Higher-valency pneumococcal conjugate vaccines in elderly, taking into account indirect protection and serotype replacement from childhood vaccination programs: A cost-effectiveness study

Pieter T. de Boer[1,*], Cornelis H. van Werkhoven[1], Albert Jan van Hoek[1], Mirjam Knol[1], Elisabeth A.M. Sanders[1,2], Jacco Wallinga[1,3], Hester E. de Melker[1], Anneke Steens[1]

1. Center for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), the Netherlands
2. Department of Pediatric Immunology and Infectious diseases, University Medical Center Utrecht, The Netherlands
3. Department of Biomedical Datasciences, Leiden University Medical Center, the Netherlands

*Corresponding author:
Pieter T. de Boer
Postbus 1 (box 75), 3720 BA,
Bilthoven, the Netherlands
Pieter.de.boer@rivm.nl

Abstract

Background

New 15- and 20-valent pneumococcal conjugate vaccines (PCV15, PCV20) have recently become available for adults, while a 21-valent pneumococcal vaccine (PCV21) for adults is currently undergoing phase 3 trials. Although cost-effectiveness assessments of these vaccines for the elderly exist, they have not considered the potential impact of indirect protection and serotype replacement following the introduction of PCV15 and PCV20 in childhood pneumococcal vaccination programs. We aimed to assess the cost-effectiveness of higher-valency conjugate vaccines for the elderly in a setting where a 10-valent pneumococcal conjugate vaccine (PCV10) program for children has been implemented, and with consideration of indirect effects from a transition to PCV13, PCV15 and PCV20 in children.

Methods

A static model parameterized for the Netherlands was utilized to assess the cost-effectiveness of various pneumococcal vaccination strategies for a 65-year-old cohort over a 15-year period. The vaccines considered were the 23-valent pneumococcal polysaccharide vaccine (PPV23), 13-valent pneumococcal conjugate vaccine (PCV13), PCV15, PCV20 and PCV21. It was assumed that indirect protection from serotypes added to the childhood vaccine would reduce the incidence of these vaccine serotypes among the elderly population by 80% (except for serotype 3, no effect), and that this reduction in overall incidence was offset by an increase in the incidence of serotypes not covered by the childhood vaccine due to serotype replacement. These indirect effects were assumed to occur gradually, reaching completion after 8 years.

Results

Among the currently available vaccines and assuming that children were continued to be vaccinated with PCV10, PCV20 was found to be the cost-effective strategy in the elderly at thresholds of €20,000 and €50,000 per quality-adjusted life year (QALY) gained. The incremental cost-effectiveness ratio (ICER) for PCV20 in the 65-year-old cohort, compared to no vaccination, was estimated at €9,000 per QALY gained. PCV21 was projected to result in higher QALY gains than PCV20, but its price is unknown. The cost-effectiveness of PCV15, PCV20 and PPV23 in the elderly was adversely impacted by indirect effects from higher-valency vaccines in children, depending on the overlap of serotypes between childhood and elderly vaccines. PCV20 remained the cost-effective strategy in the 65-year-old cohort at a threshold of €20,000 per QALY gained if PCV13 or PCV15 were used in children but not if PCV20 was also used in children. In this case, the ICER for PCV20 increased to €22,250 per QALY gained compared to no vaccination. As indirect effects progressed over time, the cost-effectiveness of PCV20 further increased for newly eligible cohorts since time of transitioning to PCV20 in children. In cohorts vaccinated three years after this transition, repeated PPV23 became the cost-effective strategy at an ICER of €35,000 per QALY gained compared to no vaccination. The cost-effectiveness of PCV21, which is in development, was found to be minimally affected by transitioning to PCV20 in children due to its coverage of a complementary range of serotypes than the childhood vaccine.

Conclusion

PCV20 proves to be economically favorable intervention for the elderly when the childhood program includes PCV10, PC13 or PCV15. However, once the childhood vaccination incorporates PCV20, the best results are found with vaccines for the elderly that have the largest difference in serotypes

covered by the childhood and elderly vaccination programs, such as PCV21. This study underscores the significance of integrating economic evaluations for both children and elderly vaccination programs to maximize the reduction of pneumococcal disease at a population level.

Introduction

The *Streptococcus pneumonia* bacterium can cause symptomatic infections with varying degrees of severity. These infections include invasive pneumococcal disease (IPD), such as bacteraemic pneumonia and meningitis, as well as non-invasive pneumococcal pneumonia (NIPP). They are responsible for significant morbidity, mortality, and economic burden [1]. Young children, immunocompromised individuals, and the elderly, in particular after 70-75 years of age, are at highest risk of severe disease. Currently, approximately 100 pneumococcal serotypes have been identified, which vary in pathogenicity. Existing vaccines cover a selected range of serotypes that are most commonly associated with severe disease.

Many countries have introduced vaccination programs for those with the highest disease burden. Since 2020, the Netherlands has implemented a vaccination program for individuals aged 60-79, using the 23-valent pneumococcal polysaccharide vaccine (PPV23) vaccine with revaccination every 5 years. This revaccination is needed because the PPV23 vaccine does not stimulate B memory cells, resulting in limited duration of protection [2]. The 13-valent pneumococcal conjugate vaccine (PCV13), which is also available for the elderly, provides better and longer-lasting protection against the serotypes covered by the vaccine due to its stimulation of B memory cells. However, the disease burden in elderly caused by serotypes covered by PCV13 has significantly decreased in the Netherlands due to indirect protection from childhood vaccination programs with high vaccination coverage [3], starting with 7-valent PCV (PCV7) in 2006 and later with 10-valent PCV (PCV10) in 2011. This decrease is less pronounced for PPV23 as serotype replacement has led to an increase in disease burden among elderly from non-PCV10 serotypes, which are partially covered by PPV23. Due to this serotype replacement and the suboptimal protection provided by PPV23, the disease burden of pneumococcal infections in elderly remains high.

In response to this challenge, there have been recent developments and ongoing efforts to create higher-valent PCVs. Currently, 15-valent PCV (PCV15) is licensed for adults and children, and 20-valent PCV (PCV20) is licensed for adults and expected to be licensed for children in the very near future. Additionally, a new 21-valent PCV (PCV21) is currently evaluated in a phase-3 among adults, containing eight serotypes that are not included in PCV20 or PPV23. Cost-effectiveness studies from several countries found PCV20 to be highly cost-effective or even cost-saving compared to PPV23, to PCV13 or to a combination of PCV13 followed by PPV23 [4-8], except one study from the US [9]. It is well-established that previous childhood PCV programs have altered the serotype distribution of pneumococcal disease among adults through via indirect protection and serotype replacement [10, 11], with potentially large consequences on the cost-effectiveness of pneumococcal vaccination programs for elderly. However, although some existing cost-effectiveness studies of these new vaccines have explored indirect protection from higher valency vaccines in children in their analysis [8, 9], none have considered serotype replacement.

In this cost-effectiveness study, we use the Netherlands as an example to assess the cost-effectiveness of different pneumococcal vaccination programs, including PCV15, PCV20, and PCV21, in the elderly population. As the Netherlands has started relatively late with pneumococcal vaccination for the elderly in 2020, our analysis primarily relies on data obtained from an unvaccinated elderly population with a matured vaccination program in children with PCV10. We explicitly take into account the indirect protection and serotype replacement from the use of higher-

valency vaccines in children based on historic observations after the introduction of vaccination programs with PCV10 and PCV13 in children.

Methods

Analysis framework

A previously published static multi-cohort model [12] was utilized and updated to quantify costs and quality-adjusted life years (QALYs) lost for different pneumococcal vaccination strategies in the elderly population of the Netherlands. The model is run in time steps of one year, in which a proportion of the cohort is hospitalized due to IPD or NIPP according to age-specific hospitalization rates, and could die following hospitalization according to age-specific case-fatality rates. The model does not consider the burden of pneumococcal disease in primary care, as the effectiveness against this outcome in elderly is uncertain [13], and the relative contribution of pneumococcal disease burden in primary care is limited [14]. As recommended by the Dutch cost-effectiveness guideline [15], the analysis adopts a societal perspective (includes medical costs as well as cost to the patient and productivity losses). Future costs were discounted to the present value at 4% per year, and future QALYs at 1.5% per year [15].

The main analysis follows a Dutch cohort of 65-year-olds (228,209 individuals) over a time horizon of 15 years. Additionally, alternative vaccination ages (60, 70, 75, 80 and 85 years) and time horizons (shorter than 15 years) have been explored. The following vaccination strategies were considered:

1) no vaccination
2) PPV23 at year 0, year 5 and year 10 (3x PPV23)
3) PCV13 at year 0
4) PCV15 at year 0
5) PCV20 at year 0
6) PCV13 at year 0, PPV23 at year 1, 6 and 11 (PCV13 + 3x PPV23)
7) PCV15 at year 0, PPV23 at year 1, 6 and 11 (PCV15 + 3x PPV23)
8) PCV20 at year 0, PPV23 at year 1, 6 and 11 (PCV20 + 3x PPV23)
9) PCV21 at year 0

We assessed the cost-effectiveness of vaccination in elderly while maintaining PCV10 in the national vaccination program for children, or while transitioning to PCV13, PCV15 and PCV20 in children. A transition to a higher-valency vaccine in children was assumed to result in indirect protection and serotype replacement, changing the pneumococcal epidemiology in the elderly population. The transition to a new vaccine type in children was assumed to occur at the same time as the first vaccination for the elderly cohort (year 0). It is important to note that the analysis does only account for indirect effects from childhood vaccination on the cost-effectiveness of vaccination of the elderly cohort; additional vaccination costs in children, direct impact in children and indirect impact to younger adults are not included in the analysis.

Input data (see Table 1 and supplemental materials)

Epidemiology

The model used Dutch pneumococcal incidence data from before 2020, when there was no vaccination of elderly with PPV23, and before the COVID-19 pandemic response measures were implemented. The incidence of IPD cases by age-group was obtained from Dutch national surveillance among sentinel laboratories, covering approximately 25% of the national population, using the average IPD incidence in the years 2017-2019 to account for seasonal fluctuations. Age-specific incidence estimates were split into different vaccine-serotype categories using the serotype

distribution among all IPD cases aged 60 or older in 2019 (Supplemental Table S2). Thirty-day case-fatality rates for IPD by age-group were obtained by re-analyzing data from Vestjens et al. [3]. The age-specific incidence of NIPP hospitalizations was estimated using Dutch national hospitalization data on all-cause community-acquired pneumonia (CAP) hospitalizations (International Classification of Diseases, ICD-10-AM codes J9-J18) for the years 2012-2014, assuming 22.1% of CAP hospitalizations to be caused by *S. pneumoniae* as observed in the placebo-group of the CAPITA trial [16]. The estimated incidence of pneumococcal-related CAP was indexed to the 2017-2019 time-period using the time-trend of the IPD. Finally, we subtracted the incidence of IPD that was explained by invasive pneumonia (80% of all IPD cases [17]) to obtain the incidence of hospitalizations from NIPP. The case-fatality rates of NIPP were based on the case-fatality rates of IPD, multiplied with a factor 0.85 (ratio of 30-day mortality between non-IPD CAP cases and IPD cases from [18]).

