC6: (PCV13 + PPV23) in 65-84 & (PCV13 + PPV23) in at risk immunocomp. 18-64 versus SC11
Meningitis cases	56(56)[45;65]	53(53)[43;61]	78(78)[61;93]	120(123)[80;150]
Pneumococcal CAP hospitalisations	1,398(1,397)[1,110;1,688]	1,298(1,298)[1,048;1,554]	1,925(1,929)[1,514;2,329]	5,384(5,366)[3,459;7,296]
Outpatient pneumococcal CAP cases	1,117(1,115)[801;1,446]	512(511)[366;662]	1,246(1,246)[803;1,691]	27,319(27,371)[15,924;37,808]
Deaths meningitis	6(6)[5;7]	13(13)[11;15]	14(14)[10;17]	35(36)[21;45]
Pneumonia deaths	90(90)[76;103]	154(155)[128;180]	264(265)[211;313]	986(986)[661;1,313]
Total deaths	96(96)[81;109]	168(168)[140;194]	278(279)[222;329]	1,021(1,021)[695;1,355]
Undiscounted total life years lost	3,621(3,636)[3,044;4,127]	2,364(2,370)[1,976;2,746]	5,178(5,198)[4,271;5,979]	12,569(12,582)[8,493;16,564]
Discounted total life years lost	1,478(1,484)[1,246;1,681]	1,594(1,596)[1,347;1,829]	3,019(3,031)[2,475;3,509]	7,446(7,453)[5,058;9,830]
Undiscounted QALY lost	3,280(3,296)[2,763;3,761]	1,699(1,691)[1,393;2,027]	4,222(4,237)[3,506;4,906]	8,819(8,829)[5,999;11,728]
Discounted QALY lost	1,443(1,449)[1,195;1,676]	1,257(1,251)[1,047;1,482]	2,497(2,501)[2,050;2,951]	5,408(5,410)[3,672;7,246]
Direct health care costs undiscounted (€)	16,628,897(16,627,460)[13,515,707;20,171,670]	13,214,139(13,167,028)[10,376,980;16,211,373]	22,269,216(22,104,644)[17,569,411;27,243,489]	54,660,274(54,821,344)[34,933,023;73,410,467]
Direct health care costs discounted (€)	11,344,115(11,312,105)[9,099,006;13,943,151]	10,454,650(10,436,827)[8,264,765;12,755,318]	18,237,487(18,092,182)[14,377,508;22,341,942]	40,358,491(40,469,319)[25,511,353;54,556,805]
Direct vaccination costs (vaccine program, administration and purchase) undiscounted	-30,812,055(-30,812,055)[-30,812,055;-30,812,055]	-41,169,979(-41,169,979)[-41,169,979;-41,169,979]	-129,921,409(-129,921,409)[-129,921,409;-129,921,409]	-1,444,002,740(-1,444,002,740)[-1,444,002,740;-1,444,002,740]
Direct vaccination costs (vaccine program, administration and purchase) discounted	-30,539,539(-30,539,539)[-30,539,539;-30,539,539]	-38,918,444(-38,918,444)[-38,918,444;-38,918,444]	-128,441,157(-128,441,157)[-128,441,157;-128,441,157]	-1,348,712,216(-1,348,712,216)[-1,348,712,216;-1,348,712,216]
ICER undiscounted	4,384(4,294)[2,915;6,114]	16,670(16,520)[12,591;21,804]	25,739(25,434)[21,120;31,804]	162,378(157,389)[116,900;234,695]
ICER discounted	13,448(13,187)[10,244;17,389]	22,881(22,667)[17,957;29,131]	44,587(44,140)[36,227;55,465]	249,544(241,831)[179,141;359,854]
Incremental cost per life year gained (undiscounted)	3,968(3,894)[2,648;5,543]	11,957(11,854)[9,243;15,425]	20,986(20,761)[17,325;26,121]	113,847(110,360)[82,861;165,674]
Incremental cost per life year	13,106(12,881)[10,111;16,777]	18,013(17,852)[14,529;22,516]	36,866(36,355)[30,471;45,945]	181,071(175,503)[131,547;261,25

gained (discounted)	2]

* Cost-effectiveness front: We only represent options that from the most cost-effective options, to options which gain more QALYs and are not dominated by other options, i.e. which do gain less QALYs than a less costly vaccination strategy.

LR: immunocompetent, not at higher risk for pneumococcal infection;
MR immunocompetent, at higher risk for pneumococcal infection
HR: immunosuppressed, at higher risk

Table 14: Avoided burden and cost-effectiveness of all plausible and implausible (theoretical) vaccination strategies versus the current situation, assuming **30% PPV23 efficacy** against non-invasive CAP: (mean(median) [95% interval] based on 1000 simulations, rounded to the nearest unit)

Avoided:	SC1: PCV13 in 65-84	SC2: PPV23 in 65-84	SC3: (PCV13 + PPV23) in 65-84	SC4: PCV13 in at risk immuno comp. 18-84	SC5: (PCV13 + PPV23) in at risk immuno comp. 18-84	SC6: (PCV13 + PPV23) in 65-84 & (PCV13 + PPV23) in at risk immunocomp. 18-64	SC7: PCV13 in at risk immuno comp. 18-49	SC8: PCV13 in at risk immuno comp. 50-64	SC9: (PCV13 + PPV23) in at risk immuno comp. 18-49	SC10: (PCV13 + PPV23) in at risk immuno comp. 50-64	SC11: PPV23 in at risk immunocomp. 18-84 & PCV13+PPV23 in at risk immmunodepr. 18-84	SC12: PPV23 in at risk immunocomp. 18-49 & PCV13+PPV23 in at risk immmunosuppr. 18-49	SC13: PPV23 in at risk immunocomp. 50-64 & PCV13+PPV23 in at risk immmunosuppr. 50-64
Meningitis cases	140(144)[76;182]	97(97)[71;117]	208(211)[153;250]	115(117)[72;143]	161(163)[122;191]	307(310)[233;363]	28(29)[21;34]	56(57)[41;67]	36(37)[29;42]	78(78)[62;90]	186(187)[148;218]	56(56)[45;65]	109(109)[88;126]
Pneumococcal CAP hospitalisations	6,502(6,532)[3,857;8,840]	3,111(3,117)[2,669;3,534]	8,667(8,680)[6,535;10,905]	4,347(4,378)[2,774;5,763]	5,546(5,546)[4,233;6,890]	11,459(11,478)[8,777;14,211]	814(813)[614;1,012]	1,907(1,905)[1,435;2,378]	938(938)[743;1,128]	2,233(2,234)[1,767;2,683]	5,624(5,630)[4,624;6,605]	1,518(1,517)[1,224;1,818]	2,997(2,992)[2,441;3,551]
Outpatient pneumococcal CAP cases	17,804(17,828)[8,840;25,402]	8,568(8,568)[7,123;10,064]	23,505(23,491)[16,055;30,887]	18,841(18,925)[10,816;26,030]	22,372(22,383)[15,309;29,294]	37,180(37,180)[25,879;48,147]	4,014(4,019)[2,699;5,282]	9,945(9,956)[6,687;13,087]	4,435(4,433)[3,180;5,659]	11,098(11,103)[8,018;14,119]	8,457(8,460)[7,075;9,787]	1,897(1,895)[1,530;2,265]	3,728(3,727)[3,108;4,354]
Deaths meningitis	37(39)[17;51]	23(23)[17;28]	53(54)[36;66]	24(25)[12;31]	33(34)[23;40]	68(69)[48;83]	3(3)[2;3]	10(10)[7;12]	3(3)[3;4]	14(14)[11;16]	33(33)[26;39]	6(6)[5;7]	19(19)[15;22]
Pneumonia deaths	1,068(1,076)[658;1,435]	512(513)[437;578]	1,422(1,423)[1,091;1,765]	614(620)[404;808]	806(807)[634;986]	1,703(1,706)[1,324;2,093]	54(55)[44;64]	211(211)[166;256]	66(66)[56;75]	244(244)[199;287]	626(626)[534;714]	94(95)[80;107]	257(257)[217;294]
Total deaths	1,105(1,113)[693;1,478]	535(536)[456;606]	1,475(1,476)[1,137;1,824]	638(644)[422;836]	840(841)[659;1,025]	1,771(1,775)[1,390;2,170]	57(58)[46;68]	221(222)[175;267]	69(70)[58;79]	258(258)[212;302]	659(659)[563;751]	100(101)[85;114]	276(277)[234;315]
Undiscounted total life years lost	14,128(14,207)[9,523;18,447]	7,641(7,661)[6,516;8,663]	19,205(19,248)[15,298;23,274]	10,505(10,570)[7,660;13,140]	13,669(13,684)[11,190;16,188]	26,727(26,748)[21,800;31,906]	2,293(2,304)[1,841;2,707]	4,612(4,619)[3,669;5,538]	2,828(2,840)[2,374;3,223]	5,590(5,599)[4,685;6,472]	12,888(12,934)[11,083;14,516]	3,814(3,833)[3,259;4,322]	6,316(6,331)[5,396;7,134]
Discounted total life years lost	8,347(8,389)[5,495;10,983]	5,135(5,146)[4,368;5,828]	11,823(11,852)[9,473;14,282]	5,816(5,850)[4,153;7,382]	7,950(7,964)[6,505;9,425]	15,552(15,591)[12,721;18,580]	901(906)[724;1,063]	2,387(2,390)[1,898;2,868]	1,143(1,148)[967;1,298]	2,949(2,951)[2,474;3,405]	7,302(7,313)[6,276;8,248]	1,565(1,572)[1,332;1,767]	3,267(3,276)[2,807;3,691]
Undiscounted QALY lost	10,248(10,259)[6,931;13,4	5,615(5,625)[4,766;6,436]	13,960(13,929)[10,916;17,111]	8,109(8,106)[6,070;10,193	10,530(10,519)[8,619;12,5	20,206(20,139)[16,309;24,272]	2,049(2,064)[1,641;2,41	3,659(3,664)[2,921;4,412]	2,533(2,545)[2,125;2,890	4,477(4,486)[3,740;5,219]	10,514(10,522)[9,025;11,952]	3,454(3,471)[2,948;3,937]	5,270(5,274)[4,495;6,044]

	68]			]	55]		7]		]					
Discounted QALY lost	6,266(6,251)[4,153;8,350]	3,879(3,886)[3,259;4,459]	8,874(8,858)[6,923;10,822]	4,617(4,612)[3,368;5,875]	6,272(6,267)[5,115;7,508]	12,123(12,092)[9,692;14,551]	866(872)[693;1,031]	1,991(1,987)[1,588;2,416]	1,098(1,103)[924;1,257]	2,481(2,487)[2,067;2,900]	6,155(6,156)[5,254;7,032]	1,532(1,540)[1,283;1,768]	2,890(2,892)[2,455;3,330]
Direct health care costs undiscounted (€)	62,886,524(63,310,308)[38,596,222;85,549,064]	31,242,037(31,287,805)[25,903,375;36,427,424]	84,345,580(84,360,103)[64,078,078;106,086,007]	50,237,878(50,445,836)[33,615,561;65,339,038]	64,502,436(64,395,276)[49,111,225;79,690,708]	119,964,838(119,953,391)[92,519,674;147,976,748]	10,821,458(10,842,533)[8,291,869;13,358,429]	23,149,839(23,143,727)[17,431,808;28,818,305]	12,803,773(12,830,209)[10,228,638;15,356,851]	27,675,592(27,700,401)[21,844,641;33,474,878]	62,375,117(62,229,090)[51,506,911;73,625,155]	17,912,981(17,899,609)[14,719,239;21,489,520]	33,113,261(33,145,650)[27,125,503;39,712,977]
Direct health care costs discounted (€)	46,230,231(46,481,240)[27,610,993;63,419,992]	27,112,457(27,129,095)[22,462,327;31,632,667]	65,140,343(65,154,500)[49,605,993;81,748,062]	38,390,508(38,484,150)[25,319,181;50,286,829]	51,340,349(51,239,610)[39,110,553;63,329,055]	92,437,603(92,481,919)[71,248,341;113,910,217]	7,640,541(7,649,766)[5,768,143;9,561,514]	17,264,589(17,238,438)[12,872,614;21,635,517]	9,204,004(9,226,117)[7,284,111;11,160,196]	21,111,705(21,118,547)[16,588,600;25,518,006]	49,870,003(49,710,297)[41,257,829;58,844,651]	12,559,509(12,520,894)[10,185,464;15,192,742]	24,845,191(24,816,406)[20,291,650;29,869,504]
Direct vaccination costs (vaccine program, administration and purchase) undiscounted	-958,659,852(-958,659,852)[-958,659,852;-958,659,852]	-389,969,119(-389,969,119)[-389,969,119;-389,969,119]	-1,368,876,796(-1,368,876,796)[-1,368,876,796;-1,368,876,796]	-441,157,114(-441,157,114)[-441,157,114;-441,157,114]	-615,572,505(-615,572,505)[-615,572,505;-615,572,505]	-1,645,906,183(-1,645,906,183)[-1,645,906,183;-1,645,906,183]	-59,535,651(-59,535,651)[-59,535,651;-59,535,651]	-161,228,777(-161,228,777)[-161,228,777;-161,228,777]	-83,688,667(-83,688,667)[-83,688,667;-83,688,667]	-227,013,545(-227,013,545)[-227,013,545;-227,013,545]	-201,903,442(-201,903,442)[-201,903,442;-201,903,442]	-30,812,055(-30,812,055)[-30,812,055;-30,812,055]	-71,982,033(-71,982,033)[-71,982,033;-71,982,033]
Direct vaccination costs (vaccine program, administration and purchase) discounted	-894,655,107(-894,655,107)[-894,655,107;-894,655,107]	-365,044,135(-365,044,135)[-365,044,135;-365,044,135]	-1,276,494,557(-1,276,494,557)[-1,276,494,557;-1,276,494,557]	-430,920,617(-430,920,617)[-430,920,617;-430,920,617]	-601,016,164(-601,016,164)[-601,016,164;-601,016,164]	-1,546,611,356(-1,546,611,356)[-1,546,611,356;-1,546,611,356]	-57,855,972(-57,855,972)[-57,855,972;-57,855,972]	-153,815,665(-153,815,665)[-153,815,665;-153,815,665]	-81,112,281(-81,112,281)[-81,112,281;-81,112,281]	-216,104,868(-216,104,868)[-216,104,868;-216,104,868]	-197,899,140(-197,899,140)[-197,899,140;-197,899,140]	-30,539,539(-30,539,539)[-30,539,539;-30,539,539]	-69,457,984(-69,457,984)[-69,457,984;-69,457,984]
ICER undiscounted	90,124(87,274)[64,926;132,657]	64,290(63,736)[55,053;76,367]	93,248(92,165)[73,814;119,696]	49,256(48,140)[36,852;66,787]	52,896(52,355)[42,986;65,585]	76,359(75,710)[61,593;95,153]	24,067(23,644)[19,273;31,085]	38,246(37,657)[30,041;49,309]	28,204(27,829)[23,691;34,360]	44,908(44,454)[37,211;54,807]	13,379(13,249)[10,859;16,615]	3,785(3,703)[2,429;5,352]	7,457(7,329)[5,499;9,862]

ICER discounted	140,038(135,406)[100,088;208,785]	87,681(86,927)[74,766;104,840]	138,331(136,768)[110,204;177,229]	87,100(84,941)[64,623;120,059]	88,591(87,815)[72,023;109,928]	121,313(120,310)[98,472;152,002]	58,704(57,709)[47,060;74,444]	69,515(68,558)[54,813;89,093]	66,002(65,280)[55,808;79,811]	79,261(78,353)[65,938;96,247]	24,238(24,018)[20,000;29,582]	11,859(11,642)[8,970;15,254]	15,586(15,357)[12,233;19,829]
Incremental cost per life year gained (undiscounted)	65,427(63,033)[47,439;96,852]	47,215(46,773)[40,945;55,711]	67,778(66,730)[54,268;85,115]	38,075(36,938)[28,525;52,997]	40,761(40,292)[33,142;50,509]	57,743(57,037)[46,893;71,235]	21,507(21,118)[17,196;27,778]	30,341(29,867)[23,946;39,179]	25,256(25,027)[21,311;30,709]	35,964(35,573)[29,960;43,888]	10,909(10,822)[8,916;13,474]	3,426(3,371)[2,188;4,871]	6,218(6,126)[4,557;8,189]
Incremental cost per life year gained (discounted)	105,223(101,022)[75,867;157,472]	66,187(65,604)[57,399;78,253]	103,781(102,133)[83,568;129,490]	69,254(66,977)[51,651;97,721]	69,887(69,134)[57,120;86,544]	94,555(93,204)[77,246;115,956]	56,372(55,442)[45,804;71,790]	57,944(57,081)[46,205;74,146]	63,327(62,750)[54,184;75,859]	66,648(66,065)[56,121;80,575]	20,412(20,303)[17,031;24,807]	11,595(11,411)[8,867;14,959]	13,769(13,606)[10,845;17,348]

LR: immunocompetent, not at higher risk for pneumococcal infection;

MR immunocompetent, at higher risk for pneumococcal infection

HR: immunosuppressed, at higher risk

Table 15: Incremental avoided burden and incremental cost-effectiveness along the cost-effectivenes frontier*, assuming **30% PPV23 efficacy** against non-invasive CAP: (mean(median) [95% interval] based on 1000 simulations, rounded to the nearest unit)

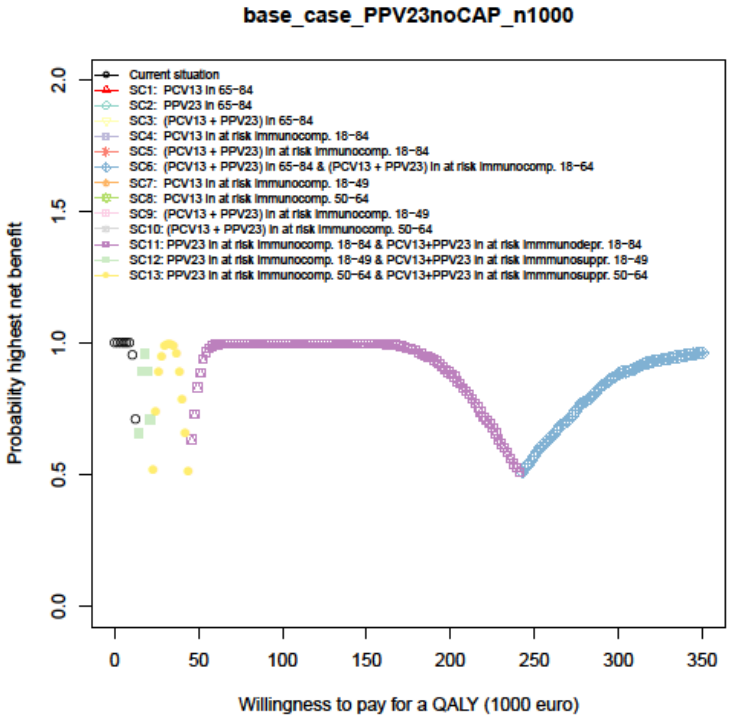
	SC12: PPV23 in at risk immunocomp. 18-49 & PCV13+PPV23 in at risk immmunosuppr. 18-49 versus current	SC13: PPV23 in at risk immunocomp. 50-64 & PCV13+PPV23 in at risk immmunosuppr. 50-64 versus SC12	SC11: PPV23 in at risk immunocomp. 18-84 & PCV13+PPV23 in at risk immmunodepr. 18-84 versus SC13	SC6: (PCV13 + PPV23) in 65-84 & (PCV13 + PPV23) in at risk immunocomp. 18-64 versus SC11
Meningitis cases	56(56)[45;65]	53(53)[43;61]	78(78)[61;93]	120(123)[80;150]
Pneumococcal CAP hospitalisations	1,518(1,517)[1,224;1,818]	1,479(1,479)[1,214;1,738]	2,627(2,629)[2,211;3,077]	5,836(5,829)[4,026;7,689]
Outpatient pneumococcal CAP cases	1,897(1,895)[1,530;2,265]	1,831(1,829)[1,553;2,098]	4,729(4,729)[3,969;5,486]	28,723(28,708)[18,491;38,555]
Deaths meningitis	6(6)[5;7]	13(13)[11;15]	14(14)[10;17]	35(36)[21;45]
Pneumonia deaths	94(95)[80;107]	163(163)[136;189]	369(369)[312;426]	1,077(1,080)[762;1,395]
Total deaths	100(101)[85;114]	176(176)[148;203]	383(383)[324;441]	1,112(1,114)[797;1,432]
Undiscounted total life years lost	3,814(3,833)[3,259;4,322]	2,502(2,508)[2,110;2,900]	6,572(6,576)[5,627;7,444]	13,838(13,869)[10,083;17,630]
Discounted total life years lost	1,565(1,572)[1,332;1,767]	1,703(1,706)[1,448;1,949]	4,035(4,038)[3,456;4,590]	8,250(8,253)[6,082;10,538]
Undiscounted QALY lost	3,454(3,471)[2,948;3,937]	1,815(1,807)[1,504;2,148]	5,244(5,243)[4,492;5,942]	9,692(9,699)[6,936;12,591]
Discounted QALY lost	1,532(1,540)[1,283;1,768]	1,357(1,352)[1,139;1,585]	3,265(3,264)[2,780;3,727]	5,968(5,961)[4,252;7,768]
Direct health care costs undiscounted (€)	17,912,981(17,899,609)[14,719,239;21,489,520]	15,200,280(15,186,468)[12,303,751;18,357,421]	29,261,856(29,147,600)[24,034,791;34,415,075]	57,589,721(57,486,603)[38,808,335;76,728,607]
Direct health care costs discounted (€)	12,559,509(12,520,894)[10,185,464;15,192,742]	12,285,682(12,292,739)[10,028,302;14,679,396]	25,024,812(24,950,693)[20,646,816;29,615,440]	42,567,600(42,497,405)[28,205,073;57,002,348]
Direct vaccination costs (vaccine program, administration and purchase) undiscounted	-30,812,055(-30,812,055)[-30,812,055;-30,812,055]	-41,169,979(-41,169,979)[-41,169,979;-41,169,979]	-129,921,409(-129,921,409)[-129,921,409;-129,921,409]	-1,444,002,740(-1,444,002,740)[-1,444,002,740;-1,444,002,740]
Direct vaccination costs (vaccine program, administration and purchase) discounted	-30,539,539(-30,539,539)[-30,539,539;-30,539,539]	-38,918,444(-38,918,444)[-38,918,444;-38,918,444]	-128,441,157(-128,441,157)[-128,441,157;-128,441,157]	-1,348,712,216(-1,348,712,216)[-1,348,712,216;-1,348,712,216]
ICER undiscounted	3,785(3,703)[2,429;5,352]	14,486(14,338)[10,885;18,946]	19,333(19,176)[16,165;23,395]	146,286(143,025)[108,786;202,075]
ICER discounted	11,859(11,642)[8,970;15,254]	19,815(19,640)[15,602;25,111]	31,909(31,627)[26,800;38,596]	223,828(219,260)[166,568;309,852]
Incremental cost per life year gained (undiscounted)	3,426(3,371)[2,188;4,871]	10,491(10,392)[8,021;13,584]	15,422(15,323)[12,918;18,604]	102,363(99,972)[77,310;139,575]
Incremental cost per life year	11,595(11,411)[8,867;14,959]	15,775(15,629)[12,635;19,789]	25,803(25,653)[21,771;31,005]	161,721(158,395)[122,899;216,85

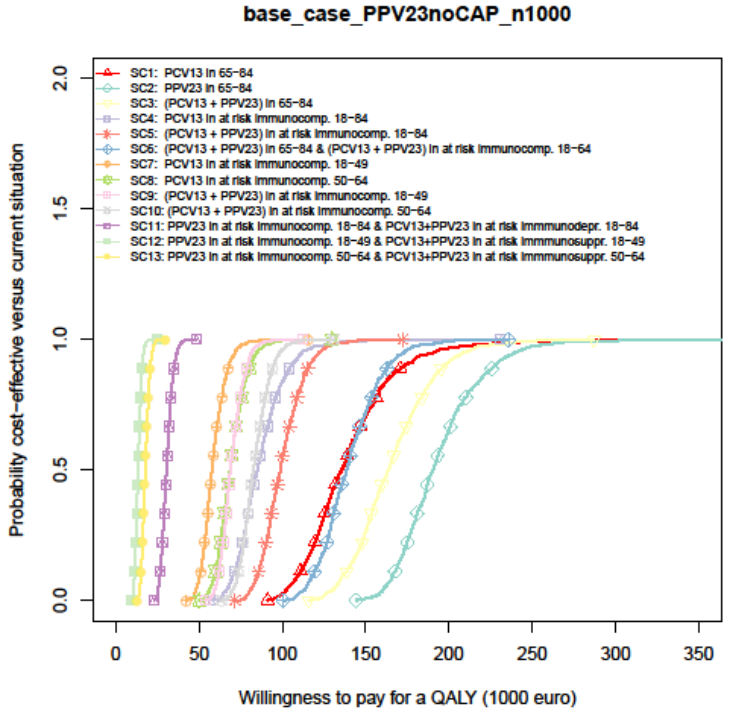
gained (discounted)	2]