Indirect effects from childhood vaccination programs

In the analysis of continuation of PCV10 in children, we assumed that the incidence for each serotype has reached a steady state in the ≥60-year-old population, as the incidence per serotype category tends to stabilize in 2019, eight years after the switch from PCV7 to PCV10 in the childhood vaccination program (Supplemental Figure S2 and [19]). For a switch from PCV10 to PCV13, PCV15, or PCV20 in children, the analysis considered indirect effects on the pneumococcal epidemiology among ≥60-year-olds based on historic data of PCV10 and PCV13 childhood programs from the multi-country studies PSERENADE and SpIDnet [10, 20, 21]. We took the following assumptions:

1) The incidence of serotypes added to the childhood vaccine reduced by 80% among elderly after 8 years, starting one year after the vaccine switch in children and occurring linearly over time. No indirect protection was assumed for serotype 3. Cross-protection from 6A to 6C was assumed [21], and the incidence of 6C in elderly followed the decline of (other) vaccine serotypes.
2) The incidence of serotypes not included in the childhood vaccine increased linearly among the elderly until the incidence of all serotypes combined has returned to the same level as the pre-indirect effects period (i.e. 100% serotype replacement). This replacement started 3 years after the vaccine transition in children and finished 8 years after the transition. The relative contribution of the different non-vaccine serotypes was assumed to remain constant while increasing.

The new steady state in pneumococcal incidence was reached after eight years and was continued for the remainder of the time horizon. The impact of indirect effects on the incidence and serotype distribution of IPD over time are visualized in Supplemental Figure S3. The assumptions on the magnitude of the indirect effects have been varied in the sensitivity analysis.

Vaccination

The impact of vaccination is modelled as a risk reduction of the incidence of pneumococcal disease caused by vaccine serotypes. Vaccination was assumed to be immediately effective in the year of administration. The vaccination coverage was set at 70%, approximating the uptake of the Dutch pneumococcal vaccination program for elderly in 2020 and 2021 [22, 23]. The vaccine effectiveness (VE) of PPV23 and the different PCVs were modelled to decrease with increasing vaccination age, and to wane over time. The waning and duration of protections were derived from an earlier cost-effectiveness analysis of pneumococcal vaccination for the Netherlands [12], and were varied in the sensitivity analysis.

For PPV23, age-specific estimates of VE against IPD were based on two observational studies from the UK [24, 25] (Supplementary Figure S4). VE against hospitalized NIPP among 65-74-year-olds was derived from a systematic review [26], and we assumed the age-trend to be equal to IPD. The VE

was assumed to be stable in the first two years (follow-up period of the data from the observational studies), followed by a linear decline to zero at five years after vaccination.

For PCVs, the age-specific VEs against IPD and hospitalized NIPP were based on vaccine efficacy estimates from the modified intention-to-treat population of the CAPiTA study, a large randomized placebo-controlled clinical trial for PCV13 among ≥65-year-olds conducted in the Netherlands in the period 2008-2013 [16] (see Supplementary Figure S5). As the population of CAPiTA was considered more healthy than the general population, we multiplied the vaccine efficacies with a factor 0.9. In absence of clinical studies for PCV15, PCV20 and PCV21 in elderly, we extrapolated the efficacy of PCV13 to the added serotypes, as well as to serotype 6C due to evidence on cross-protection via serotype 6A [20]. The VE of PCVs was assumed to be stable in the first four years (follow-up period of the CAPiTA trial [16]), followed by a linear decline to 0% at 15 years after vaccination.

For combined vaccination strategies with PCV and PPV23 we used in each time-step the VE of the vaccine type with the highest VE; hence, no additional effectiveness was assumed against serotypes shared by PCV and PPV23.

Costs

The used cost year was 2021, and all costs were inflated to this price year using the Dutch consumer price index (all sectors) [27]. All estimates of hospitalization costs, patient costs and productivity losses were based on Dutch data from various previously published studies [14, 18, 28]. Vaccine prices of PPV23, PCV15, PCV20 were based on the Dutch list price for individual use [29]. The vaccine price of PCV21 is unknown, and was assumed to be equal to PCV20. The administration cost per vaccination was based on the fee a general practitioner received in 2021 for the invitation and administration of PPV23 in the Dutch national vaccination program [30].

QALYs

The QALY losses of both IPD and hospitalized NIPP were based on a Dutch study measuring the utility loss among hospitalized non-fatal CAP cases during the acute phase and the first month of the illness using the EuroQol five dimensional instrument (EQ-5D) [14]. QALYs lost due to premature death was estimated using the life-expectancy of a general Dutch person at that age [31], adjusted for age-specific Dutch general population utilities [32].

Cost-effectiveness

Total costs and QALY losses associated with each alternative strategy were accumulated over the time-horizon of 15 years. Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in costs of two alternative strategies by the difference in QALY losses. Strategies that were found to be strongly dominated (less effective and more costly than another alternative) or extendedly dominated (less effective and higher ICER than another alternative) were removed from the comparison. Additionally, a multi-variable probabilistic sensitivity analysis using 1,000 simulations was conducted, in which multiple parameters were varied at the same time within their distributions (see Supplementary Tables S1, S3-S54). The outcomes of this analysis were presented in cost-effectiveness acceptability curves, which illustrates the cost-effective strategy (highest net monetary benefit, see [33] for details) across a range of thresholds. In the Netherlands, commonly used cost-effectiveness thresholds are €20,000 per QALY gained for preventive interventions and €50,000 per QALY gained for interventions targeting diseases with moderate health impact [34]. We also performed one-way sensitivity analyses to assess the impact of different assumptions or alternative sources on the cost-effectiveness outcomes.

Table 1: Parameter values used in the base case analysis. Distributions for the probabilistic sensitivity analysis are shown in Supplemental Table S1, in Supplemental Tables S3-S4 and in Supplemental Figures S4-S5. Alternative inputs for the one-way sensitivity analysis are shown in Supplemental Table S5.

Parameter	**Input for base case**		**Source / comment**
Epidemiology			
Incidence per 100,000 py (all serotypes)	IPD	Hospitalized NIPP	IPD: RIVM IPD surveillance data of 2017-2019;
60-64y	28	21	Hospitalized NIPP: J9-J18 data of
65-69y	34	37	2012-2014, with 20.1% caused by
70-74y	47	60	pneumococcus [35]. The NIPP
75-79y	53	100	incidence was indexed to 2017-
80-84y	66	153	2019 using the IPD trend and
85-89y	77	210	adjusted for pneumonia-related
≥90y	83	242	IPD cases from [17].
30-day case-fatality rate (all serotypes)	IPD	Hospitalized NIPP	IPD: re-analysis of [3]; Hospitalized NIPP: IPD rates*0.85,
60-69y	10%	8%	based on the ratio of 30-day
70-79y	16%	14%	mortality due to non-IPD CAP and
80-89y	23%	20%	IPD [18].
≥90y	31%	26%	
Serotype distribution	See Supplemental Table S2	Equal to IPD	RIVM IPD surveillance data of 2019
Indirect effects from higher-valency vaccines in the childhood vaccination program[1]			
Indirect protection			
Effect size	80% reduction in incidence of serotypes added to the childhood vaccine (except for serotype 3, 0% reduction)		[10, 20, 21]
Time frame	Linear decrease over 7 years, starting 1 year after transition change in childhood program		[10, 20, 21]
Serotype replacement			
Effect size	Increase in incidence of non-vaccine serotypes until overall incidence back at pre-indirect effects level		[10, 20, 21]
Time frame	Linear increase over 5 years, starting 3 years after change in childhood program		[10, 20, 21]
Vaccination			
Vaccination uptake	70%		Similar to [22, 23]
VE against vaccine-type	IPD	Hospitalized NIPP	
PCV13	Age-specific, from 81% at 60-65y to 35% at 85y	Age-specific, from 54% at 60-65y to 2% at 85y	[16, 36, 37], adjusted -10% due to relatively healthy population in the CAPITA study.
PPV23	Age-specific, from 52% at 60-65y to 33% at 85y	Age-specific, from 27% at 60-65y to 0% at 85y	Estimated from [24, 25]
Waning (IPD and CAP)			
PCV	4 years stable, in 11 years to 0	4 years stable, in 11 years to 0	As assumed in [12]
PPV23	2 years stable, in 3 years to 0	2 years stable, in 3 years to 0	Stable period consistent with data from [24, 25]. Duration of protection as assumed in [12].

Serotype coverage by vaccine (≥60 years) [2]	IPD	Hospitalized NIPP	
PPV23	80.2%	Equal to IPD	RIVM surveillance data for IPD.
PCV13	33.6%	Equal to IPD	
PCV15	44.5%	Equal to IPD	
PCV20	76.7%	Equal to IPD	
PCV21	90.9%	Equal to IPD	
QALY loss			
Hospitalization due to IPD/hospitalized NIPP	0.0709		[14]
Death due to IPD/hospitalized NIPP	Age-specific, see supplemental Figure S6		Life expectancy of general population , adjusted for health-related quality of life [32]
Costs			
Hospitalization costs	IPD	Hospitalized NIPP	[18], for 60-64 the value of 65-74 is used
60-74y	€ 13,373	€ 9,807	
75-84y	€ 18,961	€ 9,690	
≥85y	€ 8,595	€ 7,093	
Patient costs hospitalization	€ 144		Based on a patient admitted for CAP [28]
Productivity loss hospitalization	IPD	Hospitalized NIPP	[14]
60-64y	€ 4,145	€ 2,747	
65-74y	€ 330	€ 330	
≥75y	€ 0	€ 0	
Productivity loss death	IPD	Hospitalized NIPP	[14]
60-64y	€ 17,937	€ 17,937	
65-74y	€ 3,116	€ 3,116	
≥75y	€ 0	€ 0	
Vaccine price per dose			
PPV23	€ 25.94		[29]
PCV13	€ 74.72		[29]
PCV15	€ 74.73		[29]
PCV20	€ 82.17		[29]
PCV21	€ 82.17		Assumption, equal to PCV20
Administration costs per dose	€ 21.00		[30]
Discount rates			[15]
Costs	4%		
Health effects	1.5%		

[1]: transition from PCV10 to PCV13, PCV15 or PCV20.

[2]: The following serotypes are included in the different vaccines:

PCV13 serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

PCV15 serotypes: PCV13 serotypes + 22F, 33F.

PCV20 serotypes: PCV15 serotypes + 8, 10A, 11A, 12F, 15B.

PPV23 serotypes: except for 6A, all PCV20 serotypes + 2, 9N, 17F and 20.

PCV21 serotypes: 3, 6A/C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B/C, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F, 35B.

Note that PCV13, PCV15, PCV20 and PCV21 provide cross-protection against 6C [21].