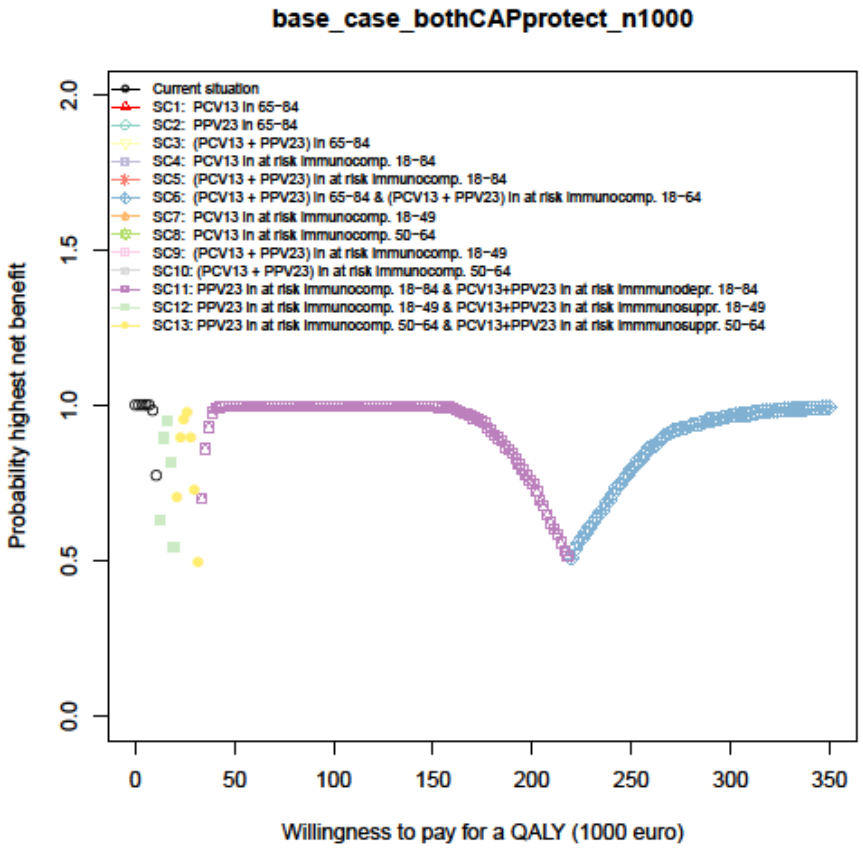
* Cost-effectiveness front: We only represent options that from the most cost-effective options, to options which gain more QALYs and are not dominated by other options, i.e. which do gain less QALYs than a less costly vaccination strategy.

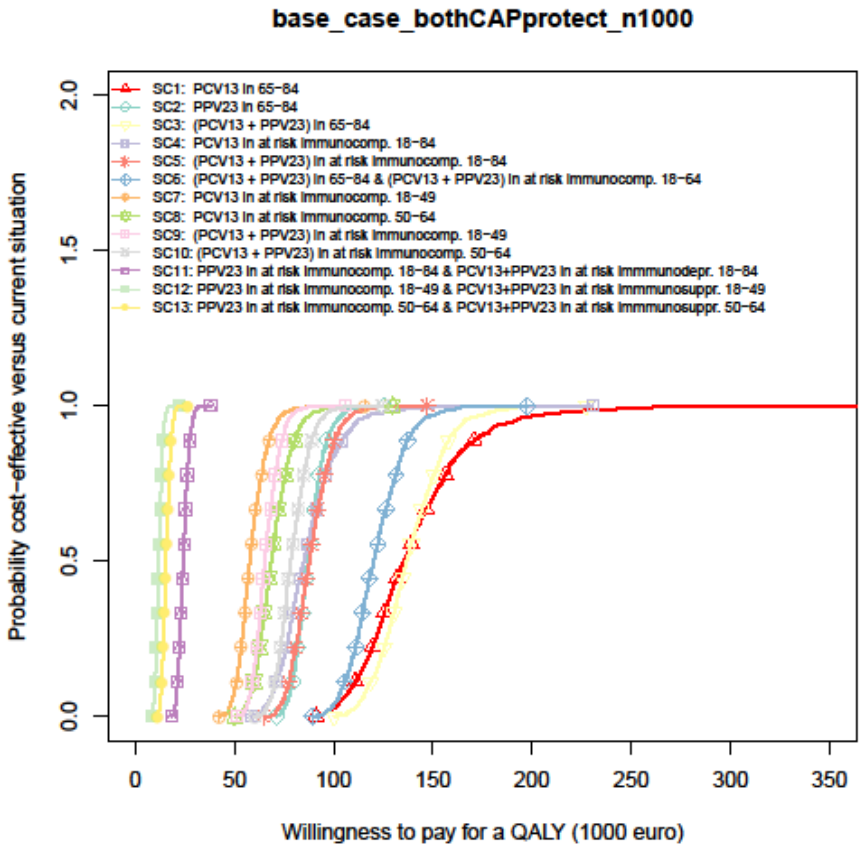
LR: immunocompetent, not at higher risk for pneumococcal infection;
MR immunocompetent, at higher risk for pneumococcal infection
HR: immunosuppressed, at higher risk

Figure 13: Cost-effectiveness acceptability frontier (left) and cost-effectiveness acceptability curves (right) including all theoretical options, assuming 0% (top) and 30% (bottom) PPV23 efficacy against non-invasive CAP



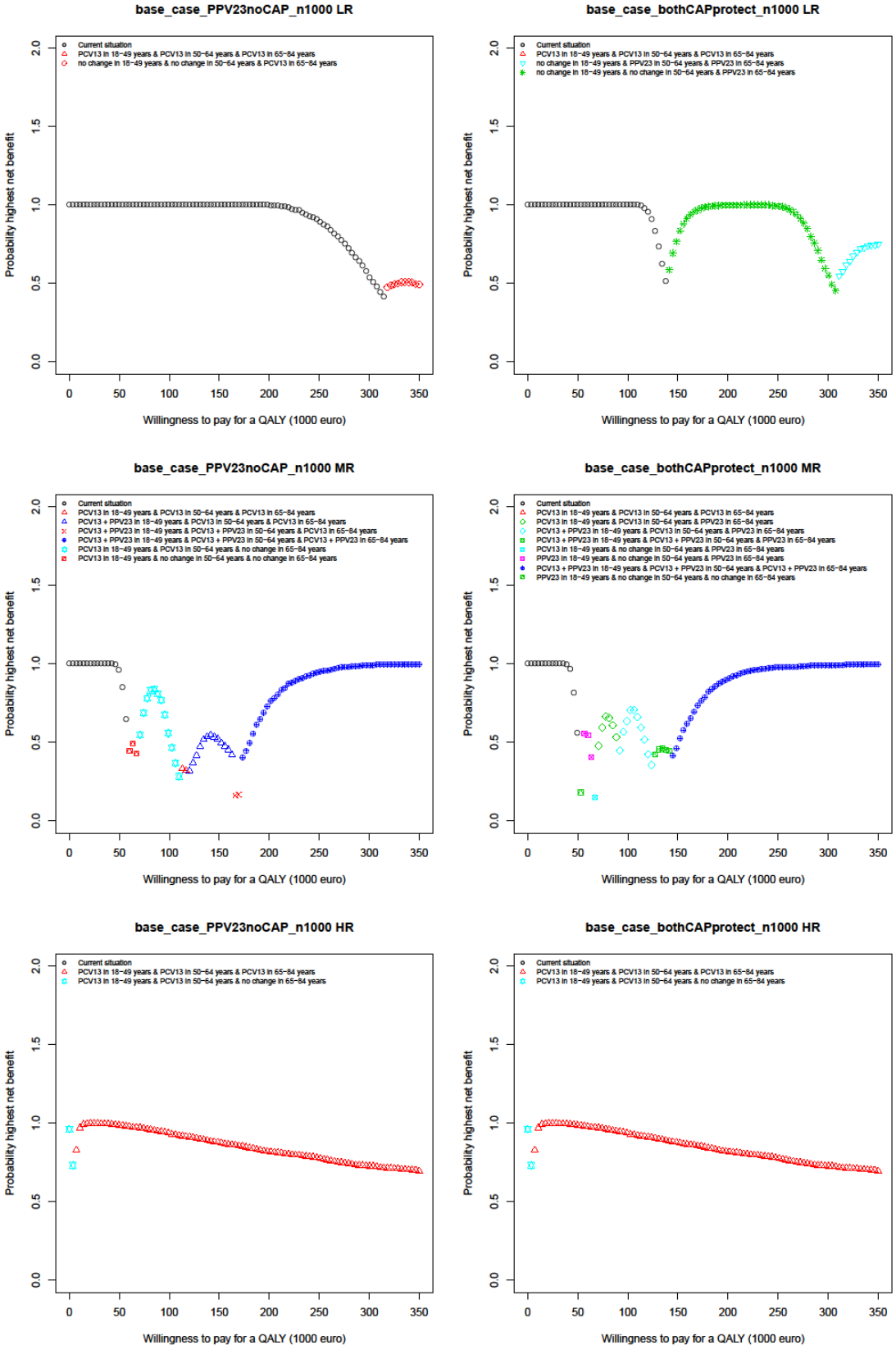



base_case_bothCAPprotect_n1000
Current situation
SC1: PCV13 in 65−84
SC2: PPV23 in 65−84
SC3: (PCV13 + PPV23) in 65−84
SC4: PCV13 in at risk immunocomp. 18−84
SC5: (PCV13 + PPV23) in at risk immunocomp. 18−84
SC6: (PCV13 + PPV23) in 65−84 & (PCV13 + PPV23) in at risk immunocomp. 18−64
SC7: PCV13 in at risk immunocomp. 18−49
SC8: PCV13 in at risk immunocomp. 50−64
SC9: (PCV13 + PPV23) in at risk immunocomp. 18−49
SC10: (PCV13 + PPV23) in at risk immunocomp. 50−64
SC11: PPV23 in at risk immunocomp. 18−84 & PCV13+PPV23 in at risk immmunodepr. 18−84
SC12: PPV23 in at risk immunocomp. 18−49 & PCV13+PPV23 in at risk immmunosuppr. 18−49
SC13: PPV23 in at risk immunocomp. 50−64 & PCV13+PPV23 in at risk immmunosuppr. 50−64
Probability highest net benefit
0.0
0.5
1.0
1.5
2.0
0
50
100
150
200
250
300
350
Willingness to pay for a QALY (1000 euro)


base_case_bothCAPprotect_n1000
SC1: PCV13 in 65−84
SC2: PPV23 in 65−84
SC3: (PCV13 + PPV23) in 65−84
SC4: PCV13 in at risk immunocomp. 18−84
SC5: (PCV13 + PPV23) in at risk immunocomp. 18−84
SC6: (PCV13 + PPV23) in 65−84 & (PCV13 + PPV23) in at risk immunocomp. 18−64
SC7: PCV13 in at risk immunocomp. 18−49
SC8: PCV13 in at risk immunocomp. 50−64
SC9: (PCV13 + PPV23) in at risk immunocomp. 18−49
SC10: (PCV13 + PPV23) in at risk immunocomp. 50−64
SC11: PPV23 in at risk immunocomp. 18−84 & PCV13+PPV23 in at risk immmunodepr. 18−84
SC12: PPV23 in at risk immunocomp. 18−49 & PCV13+PPV23 in at risk immmunosuppr. 18−49
SC13: PPV23 in at risk immunocomp. 50−64 & PCV13+PPV23 in at risk immmunosuppr. 50−64
Probability cost−effective versus current situation
0.0
0.5
1.0
1.5
2.0
0
50
100
150
200
250
300
350
Willingness to pay for a QALY (1000 euro)

10 Appendix 2: Vaccine choice per risk group

Figure 14: Cost-effectiveness acceptability frontier for the per risk group (Low Risk (LR): top; Medium Risk (MR): middle; High Risk (HR): bottom) optimal vaccine (no change, PCV13 and/or PPV23) and age group choice, with 0% (left) and 30% (right) PPV23 vaccine efficacy against non-invasive CAP



11 Appendix 3: Model input parameter background and details

11.1 PCV13 vaccine efficacy waning scenarios

Figure 15:Baseline and sensitivity PCV13 vaccine efficacy waning assumptions in 50-84 year-olds, compared to two recent studies[39, 42]

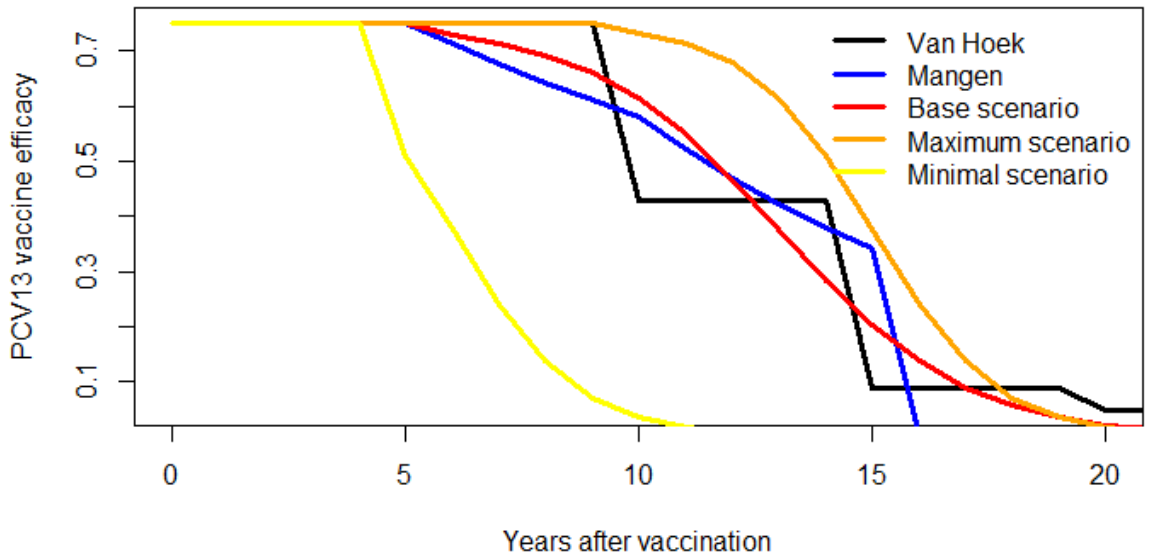


Table 16: PCV13 waning scenarios defined according to initial period without waning and time at which 0% efficacy is reached

	Expert opinion		Translation to logistic waning (see Eq. A4.1)		
Scenario	Initial period without waning	Time until reaching nearly 0%	Initial period without waning	50% point ($t_{50\%}$)	Waning rate (k)
Base case: smoothed version of [39, 42]	5	20	5	13 years	50%
Worst case	4	10	4	6 years	75%
Best case	9	20	9	15 years	75%

Assumed waning function: constant followed by logistic waning

$$VE$$ First years after vaccination, no waning

$$VE * \left(1 - \frac{1}{1 + \mathrm{e}^{-\mathrm{k}(t - t_{50\%})}}\right)$$ After the period of no waning

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 VE and k parameterising the waning speed.

11.2 PPV23 vaccine efficacy by risk and age group

Table 17: Assumed PPV23 vaccine efficacy against IPD per risk group, age at vaccination and years after vaccine administration based on [14]. Age and risk groups with not-significant vaccine efficacy are assumed to have 0% vaccine protection.

Risk\age group (age at vaccination)	18-74	75-84	85+
0-2 years after vaccination			
LR	0.61 (0.42; 0.74)[a]	0.61 (0.42; 0.74)[a]	0
MR	0.61 (0.42; 0.74)[a]	0.61 (0.42; 0.74)[a]	0
HR	0	0	0
2-5 years after vaccination			
LR	0.62 (0.21-0.82)	0	0
MR	0	0	0
HR	0	0	0
>5 years after vaccination: no vaccine protection			

[a] Calculated by pooling the counts for all immunocompetent in the ages 65-84 [14]. Calculating the vaccine efficacy as 1-OR, with OR the odds ratio of having an IPD infection of vaccinated versus non-vaccinated individuals. The confidence interval is calculated by using the normal approximation for the logarithm of the OR.

LR = Low Risk ; MR= Medium Risk, HR = High Risk

11.3 IPD incidence

Table 18: Invasive Pneumococcal Disease (IPD) incidence and meningitis proportion by age and risk group

Age-group	IPD incidence LR (per 100,000)	IPD incidence MR (per 100,000)	IPD incidence HR (per 100,000)	Meningitis proportion of IPD incidence
0-4	5.5969	119.6579	1747.1976	20.00%
5-9	1.3423	17.4990	468.0315	19.00%
10-14	0.5278	6.4049	180.9146	19.00%
15-19	0.5142	7.0829	173.5033	12.00%
20-24	0.9637	18.2410	286.5456	12.00%
25-29	1.1369	19.8227	217.4803	12.00%
30-34	2.1653	30.2017	269.7078	12.00%
35-39	2.5379	25.9003	206.5896	12.00%
40-44	3.0664	21.2663	180.0891	12.00%
45-49	3.7172	15.4663	145.0803	12.00%
50-54	2.6038	21.2179	259.0694	12.00%
55-59	3.8601	19.0635	330.2341	12.00%
60-64	5.0888	16.8537	340.3250	12.00%
65-69	5.8967	19.0632	277.6732	8.32%
70-74	7.4822	17.6349	265.9448	8.32%

75-79	10.0203	18.8874	302.5095	8.32%
80-84	19.6930	33.8723	178.2364	4.00%
85-89	28.7153	49.2177	272.7187	4.00%
90+	42.5206	80.0880	476.1115	4.00%

LR = Low Risk ; MR= Medium Risk, HR = High Risk

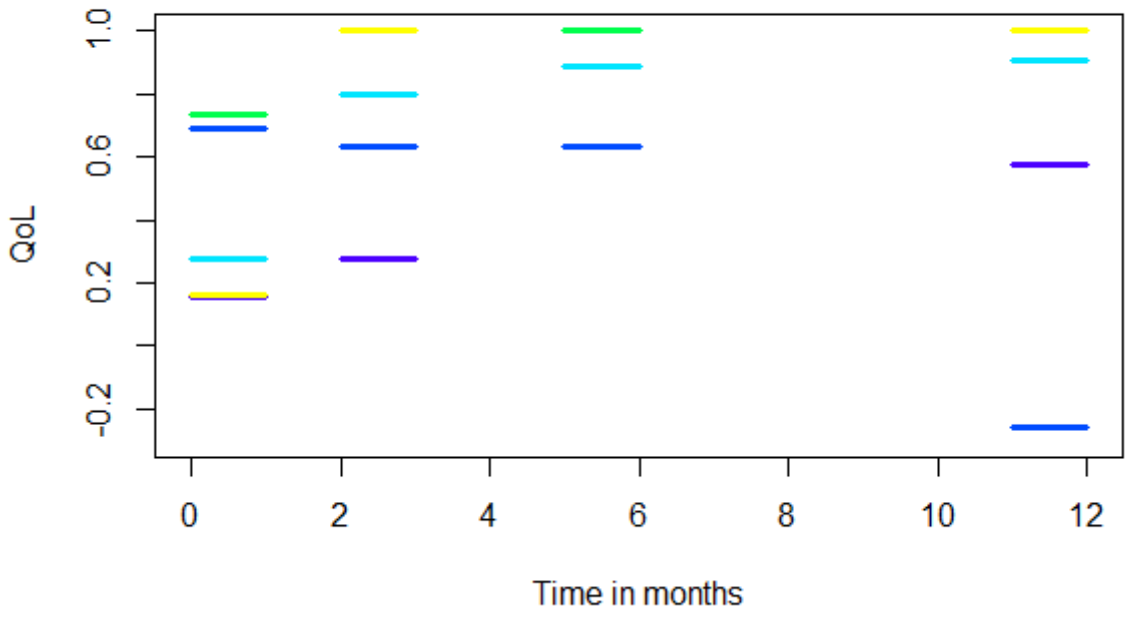
11.4 Quality of Life impact based on the "PNEUMOCOST"survey

11.4.1 Description of the dataset

The ESSEC Chair of Health Systems (prof. Gerard de Pouvourville) conducted the "PNEUMOCOST" study that aimed at deriving the treatment costs of hospitalised pneumococcal pneumonia and its consequences in terms of quality of life and mortality. This study was sponsored by Pfizer.

The PNEUMOCOST database contains 523 hospitalised pneumococcal pneumonia patients (mostly 50+ aged patients) from the time of admission (during the period 26/09/2011-30/04/2014) with a follow up of up to one year. It distinguishes between bacteremic and non-bacteremic pneumonia cases by indicating pneumococcus could be isolated from blood or from pleural fluid only. Euroqol (EQ-5D-3L) descriptive scores and utilities are obtained at different time intervals: 1 month, 3 months, 6 months and 12 months after diagnosis referring to the quality of life during the past month. Examples of measurements taken are presented in Figure. A3.2

Figure 16: Quality of Life (Qol) estimates reported for 5 random patients (one colour per patient) of the PNEUMOCOST-survey for whom a QoL measurement was available at months 1 and 12



11.4.2 Methodology

Data selection and choices

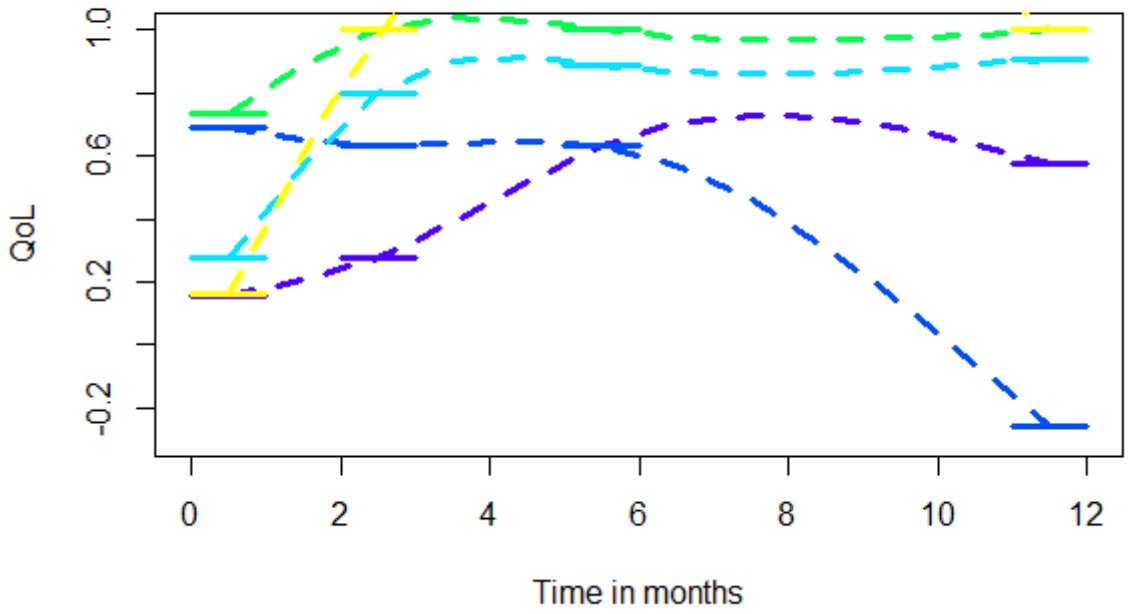
We limited analysis to survivors of a pneumonia hospitalisation because patients who died in the hospital did not have any quality of life (QoL) measurement taken. We further limited the analysis to patients for whom a QoL measurement is available at month 12. We ended up with 370 (70%) of the original 524 patients in the PNEUMOCOST-survey.

Two broad age groups of sufficiently large sample size were distinguished (<65 years, ≥65 years).

Interpolation

With the aim to estimate the Quality-Adjusted Life Years (QALYs) lost, we need to estimate intermittent QoL values. We took the average point at each month 1, 3, 6 and 12 as reference points which were interpolated by a smooth spline function (see Figure 17).

Figure 17: Quality of Life (QoL) estimates reported for 5 random patients (full lines, one colour per patient) of the PNEUMOCOST-survey for whom a QoL measurement was available at months 1 and 12 with spline interpolation per patient (dashed lines)



Risk-group specific QoL-norm estimates.

French QoL population norms were estimated from a different survey consisting of 452 adults sampled from the French population and using the EQ-5D-3L-methodology to obtain descriptive scores and utilities [29]. We use the individual data which do not distinguish risk groups. To scale French population norms to pneumococcal-specific risk groups, we used the measurements at 12 months of the hospitalised "PNEUMOCOST" pneumonia patients.

We assumed the population QoL-norm is a weighted average of the norms of specific risk groups:

1. *Norm(pop) = Pr(HR)*norm(HR) + Pr(MR)*norm(MR) + Pr(LR)*norm(LR)*

With *Pr* the proportion of a risk group in the population and *norm* the QoL-norm of a risk group. We distinguish between high risk (HR), median risk (MR) and low risk(LR). Norms and proportions are age dependent but for clarity this is dropped from the notation.

Furthermore we use QoL measurements per risk group for pneumonia patients at 12 months after hospital admission (PNEUMOCOST) to estimate ratios of QoL-norms for the per risk group population. Therefore we need to assume these ratios in the pneumonia patients and the per risk group population are the same.

2. *norm(HR) = F(HR)*norm(LR)*
3. *norm(MR)=F(MR)*norm(LR)*

Where *F()* is the ratio in QoL of a higher risk category (HR or MR) versus the lowest risk category (LR) distinguished for pneumonia patients at 12 months after hospital admission.

We can solve this system by substitution:

$$norm(LR)=norm(pop)/(Pr(HR)* F(HR) + Pr(MR)* F(MR) + Pr(LR))$$

We then obtain the following risk group specific norm estimates:

Table 19: Risk and age group specific Quality of Life norm estimation

Age group	Risk group	Population norm	Risk group proportion	Risk group specific norm
(0,64]	HR	0.8515	0.0045	0.7861
(64,120]	HR	0.7504	0.0136	0.8002
(0,64]	LR	0.8515	0.9650	0.8554
(64,120]	LR	0.7504	0.8277	0.7627
(0,64]	MR	0.8515	0.0304	0.7371
(64,120]	MR	0.7504	0.1587	0.6823

Risk group proportions for France from Long term health beneficiaries' data, France metro + overseas, 2013

QALY calculation

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). Average QALY estimates are summarized in Table A2.5:

11.4.3 Results

Table 20: QALY loss estimates of surviving hospitalised pneumococcal pneumonia patients (PNEUMOCOST-survey), with a QALY measurement up to 12 months, by age, risk group and whether the pneumonia episode was invasive (i.e. pneumococcus detected in the blood) or not.