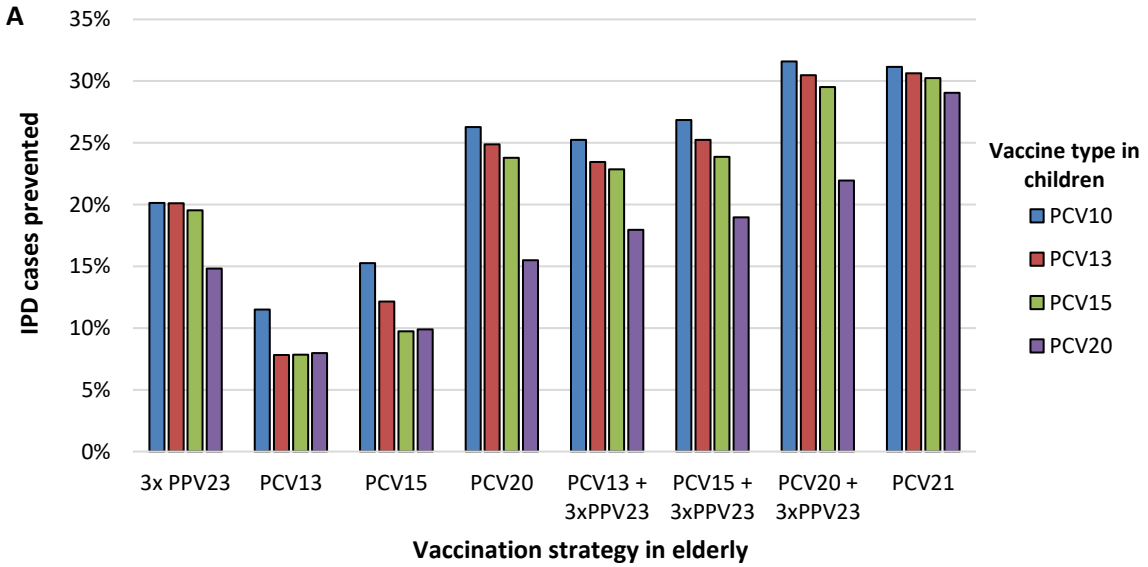
CAP: Community-acquired pneumonia, IPD: Invasive pneumococcal disease, NIPP: non-invasive pneumococcal pneumonia, PCV: Pneumococcal conjugate vaccine, PPV: pneumococcal polysaccharide vaccine, QALY: Quality-adjusted life year

Results

Clinical impact

Figure 1 shows the reduction in IPD cases and NIPP hospitalizations of the various pneumococcal vaccination strategies in a 65-year-old cohort over a 15-year time-horizon, while considering different vaccines used in the childhood vaccination program (details available in Supplemental Tables S6-S9). With PCV10 in children, the current Dutch strategy of 3x PPV23 was estimated to prevent 20% of the IPD cases (Figure 1A). PCV13 or PCV15 were found to have less impact than 3x PPV23, while PCV20 showed greater impact with a 26% reduction in IPD cases. Strategies of PCV13 or PCV15 combined with 3x PPV23 showed similar impact to PCV20. The highest reduction in IPD cases was achieved by PCV20 + 3x PPV23, resulting in a 32% reduction in IPD cases. However, a single dose of the in-development PCV21 showed similar impact. A similar ranking was found for the prevention of NIPP hospitalizations (Figure 1B), although vaccination had a relatively lower impact against this outcome compared to IPD. Furthermore, this relatively lower impact against NIPP was more pronounced for strategies involving PPV23.

We found that a transition to higher-valency vaccines in children had a diminishing effect on the impact of vaccination programs for the elderly, with the amount of reduction depending on the overlap of serotypes between the vaccines used in children and elderly. Specifically, if children transitioned from PC10 to PCV13 or to PCV15, the effectiveness of strategies with PCV13 and PCV15 in the elderly was reduced due to indirect protection. However, the impact of PPV23 and PCV20 in the elderly was minimally affected, as these vaccines also covered other serotypes that increased in incidence due to serotype replacement. If children were vaccinated with PCV20, the impact of both PPV23 and PCV20 was diminished. However, the reduction in impact was more pronounced for PCV20, resulting in comparable effectiveness between the two vaccines in reducing the number of IPD cases. On the other hand, the impact of PCV21, which covered a complementary range of serotypes than the PCV20 used in children, was minimally impacted by such a transition, consistently demonstrating the highest impact across all childhood vaccination scenarios considered.



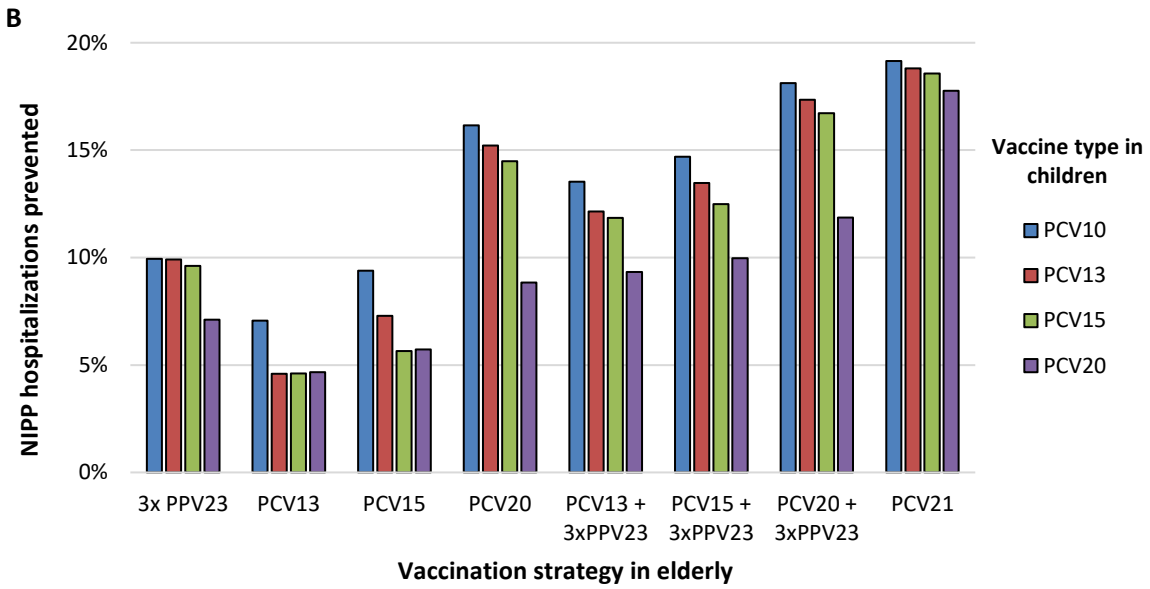


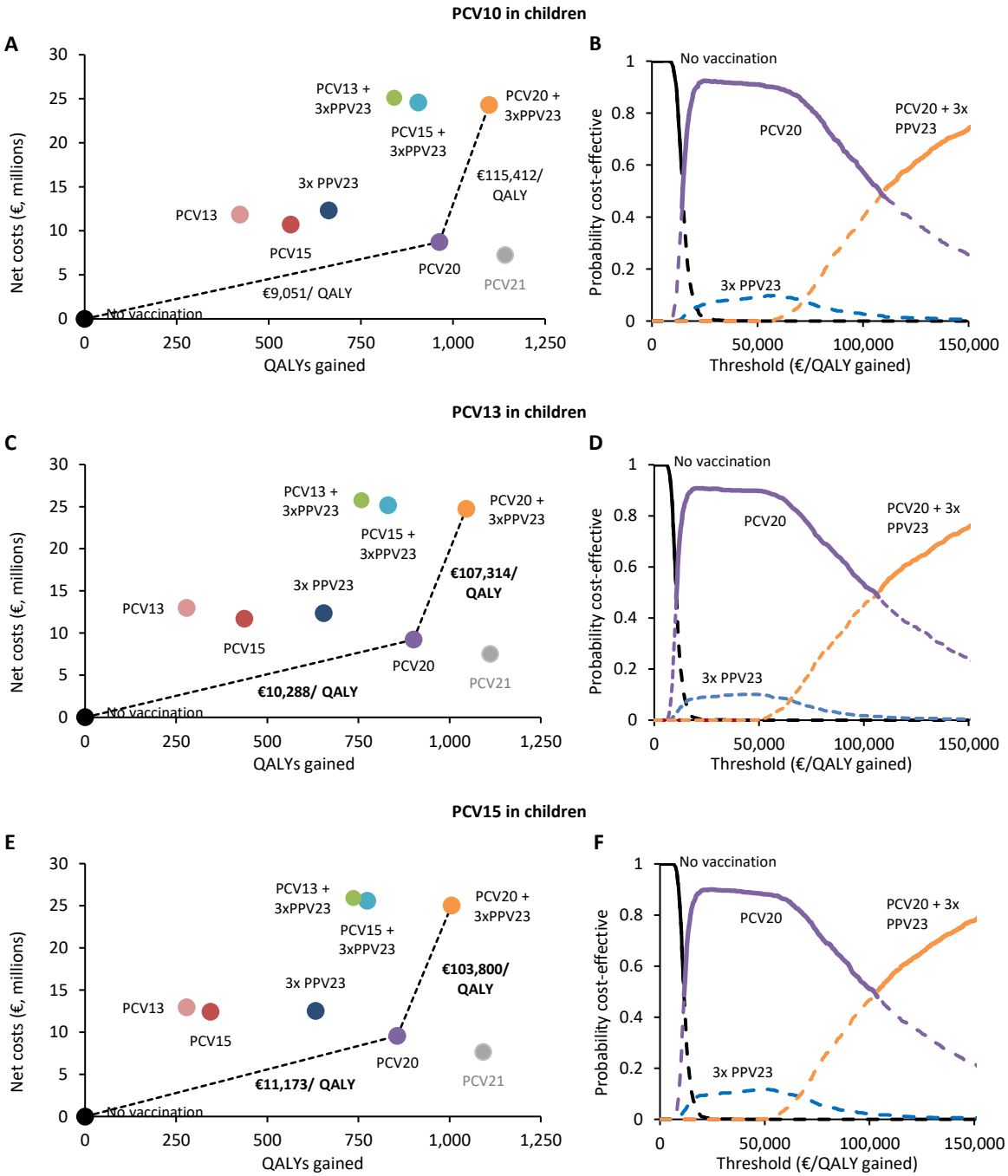
Figure 1: Proportion of (A) IPD cases and (B) NIPP hospitalizations prevented among a 65-year-old cohort for different pneumococcal vaccination strategies compared to no vaccination, while considering variations in the vaccine type used in the childhood vaccination program. Results are shown for vaccination of 70% of a cohort aged 65-years followed over a time-horizon of 15 years. 3x PPV23 means vaccination at year 0, 5 and 10, while PCV + PPV23 means vaccination with PCV at year 0, and vaccination with PPV23 at year 1, 6 and 11. PCV: Pneumococcal conjugate vaccine, PPV: pneumococcal polysaccharide vaccine, IPD: Invasive pneumococcal disease, NIPP: non-invasive pneumococcal pneumonia.

Cost-effectiveness

Figure 2 presents the discounted incremental costs and incremental QALYs associated with the various pneumococcal vaccination strategies compared to no vaccination (details available in Supplemental Tables S6-S13). When PCV10 was continued to be used in children, the current Dutch strategy of 3x PPV23 had an ICER of €18,559 per QALY gained (extracted from Figure 2A). However, the strategy of 3x PPV23 was dominated by PCV20, as this strategy resulted in higher QALY gains at a lower cost (Figure 2A). PCV20 also dominated strategies with PCV13, PCV15, PCV13 + 3x PPV23 and PCV15 + 3x PPV23, and had an ICER of €9,051 per QALY gained compared to no vaccination. The strategy of PCV20 + 3x PPV23 would result in a higher QALY gain than PCV20 but at a substantially higher ICER of €115,412 per QALY gained compared to PCV20. The cost-effectiveness acceptability curve, presenting the highest probability of being cost-effective over a range of cost-effectiveness thresholds, shows that PCV20 was the cost-effective strategy in approximately 90% of the simulations at thresholds of €20,000 and €50,000 per QALY gained (Figure 2B). As the price of in-development PCV21 is unknown, it was not included in the incremental comparison (Figure 2A). However, if the intervention costs were equal to PCV20, in-development PCV21 would dominate PCV20 and PCV20 + 3x PPV23, with an ICER of €6,352 per QALY gained.