Age group	Invasive, 1=yes	Risk group	Average QALY loss (over 1 year)	Minimum QALY loss (over 1 year)	Maximum QALY loss (over 1 year)	Number of patients
(0,64]	0	LR	0.0491	-0.3283	0.9692	69
(0,64]	0	MR	0.0708	-0.2539	0.6936	29
(0,64]	0	HR	0.1366	-0.2139	0.7024	16
(0,64]	1	LR	0.0203	-0.3288	0.5244	36
(0,64]	1	MR	0.031	-0.242	0.7798	15
(0,64]	1	HR	0.0873	-0.2139	0.5294	12
(64,120]	0	LR	0.0679	-0.2713	0.8336	21
(64,120]	0	MR	0.0985	-0.3177	0.6936	49
(64,120]	0	HR	0.2128	-0.1788	0.6174	13
(64,120]	1	LR	0.1741	-0.2768	0.671	28
(64,120]	1	MR	0.0988	-0.3921	0.7009	26
(64,120]	1	HR	0.1788	-0.1154	0.523	9

In the economic evaluation, for patients who are simulated to die of pneumonia during hospitalisation, we do not include the survivors' morbidity QALY loss over the first year after admission as outlined above, but we include their remaining quality-adjusted life expectancy.

PNEUMOCOST based QALY losses for invasive pneumococcal disease will be used in the model as estimates for all hospitalised invasive pneumococcal disease categories (Menigitis, Septicemia and bacteremic pneumonia) whereas non-invasive pneumonia QALY losses will be used as estimates for non-bacteremic hospitalised pneumonia in the model.

Uncertainty around QALY estimates derived from the PNEUMOCOST database will be included by bootstrapping directly from both the PNEUMOCOST survey and the population norm data. This method does not require assuming a distribution for these parameters.

12 Appendix 4: epidemiological parameters

12.1 Données épidémiologiques

Les données épidémiologiques constituant les paramètres du modèle sont présentés. En l'absence d'indication il s'agit des du scénario base case, la variation de ceux-ci étant basée sur les effectifs des données de l'étude ou de la base de donnée source. Pour les paramètres dont la variation a été fixée a priori et validée par le groupe de travail du Comité technique des vaccinations, les valeurs minimales et maximales des paramètres ou la variation relative de la valeur base-case sont présentés.

12.1.1 Population cible et couverture vaccinale

Les effectifs de la population française adulte résidant en métropole sont ceux de l'INSEE (Estiimation localisée de population au 01/01/2015). L'espérance de vie à chaque âge est également issus de l'INSEE (données consultables sur le site de l'INED).

Parmi la population des adultes trois groupes à risque ont été définis selon les recommandations de vaccination contre le pneumocoque chez l'adulte figurant dans l'avis du Haut Conseil de la Santé Publique (HCSP) du 25 avril 2013 (6) : groupe à risque de base, élevé et très élevé. Les populations par âge de ces trois niveaux (ou groupes) de risque ont été estimées en utilisant les dernières données disponibles en termes d'effectifs de la population française de l'INSEE (01/01/2015), la prévalence des affections de longue durée en 2013 (Source Santé publique France), la prévalence du diabète traité, la prévalence des affections respiratoires estimée par la CNAMTS et la prévalence des cancers traités par chimiothérapie de l'INCA (4,5,34). Les effectifs de la population adulte française appartenant à ces trois groupes de risque sont présentés dans le tableau 1 ; le détail de l'estimation de ces effectifs est présenté en annexe 1.

La couverture vaccinale du vaccin polysaccharidique 23-valent (PPV23) et du vaccin conjugué 13-valent (VPC13) actuellement recommandés chez certains adultes à risque a été calculée en utilisant les données de remboursement 2015 de chacun de ces deux vaccins issues de l'échantillon généralistes des bénéficiaires.

Tableau 1 : Population visée par la vaccination et données sur la vaccination anti-pneumococcique

	Groupes d'âge (année)				
Paramètre	**18-49**	**50-64**	**65-79**	**≥ 80**	**Tous ≥ 18**
Population, France métropolitaine[1]	25 738 654	12 379 418	8 158 833	3 783 026	50 059 931
Prévalence des groupes à risque					
Risque de base	96,3%	82,2%	64,5%	53,6%	84,6%
Risque élevé	3,2%	16,6%	33,7%	44,4%	11,7%
Risque très élevé	0,4%	1,2%	1,8%	2,0%	0,8%
Couverture vaccinale chez les patients à risque visés par les recommandations[2]					
Vaccin conjugué 13 valent (VPC13)	20%		20%		
Vaccin pneumococcique 23 valent (PPV23)	20%		20%		

[1] Source : Insee, population au 31 décembre 2014

[2] Couverture vaccinale du PPV23, base sur étude françaises, couverture vaccinale du VPC13 chez les patients à risque très élevé: valeur fixée a priori comme étant identique celle du PPV23

12.1.2 Incidence et nombre de cas d'infections invasives et de pneumopathies à pneumocoques chez l'adulte

Incidence et nombre de cas d'infections invasives à pneumocoque

L'incidence et le nombre de cas par an des infections invasives à pneumocoque, des bactériémies à pneumocoques et des méningites à pneumocoques en population générale ont été extraites des données du réseau Epibac (40) et sont présentées dans le tableau 2 ci-dessous.

Le nombre de cas d'infections invasives à pneumocoques survenant une année donnée parmi les personnes des différents groupes à risque, risque de base, élevé et très élevé, a été estimé en appliquant la répartition des cas entre ces trois groupes à risque observée chez les adultes inclus dans l'étude « Surveillance des infections invasives à pneumocoques chez l'adulte, SIIPA » d'octobre 2012 à décembre 2015 (43) au nombre total de cas issu des données du réseau Epibac. Les cas inclus dans l'étude SIIPA ont été classés dans les trois groupes à risque selon le regroupement figurant dans les recommandations de vaccination contre le pneumocoque du HCSP du 25 avril 2013. Le détail de cette estimation est présenté en annexe 2.

L'incidence des bactériémies à pneumocoques dans la population générale et dans chaque strate de groupe à risque a été calculée en appliquant la proportion de bactériémies pour chaque groupe d'âge issue du réseau Epibac à l'incidence des infections invasives à pneumocoques de la strate. Le nombre de cas annuel est calculé en appliquant le taux d'incidence spécifique de chaque strate à l'effectif de la population de la strate.

L'incidence des bactériémies à pneumocoques a été utilisée comme estimation de l'incidence des pneumopathies bactériémiques à pneumocoques hospitalisées (tableau 2).

Tableau 2 : Incidence des infections invasives et des à pneumocoques parmi la population adulte de France métropolitaine

	Groupes d'âge (année)				
Paramètre (base case)	**18-49**	**50-64**	**65-79**	**≥ 80**	**Tous ≥ 18**
Infections invasives à pneumocoques (IIP)					
Incidence pour 100 000 pop. en population générale[3]	3,6	9,8	16,0	40,6	10,0
Nombre de cas, France	925	1211	1309	1536	4982
Incidence pour 100 000 par groupes de risque[4] :					
Personnes à risque de base	2,2	3,8	7,3	27,0	4,4
Personnes à risque élevé	20,1	18,5	18,5	47,2	25,3
Personnes à risque très élevé	190,7	311,5	280,6	257,6	265,7
Nombre de cas par groupes de risque, France:					
Personnes à risque de base	550	382	386	547	1 866
Personnes à risque élevé	167	382	508	793	1 850
Personnes à risque très élevé	207	447	415	196	1 266
Proportion de méningites parmi les IIP[5]	12,2%	11,8%	8,3%	3,6%	
Bactériémies à pneumocoques hospitalisées[a]					
Incidence pour 100 000 pop. en population générale[a]	3,2	8,6	14,7	39,1	9,1
Nombre de cas, France[b]	812	1068	1200	1480	4561
Incidence pour 100 000 pop. par groupe de risque[a] :					
Personnes à risque de base	1,9	3,3	6,7	26,0	4,0
Personnes à risque élevé	17,6	16,4	17,0	45,5	23,4
Personnes à risque très élevé	167,4	274,7	257,3	248,2	240,6
Nombre de cas par groupes de risque, France[b]:					
Personnes à risque de base	483	337	354	528	1 701
Personnes à risque élevé	147	337	466	764	1 713
Personnes à risque très élevé	182	395	380	189	1 146

a : = Incidence des IIP X (1 - proportion des méningites parmi les IIP) dans chaque groupe d'âge

b : Pour chaque strate d'âge et de niveau de risque =Incidence de la strate X Population de la même strate / 100 000

[3] Source : Epibac, France métropolitaine 2014, Incidence redressée pour défaut de couverture et corrigée pour sous notifications

[4] Source : Epibac 2014 et étude, surveillance des infections invasives à pneumocoques chez l'adulte, SIIPA 2012-2015, données ORP-CNRP-Spilf-ANSP non publiées, estimation ANSP

[5] Source : Epibac, France métropolitaine 2010-2014

Incidence et nombre de cas de pneumopathies à pneumocoques non bactériémiques hospitalisées

L'incidence des pneumopathies à pneumocoques non bactériémiques hospitalisées a été estimée en appliquant un ratio des pneumopathies à pneumocoques non bactériémiques (PnoNB) sur les pneumopathies à pneumocoques bactériémiques à l'incidence des pneumopathies à pneumocoques bactériémiques (PnoB) calculée comme indiqué ci-dessus. Un ratio de 3 a été pris en compte basé sur l'analyse de Said et al. (36).

Ce ratio ne différant pas dans une analyse restreinte aux études menées sur des cas hospitalisés selon Said, il a été appliqué aux pneumopathies à pneumocoques bactériémiques hospitalisées (Epibac 2014).

Le même ratio a été appliqué dans chaque strate d'âge et de niveau de risque (tableau 3).

Tableau 3 : Incidence et nombre de cas de pneumopathies non bactériémiques hospitalisées

	Groupes d'âge (année)				
Paramètre (base case)	**18-49**	**50-64**	**65-79**	**≥ 80**	**Tous ≥ 18**
Bactériémies à pneumocoques hospitalisées					
Incidence pour 100 000 pop. en population générale	3,2	8,6	14,7	39,1	9,1
Nombre de cas, France	812	1068	1200	1480	4561
Incidence pour 100 000 pop. par groupe de risque :					
Personnes à risque de base	1,9	3,3	6,7	26,0	4,0
Personnes à risque élevé	17,6	16,4	17,0	45,5	23,4
Personnes à risque très élevé	167,4	274,7	257,3	248,2	240,6
Nombre de cas par groupes de risque, France:					
Personnes à risque de base	483	337	354	528	1 701
Personnes à risque élevé	147	337	466	764	1 713
Personnes à risque très élevé	182	395	380	189	1 146
% des pneumopathies à pneumocoques qui sont bactériémiques (Source : Said et al.)	24,8%	(95% CI: 21.3%, 28.9%).			
Ratio PnoNB / PnoB[a]	3,0				
Pneumopathies non bactériémiques à pneumocoques, hospitalisées[b]					
Incidence pour 100 000 pop. en population générale	9,6	26,2	44,6	118,7	27,6
Nombre de cas, France	2461	3239	3640	4489	13 830
Incidence pour 100 000 par groupes de risque[6] :					
Personnes à risque de base	5,9	10,0	20,4	78,9	12,2
Personnes à risque élevé	53,5	49,6	51,4	137,8	71,0
Personnes à risque très élevé	507,6	832,9	780,2	752,6	729,5
Nombre de cas par groupes de risque, France:					
Personnes à risque de base	1464	1021	1074	1600	5 159
Personnes à risque élevé	446	1021	1412	2316	5 195
Personnes à risque très élevé	552	1196	1154	573	3 475

[a]: = (1- % des pneumopathies à pneumocoques qui sont bactériémiques) / % des pneumopathies à pneumocoques qui sont bactériémiques

b = PnoB X ratio PnoNB / PnoB, dans chaque strate

[6] Sources : Epibac 2014 et étude, surveillance des infections invasives à pneumocoques chez l'adulte, SIIPA 2012-2015, données ORP-CNRP-Spilf-ANSP non publiées, estimation SpFrance

Incidence et nombre de cas de pneumopathies à pneumocoques communautaires

Incidence des pneumopathies à pneumocoques communautaires en population générale

L'incidence des pneumopathies à pneumocoques communautaire en population générale a été estimée en se basant sur l'incidence des pneumopathies prises en charge en médecine générale citée par Personne et al. (31) appliquée à la population des adultes en 2014, et sur la proportion des pneumopathies dues au pneumocoque issue de l'analyse de Said et al (36). Les résultats sont présentés dans le tableau 4

Tableau 4 : Estimation de l'incidence des pneumopathies à pneumocoques communautaires

	Groupes d'âge (année)		
Paramètre (base case)	**18-64**	**≥65**	**Tous ≥ 18**
Incidence (pour 100 000 hab.) des pneumopathies communautaires[a]	481,5	786,4	554,2
Proportion des pneumopathies dues au pneumocoque[b]	27,3%		
Pneumopathies à pneumocoques communautaires[c]			
Incidence pour 100 000 pop. en population générale[c]	131,5	214,7	151,3
Nombre de cas, France	50 107	25 637	75 744

[a] : Source Personne et al, application aux données de population 2014 (31
[b] : Source : Said et al (36).
[c] : =Incidence des pneumopathies communautaires X proportion des pneumopathies dues aux pneumocoque

Incidence des pneumopathies à pneumocoques communautaires selon le niveau de risque

L'incidence des pneumopathies à pneumocoques communautaires chez les personnes des différents groupes de risque composant la population adulte française a été déterminée en utilisant la prévalence de chacun des groupes de risque dans la population et le risque relatif de pneumopathie à pneumocoques de chacun de ces groupes de risque vis-à-vis du groupe à risque de base. Les risques relatifs des groupes à risque élevé et très élevée par groupe d'âge utilisés pour cette estimation sont issus d'une étude nord-américaine présentée dans la publication de Shea et al. (35). Le détail de cette estimation est présenté dans l'annexe 3.

Tableau 5 : Incidence des pneumopathies à pneumocoques communautaires selon le niveau de risque

	Groupes d'âge (année)		
Paramètre (base case)	**18-64**	**≥ 65**	**Tous ≥ 18**
Pneumopathies à pneumocoques communautaires[c]			
Incidence pour 100 000 pop. en population générale	131,5	214,7	151,3
Nombre de cas, France	50 107	25 637	75 744
Pneumopathies à pneumocoques communautaires, incidence pour 100 000 pop. par groupe de risque :[c]			
Incidence pour 100 000 pop. à risque de base	109,7	113,7	110,4
Incidence pour 100 000 pop. à risque élevé	346,3	352,5	350,1
Incidence pour 100 000 pop. à risque très élevé	702,7	770,8	734,8
Nombre de cas par groupes de risque, France:			
Personnes à risque de base	38 365	8 286	46 651
Personnes à risque élevé	9 974	15 623	25 597
Personnes à risque très élevé	1 768	1 727	3 496

12.1.3 Couverture sérotypique des vaccins pneumococcique conjugué 13-valent (VPC13) et polysaccharidique 23-valent (PPV23)

La proportion des cas de pneumopathies et d'infections invasives à pneumocoques dus à une souche de sérotype couvert par le vaccin VPC13 ou le PPV23 est basée sur les dernières données disponibles du CNR des pneumocoques lors de l'estimation des paramètres du modèle, soit 2013 pour les pneumopathies (tableau 6) et 2014 pour les infections invasives à pneumocoques (tableau 7).

Tableau 6 : Couverture sérotypique des souches isolées **d'infections pulmonaires à pneumocoques** chez l'adulte par les vaccins pneumococcique, Source : CNR des pneumocoques 2013

	Groupes de sérotypes	Nb de souches 2013	%	
≥ 18 ans	Sérotypes du VPC13	4	2,1%	
	Sérotypes du VPC13 et du PPV23	59	31,4%	33,5%
	Sérotypes du PPV23	35	18,6%	
	Sérotypes non vaccinaux	90	47,9%	
	Toutes	188		

Tableau 7 : Couverture sérotypique des souches isolées d'infections invasives (bactériémies et méningites) à pneumocoques chez l'adulte par les vaccins pneumococcique, Source : CNR des pneumocoques 2014

	Groupes de sérotypes	Nb de souches 2014	%	
≥ 18 ans	Sérotypes du VPC13	3	0,5%	
	Sérotypes du VPC13 et du PPV23	171	30,9%	31,5%
	Sérotypes du PPV23	191	34,5%	
	Sérotypes non vaccinaux	188	34,0%	
	Toutes	553	100%	

12.1.4 Projections de l'évolution de l'incidence et de la couverture sérotypique

La projection de l'évolution de l'incidence des infections invasives à pneumocoques s'est basée sur l'impact récent de l'introduction du VPC13 chez l'enfant sur les infections invasives à pneumocoques de l'adulte et les évolutions d'incidence globale observées dans après l'introduction du VPC 7-valent. En effet, l'introduction du VPC13 chez l'enfant s'est traduite par une diminution de l'incidence globale des infections invasives à pneumocoques chez l'adulte en France, contrairement à l'augmentation globale observée après l'introduction du VPC 7-valent chez les adultes en France. Cet impact indirect positif chez l'adulte a été observé dès 2014, les projections ont donc pris en compte cette diminution en faisant l'hypothèse d'une poursuite de la diminution de l'incidence globale.

L'incidence des infections invasives à pneumocoques a été projetée en estimant l'effet indirect de la vaccination des enfants avec le VPC13 depuis 2013 d'une part sur l'incidence globale en tenant compte des diminution d'incidence observée dans les pays où ces diminution ont été observées après l'introduction du VPC-7, et d'autre part sur la diminution de la part des cas dus à des souches couvertes par le VPC13.

Projection d'évolution de l'incidence des infections invasives à pneumocoques tous sérotypes confondus

L'hypothèse d'une poursuite de la diminution de l'incidence des infections invasives à pneumocoques, tous sérotypes confondus chez l'adulte jusqu'en 2018 soit 5 ans après l'introduction du VPC13. Dans le scénario base-case l'hypothèse d'une stabilisation au-delà de cette date a été retenue compte tenu des incertitudes sur l'impact indirect de la vaccination des enfants sur l'incidence chez l'adulteà long terme. Dans le scénario base-case l'incidence atteinte en 2018 serait égale à

1. 0,6 fois la valeur de l'incidence des infections invasives à pneumocoques en 2001-2002 (années précédant l'introduction du VPC 7-valent) chez l'adultes âgé de 18 à 64 ans, soit une diminution globale de 40% (la diminution observée chez les adultes âgés de 15 à 64 ans entre 2001-2002, période pré-vaccinale et 2014 étant de -25%)
2. 0,5 fois la valeur de l'incidence des infections invasives à pneumocoques en 2001-2002 (années précédant l'introduction du VPC 7-valent) chez l'adultes âgé de 65 ans ou plus, soit une diminution globale de 50%(la diminution observée entre 2001-2002, période pré-vaccinale et 2014 étant de -40%).

Un scénario d'incidence élevée (best case) et d'incidence basse (worst case) ont été formulés, correspondant pour le scénario d'incidence élevé à une augmentation progressive de l'incidence qui atteindrait le niveau pré-vaccinal en 2040, et pour le scénario d'incidence base à un baisse plus importante de l'incidence tous sérotypes confondus.

Les évolutions de l'incidence dans les trois scénarios (base case, incidence élevée et incidence basse) sont présentées dans le tableau 9.

Projection d'évolution de l'incidence des pneumopathies à pneumocoques tous sérotypes confondus

En l'absence de données françaises sur l'effet indirect de l'introduction du VPC13 chez l'enfant sur l'incidence des pneumopathies à pneumocoques tous sérotypes confondus chez l'adulte, l'hypothèse d'une stabilité de l'incidence de celles-ci a été faite, (tableau 10). Par contre, une évolution de la couverture sérotypique des pneumopathies à pneumocoques, lié à la diminution de la circulation des sérotypes du VPC13 a été prise en compte.

Tableau 9 : Scénarios d'évolution de l'incidence des **infections invasives à pneumocoques** (bactériémies et méningites), tous sérotypes confondus

Scénario d'incidence Base case			
Groupe d'âge (année)	**Période**		
	2014-2018	**2018-2020**	**2020-**
18-64	Diminution jusqu'à 0,6 X Incidence 2001-2002 en 2018	Stable	Stable
>64	Diminution jusqu'à 0,5 X Incidence 2001-2002 en 2018	Stable	Stable
Scénario « Incidence basse»			
	Période		
	2014-2018	**2018-2020**	**2020-**
18-64	Diminution jusqu'à 0,3 X Incidence 2001-2002 en 2018	Stable	Stable
>64 ans	Diminution jusqu'à 0,3 X Incidence 2001-2002 en 2018	Stable	Stable
Scénario « Incidence élevée »			
	Période		
	2014-2018	**2018-2020**	**2020-2040**
18-64	Diminution jusqu'à 0,6 X Incidence 2001-2002 en 2018	Augmentation jusqu'à la valeur de l'incidence de 2001-2002 en 2040	
>64	Diminution jusqu'à 0,5 X Incidence 2001-2002 en 2018	Augmentation jusqu'à la valeur de l'incidence de 2001-2002 en 2040	

Tableau 10 : Evolution de l'incidence **des pneumopathies à pneumocoques** (communautaires et hospitalisées), tous sérotypes confondus

Groupe d'âge (année)	**Période**		
	2014-2018	**2018-2020**	**2020-**
18-64	Stable	Stable	Stable
>64	Stable	Stable	Stable

Projection d'évolution de la couverture sérotypique

L'évolution de la couverture sérotypique du VPC13 a été basée sur les évolutions observées en termes de couverture sérotypique chez l'adulte (données 2001-juin 2015 du CNR des pneumocoques) la diminution importante des cas dus aux sérotypes du VPC 7-valent entre 2001-2002 et 2008-2009 et des cas dus aux sérotypes additionnels du VPC13 depuis 2013, avec cependant une persistance de certains sérotypes du VPC13 pour lesquels peu ou aucun effet indirect ne serait observé (ie les sérotypes 3 et 19C)

Compte tenu de ces deux éléments, la proportion des cas d'infection invasives à pneumocoque et de pneumopathies à pneumocoques dus aux sérotypes du VPC13 atteindrait en 2020, chez les adultes âgés de 18 à 64 ans, la proportion de 15%, le sérotype19C représentant 5% des cas et le sérotype 3, 10%) et chez les adultes âgés 65 ans ou plus, celle de 13% , le sérotype 19C représentant 3% des cas et le sérotype 3, 10% des cas. La part relative des cas de sérotypes du PPV23 non couverts par le VPC13 parmi les sérotypes non couverts par l'un des deux vaccins augmenterait de façon proportionnelle à celle de l'ensemble des cas de sérotypes non couverts par le VPC13, en l'absence d'émergence observée d'un sérotype non vaccinal prédominant.

Tableau 11 : Projections de l'évolution de la couverture sérotypique **des infections invasives à pneumocoques** (bactériémies et méningites) par les vaccins VPC13 et PPV23- Base Case

Groupe d'âge (année)	**Groupe de sérotypes (ST)**	**Période**		
		2014	**2015-2020**	**2020-**
18-64*	ST du VPC13	0,5%(a_1)	0% en 2020 (a_2)	Stable
	ST du VPC13 et du PPV23	30,9%(b_1)	15% en 2020 (b_2)	Stable
	ST du PPV23	34,5%(c_1)	$c_2=[1- (a_2+b_2)] X [c_1 / (c_1+d_1)]$	Stable
	ST non vaccinaux	34,0%(d_1)	$d_2= [1- (a_2+b_2)]X [d_1 / (c_1+d_1)]$	Stable
≥ 65	ST du VPC13	0,5%(a_1)	0% en 2020 (a_2)	Stable
	ST du VPC13 et du PPV23	30,9%(b_1)	13% en 2020 (b_2)	Stable
	ST du PPV23	34,5%(c_1)	$c_2= [1- (a_2+b_2)] X [c_1 / (c_1+d_1)]$	Stable
	ST non vaccinaux	34,0%(d_1)	$d_2= [1- (a_2+b_2)] X [d_1 / (c_1+d_1)]$	Stable

*Pour les infections invasives chez les 18-64 ans, les données du CNR 2001-2014 des souches isolées chez les adultes âgés de 15 à 64 ans ont été utilisées, compte tenu de l'utilisation préférentielle de cette stratification pour l'analyse de l'impact des vaccins. Le nombre de cas survenant chez les 15-19 ans représentant 2% des cas survenant chez les chez les 15-64 ans

Tableau 12 : Projections de l'évolution de la couverture sérotypique des **pneumopathies à pneumocoques** par les vaccins VPC13 et PPV23-

Groupe d'âge (année)	**Groupe de sérotypes (ST)**	**Période**		
		2013	**2014-2020**	**2020-**
18-64	ST du VPC13	2,1%(a_1)	0% en 2020 (a_2)	Stable
	ST du VPC13 et du PPV23	31,4%(b_1)	15% en 2020 (b_2)	Stable
	ST du PPV23	18,6%(c_1)	$c_2=[1- (a_2+b_2)]X [c_1 / (c_1+d_1)]$	Stable
	ST non vaccinaux	47,9%(d_1)	$d_2= [1- (a_2+b_2)]X [d_1 / (c_1+d_1)]$	Stable
≥ 65	ST du VPC13	2,1%(a_1)	0% en 2020 (a_2)	Stable
	ST du VPC13 et du PPV23	31,4%(b_1)	13% en 2020 (b_2)	Stable
	ST du PPV23	18,6%(c_1)	$c_2=[1- (a_2+b_2)]X [c_1 / (c_1+d_1)]$	Stable
	ST non vaccinaux	47,9%(d_1)	$d_2= [1- (a_2+b_2)]X [d_1 / (c_1+d_1)]$	Stable

Les figures1 et 2 représentent l'évolution de l'incidence des infections invasives à pneumocoques de sérotypes du VPC13 et tous sérotypes confondus, observée de 2001 à 2014 et projetée au-delà (base-case) sur la base des formules figurant dans le tableau 11.