A transition to a higher-valent vaccine in the childhood vaccination program was generally projected to reduce the cost-effectiveness of pneumococcal vaccination programs for elderly, although the amount of impact varied, based on the serotype overlap between the childhood and elderly vaccines. With PCV13 or PCV15 in children, PCV20 continued to dominate all other strategies in the 65-year-old cohort, except for PCV20 + 3x PPV23 (Figure 2C-F). Its ICER was €10,288 per QALY gained with PCV13 in children, and €11,173 per QALY gained with PCV15 in children. However, a transition to PCV20 in children substantially diminished the cost-effectiveness of PCV20 in elderly (Figure 2G). While PCV20 continued to dominate 3x PPV23, PCV13 and PCV15, its ICER compared to no vaccination increased to €22,250 per QALY gained. The cost-effectiveness acceptability curve shows that no vaccination was the cost-effective strategy in 76% of the simulation at a threshold of €20,000

per QALY gained (Figure 2H). Additionally, the strategies of PCV13 + 3x PPCV23 and PCV15 + 3x PPV23 resulted in higher health gains than PCV20 but were dominated by PPV20 + 3x PPV23 (Figure 2G). The ICER of PCV20 + 3x PPV23 was €81,193 per QALY gained compared to PCV20. The transition from PCV10 to PCV20 in children slightly impacted the ICER of in-development PCV21, increasing from €6,352 per QALY gained to €7,876 per QALY gained compared to no vaccination.



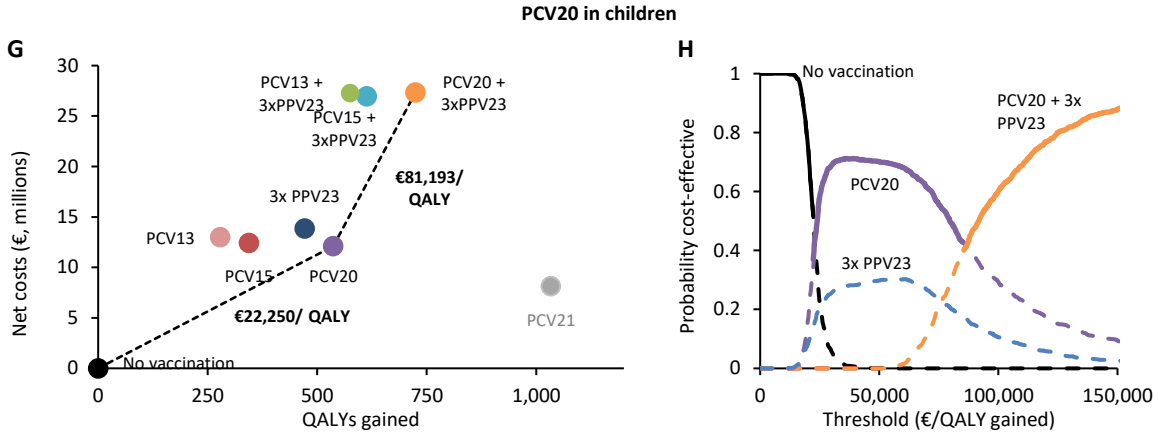


Figure 2: Cost-effectiveness of different pneumococcal vaccination strategies for elderly, while varying the childhood pneumococcal vaccine between PCV10, PCV13, PCV15 and PCV20. Panel A,C,E, and G show the discounted incremental costs and QALYs compared to no vaccination for elderly. The dotted lines show the incremental cost-effectiveness ratios (ICERs) between two alternatives, after removing strategies that were strictly dominated (alternative with higher QALY gains against lower cost) or extendedly dominated (alternative with higher QALY gain against lower ICER). As no vaccine price is available, in-development PCV21 was excluded from the incremental analysis but shown indicatively with an equal vaccine price to PCV20. Panel B, D, F, H show the cost-effectiveness acceptability curves, indicating the probability of being the cost-effective alternative across a range of cost-effectiveness thresholds. This analysis is based on 1000 simulations. 3x PPV23 means vaccination at year 0, 5 and 10, while PCV + PPV23 means vaccination with PCV at year 0, and vaccination with PPV23 at year 1, 6 and 11. PCV: Pneumococcal conjugate vaccine, PPV: pneumococcal polysaccharide vaccine, QALY: Quality-adjusted life year

As indirect effects from higher-valency vaccines in children were assumed to change the pneumococcal epidemiology among the elderly gradually over time until stabilization after 8 years after transition, the cost-effectiveness of vaccination of elderly changes over time for new cohorts eligible for vaccination in the years after transition. Figure 3 illustrates the ICER of various pneumococcal vaccination strategies in 65-year-old cohorts over time since transition to PCV20 in the childhood vaccination program. We found that 3x PPV23 became more effective in reducing IPD cases than PCV20 in a cohort that is vaccinated one year or longer after the transition to PCV20 in children, and the cost-effective alternative compared to PCV20 for cohorts vaccinated three years or more after this transition. Once the indirect effects have fully taken effect, the ICER of 3x PPV23 for these cohorts is estimated at €34,571 per QALY gained compared to no vaccination, while for PCV20 the ICER is €45,081 per QALY gained.

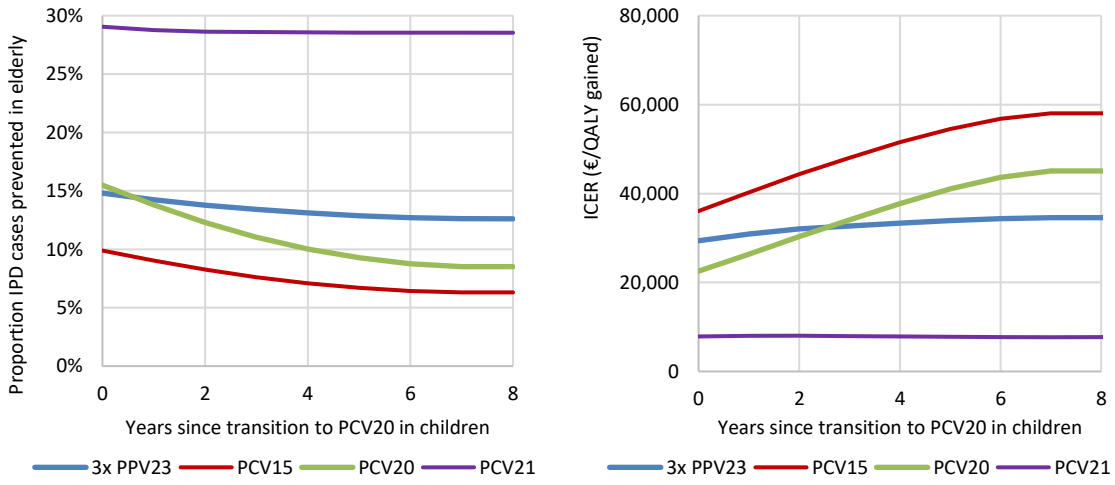


Figure 3: The impact on IPD cases and the cost-effectiveness of different vaccination strategies compared to no vaccination for new eligible cohorts of 65-year-olds over time since transition from PCV10 to PCV20 in children. The vaccine price of

PCV21 was assumed to be equal to PCV20. 3x PPV23 means vaccination at year 0, 5 and 10, while PCV + PPV23 means vaccination with PCV at year 0, and vaccination with PPV23 at year 1, 6 and 11. IPD: Invasive pneumococcal disease, PCV: Pneumococcal conjugate vaccine, PPV: pneumococcal polysaccharide vaccine, QALY: Quality-adjusted life year

Sensitivity analyses

Figure 4 displays the impact of different amounts of indirect protection and serotype replacement resulting from childhood vaccination with PCV20 on the cost-effectivess of different vaccination strategies in a 65-year-old-cohort. Varying the decline in incidence of serotypes added to the childhood vaccine in the elderly from 80% to 50% resulted in reduced ICERs for PCV15 and PCV20, and PPV23. For instance, if childhood vaccination and vaccination in elderly were implemented in the same year (Figure 4A), the ICER of PCV20 decreased from €22,550 per QALY gained to €15,552 per QALY gained. The impact on the ICER of PCV21 was minimal. However, when the level of serotype replacement was varied from a return in overall incidence to the pre-indirect effects level to an overall incidence of 75% of the pre-indirect effects level, the ICER of PCV21 increased from €7,876 per QALY gained to €9,125 per QALY gained. Also, the ICER of PPV23 increased, while it had limited effect on PCV15 and PCV20, as these vaccines contained no complementary serotypes compared to the childhood vaccine. The impact of variation in indirect effects on the ICERs was more pronounced for cohorts that were eligible for vaccination 8 or more years after the transition to PCV20 in children (Figure 4B). We found that PCV20 also dominated 3x PPV23 in a 65-year-old-cohort vaccinated 8 years after the transition to PCV20 in children.

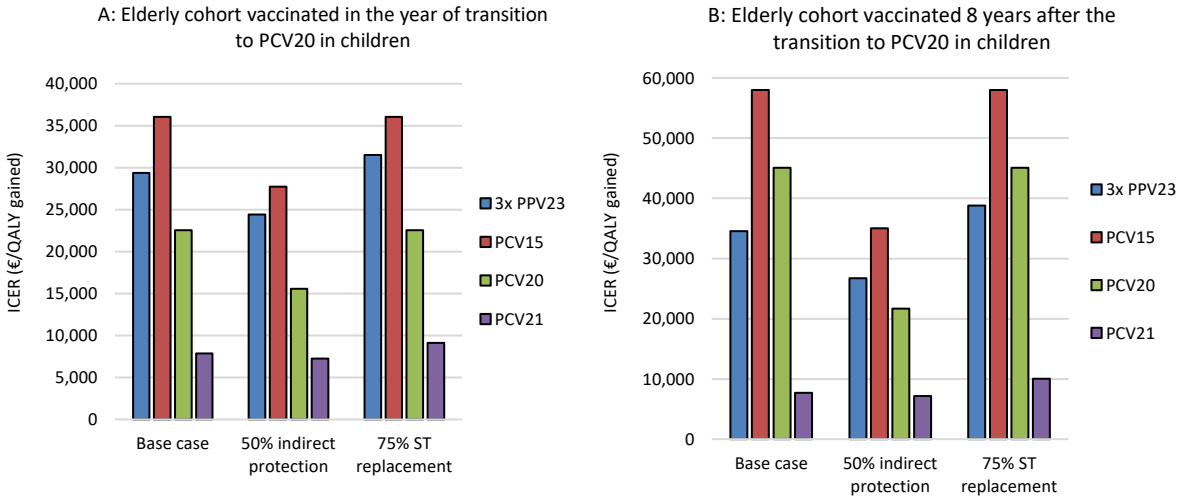


Figure 4: Cost-effectiveness of different vaccination strategies for a 65-year-old cohort after a transition to PCV20 in children, varying the level of indirect protection (base case: 80%) or the level of serotype replacement (base case: 100%). A) presents results from a cohort that is vaccinated at time of the transition, and B) presents results from a cohort that is vaccinated 8 years after the transition. The vaccine price of PCV21 was assumed to be equal to PCV20. 3x PPV23 means vaccination at year 0, 5 and 10. IPD: Invasive pneumococcal disease, PPV: pneumococcal polysaccharide vaccine, PCV: Pneumococcal conjugate vaccine, QALY: Quality-adjusted life year, ST: Serotype.