Figure 1 : Evolution de l'incidence des infections invasives à pneumocoques chez les 18-64 ans, de sérotypes du VPC13 et tous sérotypes confondus, scénario « Base case », France métropolitaine 2001-

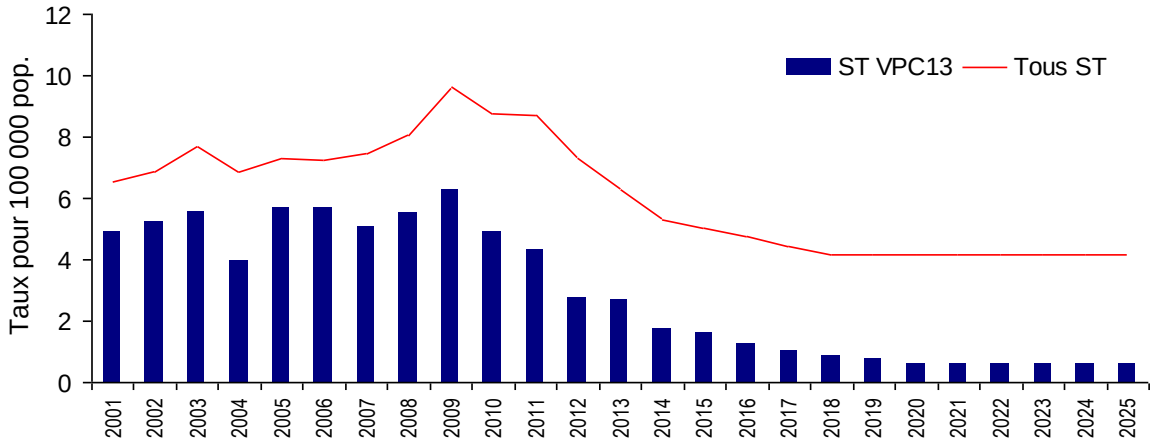
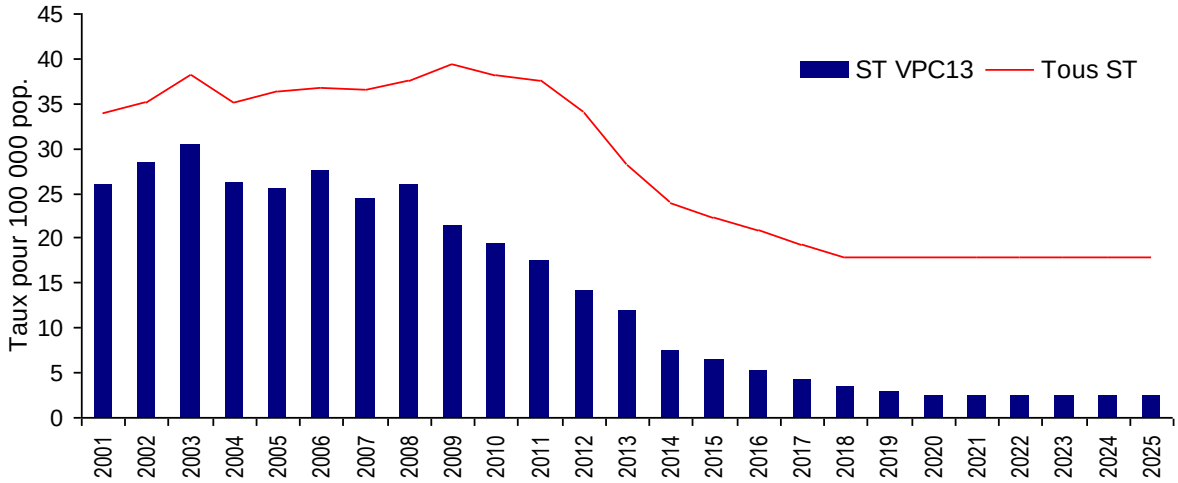


Figure 2 : Evolution de l'incidence des infections invasives à pneumocoques chez les ≥ 65 ans, de sérotypes du VPC13 et tous sérotypes confondus, scénario « Base case », France métropolitaine 2001-



12.1.5 Mortalité des infections à pneumocoques

La mortalité des infections à pneumocoques considérées dans l'analyse a été estimée à partir des données de trois études françaises récentes : l'Etude "Surveillance des infections invasives à pneumocoque chez l'adulte, SIIPA", Oct 2012-June 2015, portant sur les infections invasives à pneumcooques chez l'adulte hors méningites, l'étude CAP sur les pneumopathies (toutes causes) prises en charge en médecine générale de Partouche et al. (32), et l'étude PNEUMOCOST portant sur l'évolution des pneumopathies à pneumocoques hospitalisées et comportant un suivi post hospitalisation. Pour cette dernière étude le nombre de décès a été corrigé pour prendre en compte la non-inclusion de cas décédés avant l'inclusion. La mortalité des méningites à pneumcooques a été estimée en utlisant le nombre de décès des séjours dédoublonnés dont le code de diagnostic principal état G001 « méningites à pneumocoques »

Tableau 13 : Mortalité des infections invasives et des pneumopathies à pneumocoques

	Groupes d'âge (année)		
Paramètre base case	**18-64**	**≥ 65**	**Source**
Mortalité des pneumopathies communautaires (ambulatoire)	0,2%	0,7%	CAPA Partouche et al.
Mortalité hospitalière			
Pneumopathies à pneumocoques non bactériémiques hospitalisées	1,2%	8,5%	Pneumocost
Infections invasives à pneumocoques (hors méningites), patients à risque de base	2,9%	10,5%	SIIPA
Infections invasives à pneumocoques (hors méningites), patients à risque élevé ou très élevé	15,7%	20,7%	SIIPA
Infections invasives à pneumocoques (hors méningites), tous patients	12,7%	18,6%	SIIPA
Méningites à pneumocoques	12,7%	28,8%	PMSI 2013
Mortalité post hospitalière			
Pneumopathies à pneumocoques non bactériémiques hospitalisées	1,3%	4,3%	Pneumocost
Infections invasives à pneumocoques (hors méningites), tous patients	0,0%	1,1%	Pneumocost

Tableau 13 : Mortalité des infections invasives et des pneumopathies à pneumocoques

	Groupes d'âge (année)		
Paramètre (minimum-maximum)	**18-64**	**≥ 65**	
Mortalité hospitalière			
Pneumopathies à pneumocoques non bactériémiques hospitalisées	0,8%-2,4%	5,7%-17,1%	
Mortalité post hospitalière			
Pneumopathies à pneumocoques non bactériémiques hospitalisées	1,3% (0%-3%)	4,3 % (0%-11 %)	
Infections invasives à pneumocoques (hors méningites), tous patients	0 % (0%-4%)	1,1 % (0-6%)	

Sources :

Mortalité intra-hospitalière des infections invasives à pneumocoques chez l'adulte (hors méningites). Source : Etude "Surveillance des infections invasives à pneumocoque chez l'adulte, SIIPA", Oct 2012-June 2015 unpublished data

Mortalité intra-hospitalière des pneumopathies à pneumocoque non bactériémiques chez l'adulte PNEUMOCOST database, unpublished, *avec correction pour la non-inclusion des patients décédés à l'admission*

Mortalité post-hospitalière des infections à pneumocoque bactériémiques chez l'adulte PNEUMOCOST database, unpublished

Mortalité post-hospitalière des pneumopathies à pneumocoque non bactériémiques chez l'adulte PNEUMOCOST database, unpublished

Mortalité des pneumopathies à pneumocoque communautaire (ie prise en charge en ambulatoire) chez l'adulte Etude CAPA, base de donnée, Partouche, Prim Care Respir Med 2015

Mortalité intra-hospitalière des méningites à pneumocoques chez l'adulte : Source : Programme de médicalisation des systèmes d'information, PMSI court séjour 2013,France métropolitaine

12.2 Annexe 1 : Estimation de la prévalence des groupes à risques d'infection invasive à pneumocoquesdans la population adulte de France métropolitaine

Les groupes de risque sont définis dans les recommandations de vaccination anti-pneumococcique du Haut Conseil de santé Publique du 25 avril 2013 qui distingue les personnes à risque **élevé** atteints de maladies chroniques et non immunodéprimés, des personnes à risque **très élevé** du fait d'une immunodépression, d'un implant cochléaire ou d'une brèche ostéo-méningée (6).

Groupes à risque selon l'avis du HCSP, du 25 avril 2013 :

1) Patients à risque très élevé, ou patient à haut risque :

1. Immunodéprimés :
    1. patients aspléniques ou hypospléniques (dont les drépanocytoses majeures)
    2. patients atteints de déficits immunitaires héréditaires ;
    3. patients infectés par le VIH, quel que soit le statut immunologique ;
    4. patients sous chimiothérapie pour tumeur solide ou hémopathie maligne ;
    5. patients transplantés ou en attente de transplantation d'organe solide ;
    6. patients greffés de cellules souches hématopoïétiques ;
    7. patients traités par immunosuppresseur, biothérapie et/ou corticothérapie pour une maladie auto-immune ou inflammatoire chronique ;
    8. patients atteints de syndrome néphrotique.
2. Présentant une brèche ostéo-méningée ou candidats à des implants cochléaires.

2) Patients à risque élevé ou patients à risque :

3. cardiopathie congénitale cyanogène, insuffisance cardiaque
4. insuffisance respiratoire chronique, bronchopneumopathie obstructive, emphysème ;
5. asthme sévère sous traitement continu ;
6. insuffisance rénale ;
7. hépatopathies chroniques de toutes origines ;
8. diabète non équilibré par le simple régime.

La prévalence de ces différentes affections a été estimée en utilisant les effectifs des personnes inscrites en affection de longue durée (ALD) pour celles de ces pathologies pour laquelle une ALD ou un sous-groupe de pathologies d'une ALD donnée existait. Il s'agit des ALD 2, 5, 6,7, 10 (Code CIM D57, drépanocytose), 19, 28 et 30 (avec correction) présentées dans le tableau X1.

La prévalence a été calculée en divisant les effectifs des patients sous ALD par tranche d'âge quinquennale en 2013, par les effectifs de la population française de cette tranche d'âge en 2013.

Pour trois groupes de pathologies : le diabète non équilibré par un simple régime, les pathologies respiratoires chroniques et les patients traités par chimiothérapie pour un cancer l'estimation a utilisé une source complémentaire ou alternative à celle des ALD.

Les effectifs des patients atteints de diabète traités, ont été calculés en utilisant l'estimation de la prévalence du diabète traité pharmacologiquement en 2013 réalisée par le département des maladies chroniques de l'InVS (34).

Afin d'utiliser une estimation de prévalence des affections respiratoire chronique (BPCO, Asthme sévère) plus proche des ordres de grandeur cités dans les estimations françaises , une prévalence estimée de 7,5% est citée dans Fuhrman et al.) que la prévalence de 0,9% de l'ALD 14, correspondant à une insuffisance respiratoire chronique grave, la prévalence des BPCO, asthme et autres pathologies respiratoires chroniques a été estimée en utilisant les données de l'ALD 14, et la prévalence des maladies respiratoires chroniques tous âges confondus parmi les assurés du régime général estimée à 4,9% (2 859 500 / 58 753 200) en 2013 par la CNAMTS (33). Les effectifs par tranche d'âge quinquennale de l'ALD14 ont été multipliés par un facteur multiplicatif c de 5,4. Ce facteur c (= 5,4) a été calculé en divisant la prévalence globale des maladies respiratoires chroniques (5,9%) par celle de l'ALD 14 (0,9%), tous âges confondus. Du fait d'une sous estimation de la prévalence des facteurs de risque dans la population, les effectifs des pathologies respiratoires chroniques ont été additionnés aux effectifs des personnes atteintes d'insuffisance respiratoire grave.

Les effectifs des patients atteints de cancer traités par chimiothérapie ont été estimés en appliquant la proportion des cancers traités par chimiothérapie tous âges confondus estimé par l'INCA (5) variable selon le type de cancer et leur localisation, aux effectifs de cancers identifiés par leur code CIM inscrits en ALD30. Globalement l'effectif des cancers inscrits en ALD30 était de 2 388 955, celui des cancers traités par chimiothérapie était de 315 520 soit 13% de l'ensemble des cancers, la prévalence de la chimiothérapie de certains cancers fréquents tels que le cancer de la prostate étant faible.