The one-way sensitivity analyses generally indicate that the cost-effectiveness outcomes were most sensitive to the vaccine price, the VE, the VE waning rate and the proportion of CAP caused by *S. pneumoniae* (Supplemental Figure S8). PCV20 remained to be the cost-effective scenario at a threshold of €20,000 per QALY gained for most scenarios when PCV10 was continued in the childhood vaccination program, or when a transition to PCV13 or PCV15 for children was assumed (Supplemental Figure S8A-C). Only if no VE against CAP was assumed, PCV20 failed to be cost-effective at the threshold. PPV23 became the most cost-effective strategy if the lower bound of the

VE for the PCVs was used. In the scenario of transitioning to PCV20 in children, PCV20 in a 65-year-old cohort was not cost-effective to a threshold of €20,000 in the base case but became cost-effective if the upper bound of the VE of the PCVs was used, if there was no waning of PCV within the first 8 years, if the proportion of CAP caused by pneumococcus was 30%, or if there was a 13% or 50% reduction in vaccine price (Supplemental Figure S8D). Furthermore, PPV23 became the cost-effective scenario at the threshold of €50,000 per QALY gained if the upper bound of the VE of PPV23 was assumed, if there was no waning of PPV23 over 5 years after vaccination, or if there was a 50% price discount for PPV23.

When we varied the age of vaccination between 60-85 year, we generally found vaccination at ages 70 and 75 years being optimal in terms of cost-effectiveness, while vaccination at 85 years resulted in substantially higher ICERs, not being cost-effective at a threshold of €50,000 per QALY gained (Supplemental Figure S9, details in Supplemental Tables S14-S23). Furthermore, the ranking of the cost-effectiveness of the different vaccination strategies and the impact of indirect effects from a transition to higher-valency vaccines in children remained consistent with our findings for the main analysis in a cohort of 65 years of age (Supplemental Figures S9-S10), except for the vaccination age of 85 years. At that age, one dose of PPV23 had a lower ICER than one dose of PCV20.

A sensitivity analysis of the time-horizon for vaccination of a 65-year-old cohort, while continuing PCV10 in children, shows that PCV20 becomes cost-effective to a threshold of €20.000 per QALY gained at 7 years after vaccination, and dominates PPV23 from 5 years onwards after vaccination (Supplemental Figure S7).

Discussion

We analyzed the cost-effectiveness of higher-valency vaccines for the elderly population in the Netherlands, considering the potential indirect effects of from a transition to higher valent vaccines in childhood vaccination programs.

Our analysis revealed that if PCV10, PCV13 or PCV15 is used in the childhood vaccination program, PCV20 was the cost-effective strategy for a 65-year-old cohort, considering thresholds of €20,000 and €50,000 per QALY gained. PCV20 dominated (i.e., more effective against lower costs) the current strategy of PPV23 every 5 years, as well as single-doses of PCV13 or PCV15, alone or combined with PPV23. However, we found that indirect protection and serotype replacement from higher-valent PCVs in the childhood vaccination program could significantly reduce the cost-effectiveness of pneumococcal vaccination for the elderly. The magnitude of this reduction depended on the serotype overlap between the childhood and elderly vaccines. In the scenario of transitioning to PCV20 in children, no vaccination became the cost-effective strategy in elderly given at the €20,000 per QALY gained threshold, and eventually, as indirect effects occurred gradually, PPV23 became the cost-effective strategy at a threshold of €50,000 per QALY for cohorts vaccinated at least 3 years after the transition. PCV21, which is currently under development, was projected to dominate PCV20 if an equal vaccine price was assumed, as PCV21 covers a higher proportion of serotypes currently causing IPD among elderly in the Netherlands. Additionally, its cost-effectiveness was minimally affected by assumed indirect effects from higher-valency vaccines in children due to a complementary range of serotypes covered compared to the childhood vaccine.

Outcomes were most sensitive to the amount of indirect protection, the VE, the waning of VE over time, and the vaccine prices but the cost-effectiveness ranking of the strategies remained largely unchanged. Across age, we found vaccination at 70 or at 75 years to be economically more favorable

compared to 65 years, while vaccination at 85 years was not cost-effective. The latter was explained by the lower VE with increasing age, and a lower life expectancy.

Our finding that PCV20 dominates PCV13, PCV15 and PPV23 in the elderly when PCV10 or PCV13 is used in childhood vaccination aligns with two independent studies from Japan [4] and the US [8], as well as three industry-funded studies from Denmark [5], England [6] and Italy [7]. Another independent study from the US did not find PCV20 to be cost-effective compared to PPV23, which may be explained by a relative higher price difference between PCV20 and PPV23, a relatively lower proportion of IPD serotypes covered by the vaccines given the different epidemiological situation in the US, and the absence of cross-protection of PCV20 against serotype 6C [9]. Our cost-effectiveness estimate of PPV23 under current conditions is less favorable than an earlier study for the Netherlands from 2018 [12] due to an update of data on pneumococcal incidence and serotype distribution, and the use of a higher administration fee (€21 *versus* €10).

None of the previously mentioned cost-effectiveness analyses of higher-valency PCVs in elderly accounted for the impact of indirect protection and serotype replacement from a transition to higher-valent vaccines in children, and only two analyses included a measure of indirect protection [8, 9]. We demonstrated the importance of considering both indirect protection and serotype replacement for evaluating the impact and cost-effectiveness of vaccination of the elderly. However, projecting indirect effects, including its amount and speed of occurrence, is challenging. Our assumptions were based on previous experiences with PCV10 and PCV13 in childhood programs from multi-country studies [10, 20], where indirect protection started earlier than serotype replacement, and indirect effects tended to be completed after eight years. At that time, zero net-effects on the IPD incidence in non-vaccinated age groups were found, although with heterogeneity between countries. Similar timescales were observed after the introduction of PCV7 [38]. Our sensitivity analyses with PC20 in the childhood vaccination program demonstrated that in case of less indirect protection, the ICERs of PPV23, PCV15 and PCV20 were reduced without affecting the ICER of PCV21. Furthermore, in this scenario PCV20 was also cost-effective compared to PPV23 for cohorts vaccinated at the time when indirect effects were completed. In case of partial (75%) replacement instead of full replacement, the ICER of PPV23 and PCV21 would slightly increase. Note that we did not vary the serotype distribution among the non-vaccine serotypes or the invasive capacity of the non-vaccine serotypes, while increasing their incidence as a result of serotype replacement.

Our analysis has several limitations that need to be considered. Firstly, there is uncertainty regarding various variables related to pneumococcal epidemiology and vaccines, including the incidence and serotype distribution of NIPP, VE against NIPP, the duration of vaccine protection and the change in VE with age. We aimed to account for this uncertainty by doing extensive sensitivity analysis, finding consisting results through most of these scenarios. Additionally, we extrapolated the VEs of PCV13 against vaccine-type IPD and NIPP to the additional serotypes covered by PCV15, PCV20 and PCV21, as no clinical studies have been conducted for these higher-valency vaccines. Although immunogenicity data showed somewhat lower immune responses for PCV20 compared to PCV13 in all thirteen shared serotypes, the clinical significance of these findings is unknown, and non-inferiority criteria were met in a phase 3 study [39]. We also used epidemiological data from the pre-COVID-19 period of before 2020, while the IPD incidence was substantially decreased due to response measures in the pandemic years of 2020 and 2021 [40]. However, recent data indicates that the incidence of IPD has returned to pre-pandemic levels in 2022/2023 (data not shown). The use of a simplified static model may also be a limitation, as it does not capture the actual transmission dynamics of pneumococcal bacteria and the contributions of different serotypes in the

future. Modelling pneumococcal carriage and transmission is complex, and the wide range of scenarios considered in our analysis based on trends after the implementation of previous childhood vaccination programs provided valuable insights into potential outcomes. Furthermore, our analysis only accounted for pneumococcal-related mortality up to 30 days after hospitalization, while vaccination may also prevent mortality outside the hospital, or across a longer period after hospitalization. For instance, literature indicates that the risk of mortality and reduction in quality of life may extend even up to a year after disease [17]. However, the extent to which this finding is attributable to the presence of co-morbidities is uncertain, and, otherwise, our estimates can be considered as conservative. Finally, we did not include effects from side effects but no difference between vaccines are expected, and we did not incorporate additional implementation costs of a switch to a new vaccination strategy.

Strong points of our analysis include the utilization of high-quality data for many model parameters that were collected within a single country. These parameters encompassed age- and serotype-specific IPD data, age-specific vaccine efficacy data for PCV, and cost- and quality-of-life data related to pneumococcal infections that were nested into this RCT. Additionally, the timing of the introduction of PPV23 in elderly in 2020 in the Netherlands provided us with recent IPD epidemiology data from an unvaccinated population. This eliminated the need for counterfactual calculations to include the scenario of no pneumococcal vaccination. To estimate the VE of PPV23, we relied on data from the UK, as they report estimates of VE shortly after vaccination, which represents the VE before waning occurs. Recently, the first estimates of the impact of the actual PPV23 vaccination program in the Netherlands became available [41]. The VE against IPD one year after vaccination ranged, depending on the method used, between 47% (95% credibility intervals [CrI]: 30-59%) and 59% (95% CrI: 41-70%) among individuals aged 73-79 years and between 53% (95% CrI 38-63) and 56% (95% CrI 41-66) among those aged 69-73. After two years, the VE among those aged 73-79 at vaccination was estimated between 45% (95%CrI 14-61%) and 48% (95% CrI 16-64%) (personal communication, A. Niessen, RIVM). These estimates align reasonably well with the VE of PPV23 used in our model for those age-groups.

Altogether, we have presented the impact and cost-effectiveness of higher-valency vaccines for elderly in the context of that these vaccines are also currently or will soon be available for childhood vaccination programs. Our findings have several implications for policy making, not only in the Netherlands but also for other countries facing similar decisions. Our analysis highlighted the substantial impact that indirect effects from childhood vaccination programs can have on determining the optimal vaccination strategy for the elderly. Moreover, the timing of introduction of higher-valent vaccines in elderly, relative to children, is important. Once transitioned to PCV20 in children, the vaccination strategy with the lowest ICER changed from PCV20 to PPV23 over time. However, a switch back to PPV23 does not seem feasible due to its impact on public trust in the vaccination program and the implementation costs, which are not accounted for in this analysis. A more realistic alternative seems to be a change to PCV21 when available. In that case, the cost-effectiveness of PCV21 should be reexamined also for cohorts with existing immunity from previous PCV20. Another potential strategy could involve the continuation of the use of PPV23 until PCV21 becomes available. However, the completion of indirect effects takes time with uncertain order of magnitude, while the benefits of introduction of PCV20 in the elderly would start directly after implementation. Clearly, decisions regarding these strategies and their timings are dependent on availability of PCV20 for children and PCV21 for adults in the (near) future, and should include their respective prices.

Conclusion

Our analysis suggests vaccination of elderly with PCV20 to be the cost-effective vaccination strategy in the Netherlands, given a threshold of €20,000 per QALY, as long as children are vaccinated with PCV10, PCV13 or PCV15. However, once PCV20 is introduced into the childhood vaccination program, none of the currently available vaccination strategies was found to be cost-effective to the threshold. To ensure long-term cost-effectiveness of pneumococcal vaccination programs for elderly, we found the best results for PCV21, as it covers a complementary range of serotypes than the different childhood vaccines explored. We assert that policy decisions aimed at reducing the total burden of pneumococcal disease in all age groups should consider both childhood and adult vaccination programs in a combined economic evaluation.

Acknowledgements

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Supplemental materials

Higher-valency pneumococcal conjugate vaccines in elderly, taking into account indirect protection and serotype replacement from childhood vaccination programs: A cost-effectiveness study

Pieter T. de Boer[1], Cornelis H. van Werkhoven[1], Albert Jan van Hoek[1], Mirjam Knol[1], Elisabeth A.M. Sanders[1,2], Jacco Wallinga[1,3], Hester E. de Melker[1], Anneke Steens[1]

1. Center for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), the Netherlands
2. Department of Pediatric Immunology and Infectious diseases, University Medical Center Utrecht, The Netherlands
3. Department of Biomedical Datasciences, Leiden University Medical Center, the Netherlands

Supplemental methods

Model design

We adapted an earlier developed static multi-cohort model [1], consisting of single year age cohorts of 60 years and older that were followed over time in annual time-steps. A schematic overview is presented in Figure S1. Each year, people had a probability of acquiring IPD or hospitalized NIPP based on the incidence corresponding to their age-group. We assumed all IPD patients to be hospitalized. Subsequently, IPD or hospitalized NIPP patients could die according to age-specific hospitalization-fatality rates. Population sizes and all-cause mortality of 2019 from Statistics Netherlands were used to obtain realistic aging of the cohorts [2, 3]. To be able to determine the impact of vaccination, the hospitalized cases were distributed among different sets of pneumococcal serotypes covered by the various vaccines. The impact of pneumococcal vaccination is modelled as a risk reduction of the incidence of vaccine-type hospitalizations, which is the multiplication of vaccine uptake and vaccine-type vaccine effectiveness (VE). VE is modelled as a function of the VE at the moment of vaccination (take) and an annual waning rate. VE at take differs by vaccine type (PPV or PCV), outcome (IPD or NIPP), and age of vaccination. We did not include an effect of vaccination against lower-respiratory infections in primary care, given the uncertainty whether pneumococcal vaccination provides significant protection against this outcome [4]. Furthermore, the relative contribution of pneumococcal disease burden in primary care on the cost-effectiveness outcomes has shown to be limited [5].

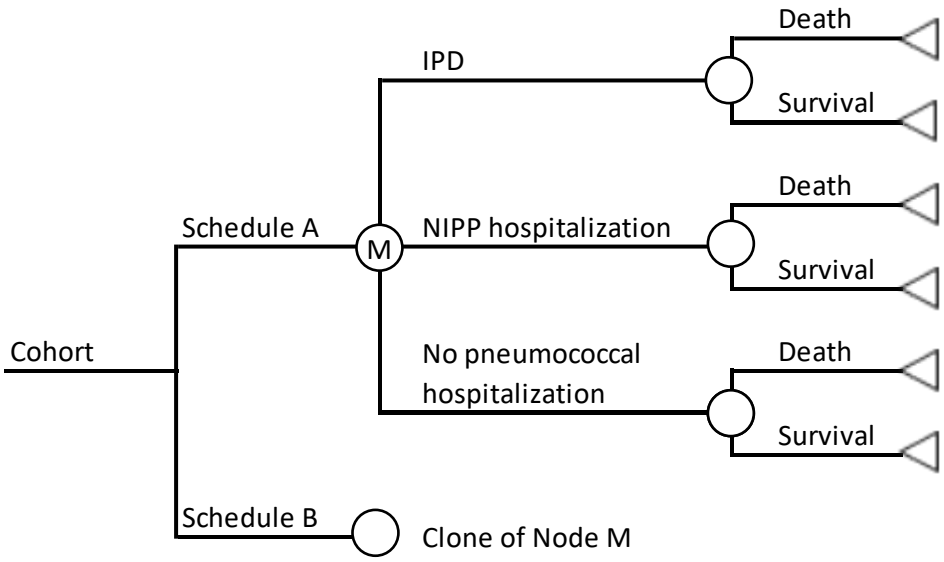


Figure S1: Schematic overview of the model. Node M represents a Markov node that uses annual time steps to follow the cohort over increasing age. IPD: Invasive pneumococcal disease, NIPP: Non-invasive pneumococcal pneumonia.

Epidemiology

As response measures against the COVID-19 pandemic affected the epidemiology of pneumococcal disease from 2020 to 2022 [6], we parametrized the model with Dutch epidemiology data from the period 2012-2019, when the pneumococcal vaccination program for the elderly was still not

implemented in the Netherlands and PCV10 was used in the national childhood vaccination program.

Serotype-specific numbers of hospitalized IPD cases per 5-years age-group (60-64, 65-69, … ≥90) were obtained from Dutch national IPD surveillance data of the National Institute for Public Health and the Environment based on data sent in by sentinel laboratories to the National Reference Laboratory for Bacterial Meningitis for the years 2004-2019. Numbers were converted to incidence using national population sizes by year [2], taking into account that the sentinel laboratories cover approximately 25% of the Dutch population. For the analysis we used the average incidence of all serotypes by age-group in the years 2017-2019, and partitioned these to incidence per set of vaccine serotypes using the serotype distribution of all IPD cases aged ≥60 years in 2019 (Supplemental Table S2). We used incidence data from 2017-2019 to account for yearly fluctuations of IPD cases per year, for instance, due to variation in size of influenza epidemics [7]. However, for the serotype distribution we used the most recent pre-COVID19 pandemic data from 2019 to account for the latest trend over time (Supplemental Figure S2). IPD cases with missing serotype (3.4% of total) were divided among the different sets of (vaccine) serotypes proportionally to the distribution of the serotyped IPD cases.

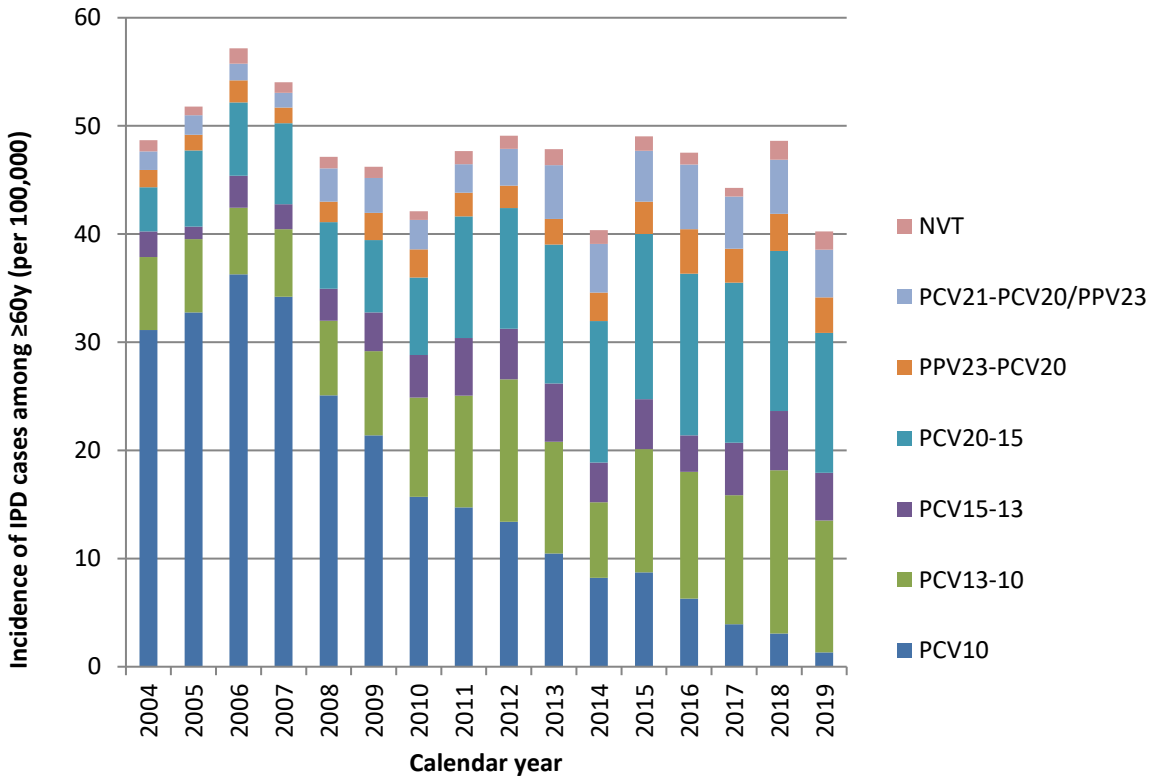


Figure S2: The annual incidence of IPD cases in the Netherlands among adults aged ≥60 years per 100,000 inhabitants over the period 2004-2019 by serotype category covered by the different vaccines. For visualization reasons we merged the serotype categories of Table S2 as follows: PCV10: PCV10 minus 7F + ST7F, PCV13-10: ST6A + ST3 + ST19A + ST6C (cross-protection from 6A), PCV20-15: PCV20 minus PCV15 minus 15B + ST15B, PPV23-PCV20: PCV21/PPV23 minus PCV20 minus ST2 + ST2. PCV: Pneumococcal conjugate vaccine, PPV: pneumococcal polysaccharide vaccine, IPD: Invasive pneumococcal disease.

The annual incidence of NIPP hospitalizations was based on multiple data sources. Annual numbers of hospitalizations from all-cause community-acquired pneumonia (CAP) (International Classification of Diseases, ICD-10-AM codes J9-J18) per 5-years age-group (60-64, 65-69, …, ≥90) were obtained

from national Dutch hospital surveillance data for the years 2012-2014, and converted to incidence using national population sizes. From these all-cause CAP hospitalizations, we assumed 22.1% to be caused by *S. pneumoniae*, as observed in the placebo-arm of the CAPITA trial [8]. Subsequently, the incidence of pneumococcal CAP was adjusted for the time-trend of pneumococcal disease from 2012-2014 to 2017-2019, based on the change in incidence of IPD hospitalizations among elderly aged ≥60 years across this period. Eventually, the incidence of NIPP hospitalizations was obtained by subtracting the incidence of invasive pneumococcal pneumonia hospitalizations from the incidence of pneumococcal CAP cases, taking into account that 80% of the IPD cases are invasive pneumonia cases in the Dutch surveillance data. To validate the estimated incidence of NIPP, we compared the ratio between the incidence of NIPP and IPD in the age-range 65-79 years with the ratio of NIPP and IPD cases observed in the placebo-arm of the CAPITA trial [8], which appeared to be reasonably similar (1.6 in our analysis *versus* 1.7 in CAPITA). In absence of data on the serotype distribution of NIPP hospitalizations, we also used the serotype distribution of IPD cases for NIPP.