Les effectifs et prévalence sont présentés dans le tableau X2.

Tableau X1 : ALD ou autres sources de données utilisées pour estimer la prévalence des groupes à risque dans la population française

ALD	Libellé ALD ou de la pathologie	Groupe à risque	Précisions
2	Insuffisances médullaires et autres cytopénies chroniques	Haut risque	
7	Déficit immunitaire primitif grave nécessitant un traitement prolongé et infection par le VIH	Haut risque	
10	Hémoglobinopathies, hémolyses, chroniques constitutionnelles, acquises sévères	Haut risque	Seulement code CIM : 'D57' (drépanocytose)
19	Syndrome néphrotique	Haut risque	ALD19, code CIM N04 (=syndrome néphrotique)
28	Suites de transplantation d'organe	Haut risque	
30	Tumeurs malignes traitées par chimiothérapie	Haut risque	ALD30, % sous chimiothérapie selon l'estimation de l'INCA (5)
5	Insuffisance cardiaque grave, troubles du rythme graves, cardiopathies valvulaires graves, cardiopathies congénitales graves	A risque	Sauf codes CIM I47-I49 (I47 : tachycardie, I48 : Fibrillation ou flutter auriculaire, I49 : autres arythmies)
6	Maladies chroniques actives du foie et cirrhoses	A risque	
14	Insuffisance respiratoire chronique grave	A risque	X facteur correcteur c= 5,4
19	Néphropathie chronique grave- autres	A risque	ALD19 sauf code CIM N04
-	Diabète de type 1 et diabète de type 2	A risque	Estimation InVS (34)

Tableau X2 : Effectifs et prévalence dans la population âgée de 18 ans et plus des personnes risque élevé et très élevé, France métropolitaine, 2013

		18-49	50-64	65-79	80 et +	Tous ≥ 18	Données sources
A	Insuffisances médullaires et autres cytopénies chroniques	2 564	3 442	7 545	8 579	22 130	ALD 2
B	Insuffisance cardiaque grave, cardiopathies valvulaires graves, cardiopathies congénitales graves	46 478	102 698	197 232	262 840	609 248	ALD 5 - codes CIM I47-I49
C	Maladies chroniques actives du foie et cirrhoses	54 423	84 058	47 757	11 791	198 029	ALD 6
D	Déficit immunitaire primitif grave et infection par le VIH	65 424	39 699	7 674	703	113 500	ALD 7
E	Diabète traité	282 664	967 507	1 204 663	502 411	2 957 245	InVS
F	Drépanocytose	3 976	548	91	10	4 625	ALD 10, code CIM D57
G	Insuffisance respiratoire grave	51 931	104 197	141 190	100 088	397 406	ALD 14
H	Syndrome néphrotique	3 384	1 834	1 311	523	7 052	ALD 19, code CIM NO4
I	Insuffisance rénale	24 188	31 475	41 854	41 024	138 541	ALD 19 sauf code NO4
J	Transplantation	3 304	3 988	2 550	308	10 150	ALD
K	Cancer traité par chimiothérapie	30 737	93 489	124 153	64 583	312 962	ALD30 + correction proportion sous chimiothérapie
L	Maladies respiratoires chroniques (Asthme, BPCO)	378 984	760 415	1 030 385	730 429	2 900 213	ALD14 X **5,4**
	Total patient à risque élevé (B+C+E+G+I+L)	838 668	2 050 350	2 663 081	1 648 582	7 200 681	
	Total patients à risque très élevé (A+D+F+H+K)	109 390	143 000	143 324	74 706	470 420	
	Population France métropolitaine, 2013	25 907 560	12 323 750	7 907 250	3 711 711	49 850 271	
	Prévalence pathologie à risque élevé	**3,2%**	**16,6%**	**33,7%**	**44,4%**	**14,4%**	
	Prévalence pathologie à risque très élevé	**0,4%**	**1,2%**	**1,8%**	**2,0%**	**0,9%**	

12.3 Annexe 2 : Estimation du nombre d'infections invasives à pneumocoques survenant dans la population adulte française selon leur niveau de risque vis-à-vis des infections invasives à pneumocoques

L'incidence et le nombre de cas par an des infections invasives à pneumocoques, des bactériémies à pneumocoques et des méningites à pneumocoquesen population générale ont été extraites des données du réseau Epibac (40) et sont présentées dans le tableau 2 ci-dessous.

Le nombre de cas d'infections invasives à pneumocoquessurvenant une année donnée parmi les personnes à risque de base, élevé et très élevé, a été estimé en appliquant la répartition des cas entre ces trois groupes à risque observée chez les adultes inclus dans l'étude « Surveillance des infections invasives à pneumocoques chez l'adulte, SIIPA » d'octobre 2012 à décembre 2015 (43) au nombre total de cas issu des données du réseau Epibac. Les cas inclus dans l'étude SIIPA ont été classés dans les trois groupes à risque selon le regroupement figurant dans les recommandations de vaccination contre le pneumocoque du HCSP du 25 avril 2013.

Tableau X3 : Incidence et effectifs des infections invasives à pneumocoques selon leur niveau de risque

	Groupes d'âge (année)				
Paramètre (base case)	**18-49**	**50-64**	**65-79**	**≥ 80**	**Tous ≥ 18**
Infections invasives à pneumocoques (IIP)					
Incidence pour 100 000 pop. en population générale	3,6	9,8	16,0	40,6	10,0
Nombre de cas, France	925	1211	1309	1536	4982
Proportion d'IIP selon le niveau de risque (Source : SIIPA 2012-2015, n=598)					
Proportion chez les personnes à risqué de base	59%	32%	30%	36%	37%
Proportion chez les personnes à risqué élevé	18%	32%	39%	52%	37%
Proportion chez les personnes à risqué très élevé	22%	37%	32%	13%	25%
Nombre de cas par groupes de risque, France[a]:					
Personnes à risque de base	550	382	386	547	1 866
Personnes à risque élevé	167	382	508	793	1 850
Personnes à risque très élevé	207	447	415	196	1 266
Incidence pour 100 000 par groupes de risque [b]:					
Personnes à risque de base	2,2	3,8	7,3	27,0	4,4

Personnes à risque élevé	20,1	18,5	18,5	47,2	25,3
Personnes à risque très élevé	190,7	311,5	280,6	257,6	265,7

a : = Incidence des IIP en populations générale X proportion des IIP survenant dans le groupe de risque pour le groupe d'âge considéré

b : Pour chaque strate d'âge et de niveau de risque : Incidence = Nb de cas X 100 000 / Population de la même strate

12.4 Annexe 3 : Estimation de l'incidence des pneumopathies à pneumocoques communautaires selon le niveau de risque

L'incidence des pneumopathies à pneumocoques communautaires chez les personnes des différents groupes de risque composant la population adulte française a été déterminée en utilisant la prévalence de chacun des groupes de risque dans la population et le risque relatif de pneumopathie à pneumocoquesde chacun de ces groupes de risque vis-à-vis du groupe à risque de base basée sur la publication de Shea (35). Les cas de pneumopathies à pneumocoques communautaires survenant en population générale étant la somme des cas survenant dans chacun des groupes de risque, l'incidence des pneumopathies à pneumocoques communautaires dans un groupe d'âge et de risque donnés peut être exprimée en fonction de l'incidence en population générale, de la prévalence de chacun des trois groupes de risque et du risque de pneumopathies à pneumocoques communautaires dans ce groupe d'âge et de risque vis-à-vis du risque dans la population à risque de base appartenant au même groupe d'âge. Les formules ci-dessous explicitent les modalités de calcul, de l'incidence dans la population à risque de base d'une part puis de celles dans les populations à risque élevé et très élevé.

1. $TI \times Pop. = TI_{RB} \times 1 \times Pop._{RB} + TI_{RE} \times Pop._{RE} + TI_{RTE} \times Pop_{RTE}$
2. $TI_{RE} = TI_{RB} \times RR_{RE}$ et $TI_{TRE} = TI_{RB} \times RR_{TRE}$, de (1) et (2) ont peut écrire (3)
3. $TI \times Pop = TI_{RB} \times 1 \times Pop_{RB} + TI_{RB} \times RR_{RE} \times Pop_{RE} + TI_{RB} \times RR_{TRE} \times Pop_{RTE}$

qui équivaut à :

4. $TI = [TI_{RB} \times 1 \times Pop.RB + TI_{RB} \times RR_{RE} \times Pop._{RE} + TI_{RB} \times RR_{TRE} \times Pop_{RTE}] / Pop$

Qui équivaut à :

5. $TI = TI_{RB} \times 1 \times P_{RB} + TI_{RB} \times RR_{RE} \times P_{RE} + TI_{RB} \times RR_{TRE} \times P_{RTE}$

qui équivaut à :

6. $TI = TI_{RB} \times [1 \times P_{RB} + RR_{RE} \times P_{RE} + RR_{TRE} \times P_{RTE}]$

de l'expression (6) on peut exprimer le taux d'incidence dans la population à risque de base :

7. $TI_{RB} = TI / [1 \times P_{RB} + RR_{RE} \times P_{RE} + RR_{TRE} \times P_{RTE}]$

Le taux d'incidence dans les populations à risque est exprimé en fonction de celui de la population à risque de base et du risque relatif :

$TI_{RE} = TI_{RB} \times RR_{RE}$ et $TI_{TRE} = TI_{RB} \times RR_{TRE}$

Avec :

TI : Taux d'incidence pour 100 000 dans la population d'un groupe d'âge donné

RB, RE, RTE : risque de base, risque élevé, risque très élevé

RR_{RTE} : risque relatif dans la pop. a risque élevé vs pop. à risque de base

P_{RB}, P_{RE}, P_{RTE} : prévalence du risque de base, du risque élevé et du risque très élevé

Une contrainte supplémentaire a été introduite : le nombre (et l'incidence) des pneumopathies à pneumocoques communautaires dans un groupe d'âge et de risque donnés ne devait pas excéder le nombre de pneumopathies à pneumocoques hospitalisées dans ce groupe d'âge et de risque, ce dernier étant par ailleurs estimé à partir des données d'Epibac pour l'l'incidence des bactériémies à pneumocoques et de l'étude SIIPA pour la répartition des bactériémies à pneumocoques entre les trois groupes de risque. L'incidence des pneumopathies à pneumocoques communautaires dans le groupe à risque très élevé âgé de 65 ans et plus a ainsi été fixée au même niveau de 770,8 cas / 100 000 hab. que celle des pneumopathies à pneumocoques hospitalisées, ce qui correspond à un risque relatif de 6,8, différent du risque relatif de 4,3 de la publication de de Shea (35). La prévalence des risques très élevé estimée dans la population des adultes français est inférieure à celle observée dans la population sur laquelle a été basée l'analyse de Shea et al, la différence étant particulièrement importante pour les adultes âgés de 65 ans ou plus, 2% dans notre estimation *versus* 15% dans la publication de Shea et al. Par ailleurs le nombre et l'incidence des pneumopathies toutes causes est issue d'une analyse portant sur les cas vus en médecine générale, il est vraisemblable que celui-ci constitue une sous estimation, certains cas pouvant être diagnostiqué aux urgences ou par un médecin spécialiste, d'autant plus chez ces patients âgés et atteints d'une pathologie à risque très élevé. La contrainte introduite conduit à estimer un nombre de cas qui a été jugé plus plausible.

Tableau X4 : Incidence des pneumopathies à pneumocoques communautaires selon le niveau de risque

	Groupes d'âge (année)		
Paramètre (base case)	**18-64**	**≥ 80**	**Tous ≥ 18**
Pneumopathies à pneumocoques communautaires[c]			
Incidence pour 100 000 pop. en population générale[a]	131,5	214,7	151,3
Nombre de cas, France	50 107	25 637	75 744
Prévalence du risque de base (RB)	91,8%	61,0%	
Prévalence du risque élevé (RE)	7,6%	37,1%	
Prévalence du risque très élevé (RTE)	0,7%	1,9%	
Risque relatif RE vs RB[b]	3,2	3,1	
Risque relatif RTE vs RB[b]	6,4	6,8	
1 X prévalence RB (1)	91,8%	61,0%	
RR RE X prévalence MR (2)	23,9%	115,0%	

RR RTE X prévalence HR (3)	4,2%	12,7%	
(4) = (1) + (2) + (3)	119,9%	188,8%	
Incidence pour 100 000 pop. par groupe de risque :[c]			
Incidence pour 100 000 pop. à RB	109,7	113,7	110,4
Incidence pour 100 000 pop. à RE	346,3	352,5	350,1
Incidence pour 100 000 pop. à RTE	702,7	770,8	734,8
Nombre de cas par groupes de risque, France:			
Personnes à risque de base	38 365	8 286	46 651
Personnes à risque élevé	9 974	15 623	25 597
Personnes à risque très élevé	1 768	1 727	3 496

[a] : Source : Personne et al. CAPECO: Cost evaluation of community acquired pneumonia managed in primary care (31)

[b] : Source : Shea et al. Pneumococcal Disease in Adults (35).