Thirty-day case-fatality rates for IPD by age-group were obtained by re-analyzing data of Vestjens et al. [9] from January 2008 to May 2011 and from January 2013 to May 2016. The case-fatality rates of NIPP were obtained by multiplying the age-specific case-fatality rates of IPD with 0.85, based on the ratio of 30-day case fatality rates between IPD cases and non-IPD CAP hospitalized patients from a Dutch study conducted in the period 2008-2013 [10].

Distributions used for the probabilistic sensitivity analysis are shown in Supplemental Table S1.

Table S1: Epidemiological parameter values that were used in the base case analysis (mean value) and their distributions used in the probabilistic sensitivity analysis.

Parameter	Mean	Standard error	Distibution
Projected cohort sizes (2025)			
60y	254,920		Fixed
65y	228,209		Fixed
70y	196,004		Fixed
75y	175,878		Fixed
80y	126,470		Fixed
85y	77,765		Fixed
IPD incidence (per 100,000)			
60-64y	28.4	1.87	Beta
65-69y	33.5	2.11	Beta
70-74y	46.6	2.68	Beta
75-79y	52.7	3.45	Beta
80-84y	65.6	4.61	Beta
85-89y	76.6	6.44	Beta
≥90y	81.5	9.28	Beta
Proportion invasive pneumonia			
All ages	79.8%	2.38%	Beta
CAP incidence (per 100,000)			
60-64y	225	2.66	Beta
65-69y	327	3.41	Beta
70-74y	497	4.96	Beta
75-79y	724	6.82	Beta
80-84y	1,050	9.59	Beta
85-89y	1,385	14.42	Beta
≥90y	1,575	21.88	Beta
Proportion of CAP caused by *S. pneumoniae*			
All ages	22.1%	1.48%	Beta
Trend adjustment factor NIPP from 2012-2014 to 2017-2019			
All ages	0.97		Fixed
Case-fatality rate IPD			
60-69y	9.9%	0.93%	Beta
70-79y	16.4%	1.18%	Beta
80-89y	23.3%	1.62%	Beta
≥90y	31.4%	3.73%	Beta
Relative risk hospitalized NIPP/IPD mortality			
All ages	13.1%	0.81%	Beta

IPD: Invasive pneumococcal disease, NIPP: Non-invasive pneumococcal pneumonia, CAP: Community acquired pneumonia

Table S2: (vaccine) serotype sets distinguished in the model and the serotype distribution using 2019 data. Isolates with missing serotype were divided among the categories proportionally to the distribution of the serotyped isolates. ST: Serotype, PCV: pneumococcal conjugate vaccine, PPV: Pneumococcal polysaccharide vaccine

Category	Included ST	%	PCV 10	PCV 13	PCV 15	PCV 20	PCV 21	PPV 23
PCV10 minus 7F	4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5	2.8 %	X	X	X	X		X
ST7F	7F	0.5 %	X	X	X	X	X	X
ST3	3	8.6 %		X	X	X	X	X
ST6A	6A	0.2 %		X	X	X	X	
ST6C (cross-protection from 6A)*	6C	4.4 %		X	X	X	X	
ST19A	19A	17.0 %		X	X	X	X	X
PCV15 minus PCV13	22F, 33F	11.0 %			X	X	X	X
PCV20 minus PCV15 minus 15B	8, 10A, 11A, 12F	30.1 %				X	X	X
ST15B*	15B	2.1 %				X		X
PCV21/PPV23 minus PCV20 minus ST2	9N, 17F, 20	8.2 %					X	X
ST2	2	0.0 %						X
PCV21 minus PCV20/PPV23	15A, 15C, 16F, 23A, 23B, 24F, 31, 35B	11.0 %					X	
Non-vaccine types minus ST6C	Other STs + non-typeable pneumococci	4.2 %						
Total coverage		100 %	3.3%	33.6 %	44.5 %	76.7 %	90.9 %	80.2 %

PCV: Pneumococcal conjugate vaccine, PPV: pneumococcal polysaccharide vaccine, ST: Serotype

* From PCV13 it has become clear that the serotype 6A antigen clinically effectively protects against 6C disease [11]. Although the serotype 15C in PCV21 (deOAc15B) induces cross-reactive antibodies [12], no vaccine effectiveness data is currently available, and we assumed no clinical protection from PCV21 to this serotype in our analysis.

Indirect effects of vaccine type used in children on the epidemiology in elderly

Data from countries using PCV10 showed that indirect effects of pneumococcal childhood vaccination programs on the epidemiology in elderly more or less stabilized after eight years [11, 13, 14]. Given that the incidence of IPD among ≥60-year-olds in the Netherlands has been relatively stable since 2011 (Supplemental Figure S2), we kept the incidence and serotype distribution of pneumococcal disease in elderly constant over time if PCV10 was continued in the childhood vaccination program. The overall incidence in the ≥60-year-old population does slightly increase over time due to a change in age-distribution in the model; the age-specific incidence rates are kept the same. In case of a switch to PCV13, PCV15 or PCV20 in the childhood vaccination program, we assumed the following changes over time:

1) an 80% decline in the incidence of serotypes added to the childhood vaccine among ≥60-year-olds, starting one year after the vaccine switch in children, and occurring linearly over a period of 7 years. No indirect protection was assumed for serotype 3.
2) a linear increase in the incidence among ≥60-year-olds of serotypes not included in the childhood vaccine until the total incidence returned to the same level as the pre-indirect effects period (i.e. 100% serotype replacement). This replacement started 3 years after the vaccine switch in children, and occurred over a period of 5 years. The relative contribution of the non-vaccine serotypes was assumed to remain constant.

The assumptions on the extent of indirect effects and the time-frame in which this occurs were based on trends observed in the IPD incidence in countries using PCV10 and/or PCV13 in their childhood vaccination program, found by the multi-country studies PSERENADE and SpIDnet [14-16]. Indirect protection started earlier than serotype replacement, but overall, indirect effects had completed after eight years and let to zero net-effects on the IPD incidence in non-vaccinated age groups (though, with large heterogeneity between countries).

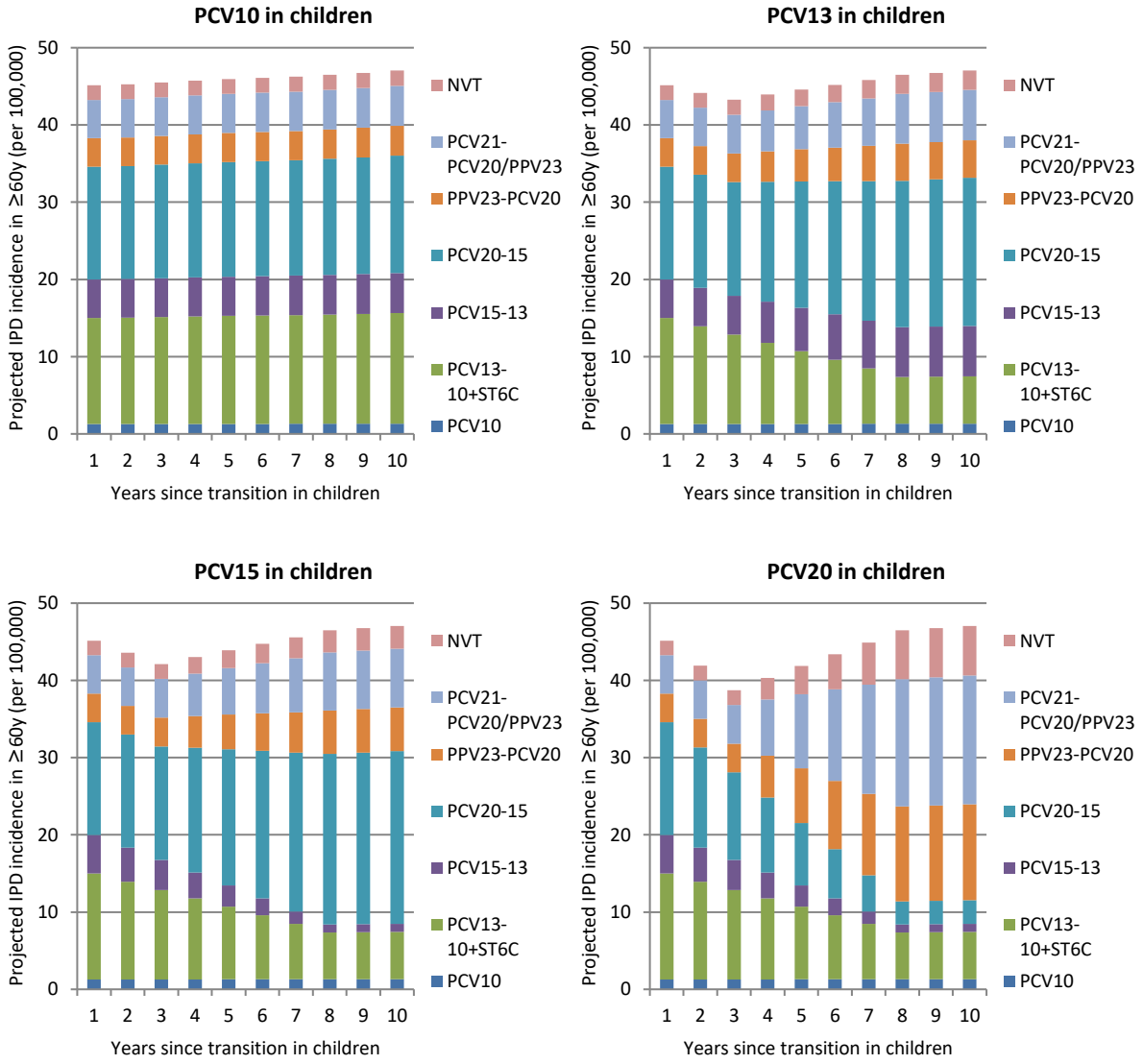


Figure S3: Projected incidence and change in serotype distribution among ≥60-year-olds per 100,000 inhabitant with PCV10 in children (stable) and after a transition from PCV10 to PCV13, PCV15 or PCV20. For visualization reasons we merged the serotype categories of Table S2 as follows: PCV10: PCV10 minus 7F + ST7F, PCV13-10: ST6A + ST3 + ST19A + ST6C (cross-protection from 6A), PCV20-15: PCV20 minus PCV15 minus 15B + ST15B, PPV23-PCV20: PCV21/PPV23 minus PCV20 minus

ST2 + ST2. PCV: Pneumococcal conjugate vaccine, PPV: pneumococcal polysaccharide vaccine, IPD: Invasive pneumococcal disease.

Vaccination

The vaccine uptake in elderly was assumed at 70%, approximately matching the actual estimated uptake of pneumococcal vaccination in the Netherlands in the calendar years 2020 and 2021 [15, 16].

VE of PPV23 against vaccine-type IPD at take was based on two observational cohort studies from the UK [17, 18], which presented VE estimates for the age-groups 65-74 years, 75-84 years and ≥85 years within two years after vaccination (Supplemental Figure S4). We used an average age of 69 years for the age-group 65-74 years, 79 years for the age-group 75-84 years and 88 years for the age-group ≥85 years. Then, we fitted a third-order polynomial function through the data points of the two studies with the size of the confidence intervals used as weights (Figure S4). For the VE of PPV23 against hospitalized NIPP, we used an estimate from a recent meta-analysis of observational studies with data up to 5 years after vaccination for the age-group 65-74 years (26% [95%CI: -0.05-0.49]). As no age-specific data was available for this outcome, we used this estimate for the age of 69 years, and applied the age-trend of VE against IPD to obtain VE estimates over age.

VE of PCV against vaccine-type IPD and vaccine-type NIPP was derived from the vaccine efficacy data as found in the CAPITA study [8], a large placebo-controlled randomized clinical trial of PCV13 in persons aged ≥65 years conducted in the Netherlands in the period 2008-2014. A *post-hoc* analysis of CAPITA data showed a significant decline in VE against vaccine-type IPD or NIPP with increasing age at vaccination. Therefore, we used single-year age-specific estimates of VE against IPD and VE against NIPP from Cox proportional hazards models that were applied on the modified intention to treat data of persons aged 65-89 years of CAPITA (Supplemental Figure S5) [19]. For the age-range 60-64 years we assumed the same VE as persons aged 65 years. For the probabilistic sensitivity analysis we obtained 1000 runs from the Cox proportional hazards model used to estimate the 95% credibility intervals. To account for the healthier population of the CAPITA trial, the VE estimates were multiplied by a factor 0.9. No evidence of waning was reported throughout the 4 years of follow-up in the CAPITA study, but vaccine efficacy data after this period is lacking. In line with a previous cost-effectiveness analysis for the Netherlands, we assumed no waning over the first four years after vaccination, followed by a linear waning to 0% after 15 years. We assumed that PCVs that include ST6A, also provide cross-protection against ST6C [11].

For combination strategies of a PCV with PPV23 in elderly, we modelled the VE over time separately for each vaccine. For serotypes present in both vaccines we used the highest VE in each time-step. In practice, the VE of PCV was higher than PPV in most of the analysis years, except for a short period after a revaccination with PPV23 at year 6 and year 11. Hence, we did not assume that the combination of PCV and PPV results in a higher efficacy against shared serotypes compared to using one of the vaccines.

For both vaccines we assumed that during the simulations of the probabilistic sensitivity analysis simulation, the VE could not be negative; those simulations were truncated to 0% effectiveness.

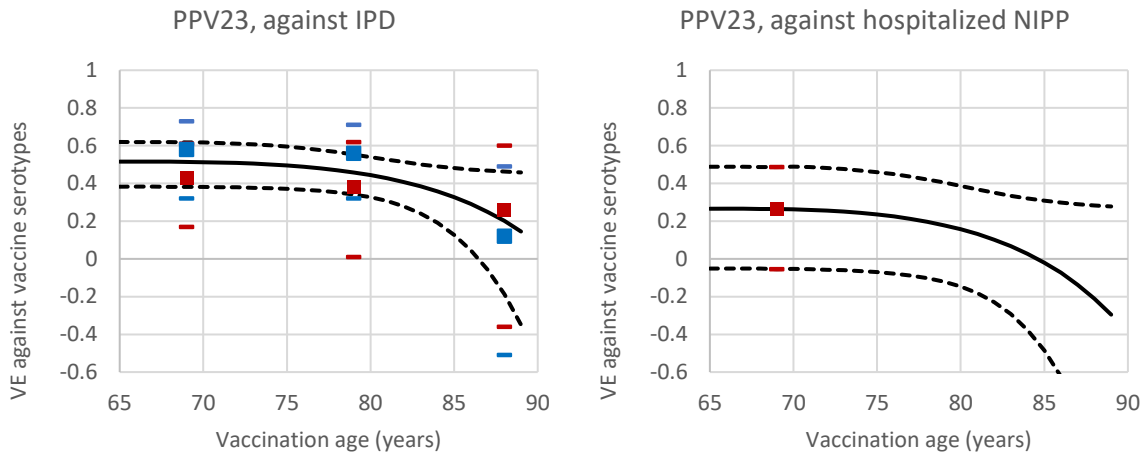


Figure S4: Estimated vaccine effectiveness (VE) of PPV23 against vaccine-type IPD and vaccine-type hospitalized NIPP (straight lines) with the 95% credibility interval (dashed line)). The VE against IPD is fitted to data from Andrews et al. (red markers) and Djennad et al. (blue markers). The VE against NIPP is based on a VE estimate for the age-group 65-74 years from a meta-analysis by Farrar et al. (red marks), and extrapolated across age using the trend of the VE of PPV23 against IPD. PPV: pneumococcal polysaccharide vaccine, IPD: Invasive pneumococcal disease, NIPP: non-invasive pneumococcal pneumonia.

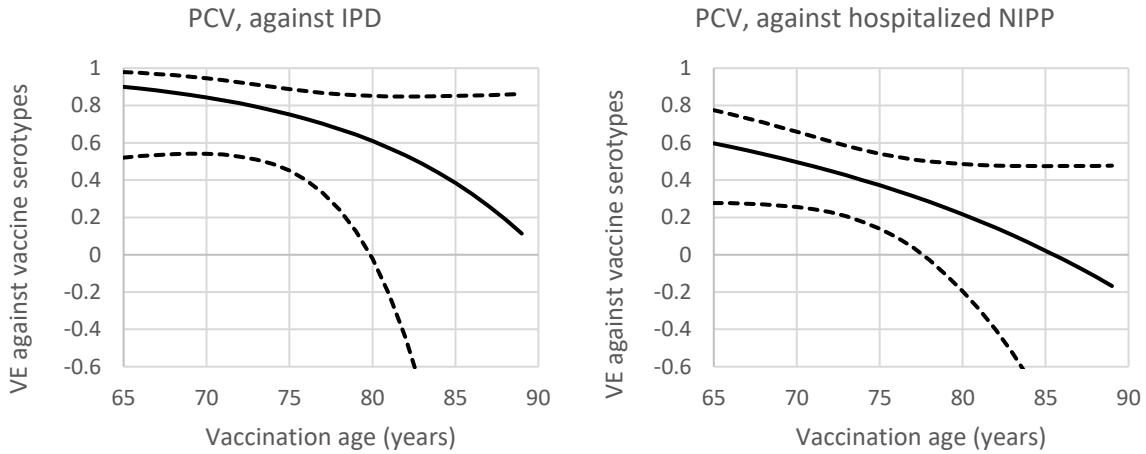


Figure S5: Estimated vaccine effectiveness (VE) of PCV against vaccine-type IPD and vaccine-type hospitalized NIPP based on CAPITA trial data of participants aged below 90 years. The full line represents the median estimate, and the dashed lines the lower and upper limits of the 95%-credibility intervals. Results presented in the graph are unadjusted for the relative healthier population of the CAPITA trial (see text). Data is shared by C.H. Van Werkhoven, and methods are presented in [19]. PCV: Pneumococcal conjugate vaccine, IPD: Invasive pneumococcal disease, NIPP: non-invasive pneumococcal pneumonia.

Costs

The used cost year was 2021, and all costs were inflated to this price year using the Dutch consumer price index (all sectors) [20]. Vaccine prices of PPV23, PCV15, PCV20 were based on the Dutch list price for individual use [21]. The vaccine price of PCV21 is unknown, and was assumed to be equal to PCV20. The administration cost per vaccination was based on the fee a general practitioner received in 2021 for the invitation and administration of PPV23 in the national vaccination program [22]. Age-specific costs of hospitalizations due to IPD and NIPP were based on a Dutch study conducted in parallel to the CAPITA trial [10]. The hospitalizations cost of NIPP were based on costs from patients

with a non-IPD CAP episode. Indirect health care cost, which are non-pneumococcal related medical costs in gained life years, were only included in a sensitivity analysis. Patient costs due to IPD or hospitalized NIPP were based on data from a cluster-randomized cross-over trial of antibiotic treatment strategies [23]. We used the weighted average of the three study groups. Estimates of productivity losses due to IPD, hospitalized NIPP and death following hospitalization were derived from a previous cost-effectiveness analysis of PCV13 for the Netherlands [5]. For pneumococcal-related deaths, the productivity losses were estimated using the friction method as recommended by the Dutch cost-effectiveness guideline, with a maximum friction period of 160 days. We did not consider productivity losses above the age of 75 years.

Distributions used for the probabilistic sensitivity analysis are shown in Supplemental Table S3.

Table S3: Parameter values of costs that were used in the base case analysis (mean value) and their distributions used in the probabilistic sensitivity analysis.

Parameter	Mean	Standard error	Distribution
Vaccination costs			
Vaccine cost per dose			
PPV23	€25.94		Fixed
PCV13	€74.72		Fixed
PCV15	€74.73		Fixed
PCV20	€82.95		Fixed
PCV21	€82.95		Fixed
Administration costs	€21.00		Fixed
Direct healthcare costs			
IPD in-patient			
60-64y	Equal to 65-74y		
65-74y	€13,373	1.05097	Lognormal
75-84y	€18,961	1.07177	Lognormal
85+y	€8,595	1.16543	Lognormal
CAP in-patient survivor			
60-64y	Equal to 65-74y		
65-74y	€9,807	1.00251	Lognormal
75-84y	€9,690	1.00252	Lognormal
85+y	€7,093	1.00288	Lognormal
Indirect healthcare costs (in sensitivity analysis only)			
Healthcare costs in gained life years	Age-specific		
Direct non-healthcare costs (patient costs)			
IPD/NIPP hospitalization	€144	€12	Gamma
Indirect non-healthcare costs (productivity losses)			
IPD hospitalization			
60-64y	€4,145	€ 300	Gamma
65-74y	€330	€ 24	Gamma
75+y	€0		Fixed
NIPP hospitalization			
60-64y	€2,747	€ 66	Gamma
65-74y	€330	€ 8	Gamma
75+y	€0		Fixed

Death (either IPD or NIPP, additional to hospitalization costs)		
60-64y	€17,937	Fixed
65-74y	€3,116	Fixed
75+y	€0	Fixed

PCV: Pneumococcal conjugate vaccine, PPV: pneumococcal polysaccharide vaccine, IPD: Invasive pneumococcal disease, NIPP: non-invasive pneumococcal pneumonia

Health effects

Quality-adjusted life year (QALY) loss inputs and their distribution for the probabilistic sensitivity analysis are shown in Table S4. The QALY losses of both IPD and hospitalized NIPP were based on a Dutch study measuring the utility loss among hospitalized non-fatal CAP cases during the acute phase and the first month of the illness using the EuroQol five dimensional instrument (EQ-5D) [9]. QALYs lost due to premature death was estimated using the life-expectancy of a general Dutch person at that age [2], adjusted for age-specific Dutch general population utilities [26] (Figure S6).

Distributions used for the probabilistic sensitivity analysis are shown in Supplemental Table S4.

Table S4: Parameter values of quality-adjusted life years (QALY) lost that were used in the base case analysis (mean value) and their distributions used in the probabilistic sensitivity analysis.

Parameter	Mean	Standard error	Distribution
QALY loss IPD / NIPP hospitalization	0.0709	0.0200	Beta
Life years lost due to IPD/NIPP mortality	Age-specific, see Figure S6		Fixed
General population utilities			
60-69y	0.839	0.0142	Beta
≥70y	0.852	0.0144	Beta

IPD: Invasive pneumococcal disease, NIPP: non-invasive pneumococcal pneumonia, QALY: Quality-adjusted life year

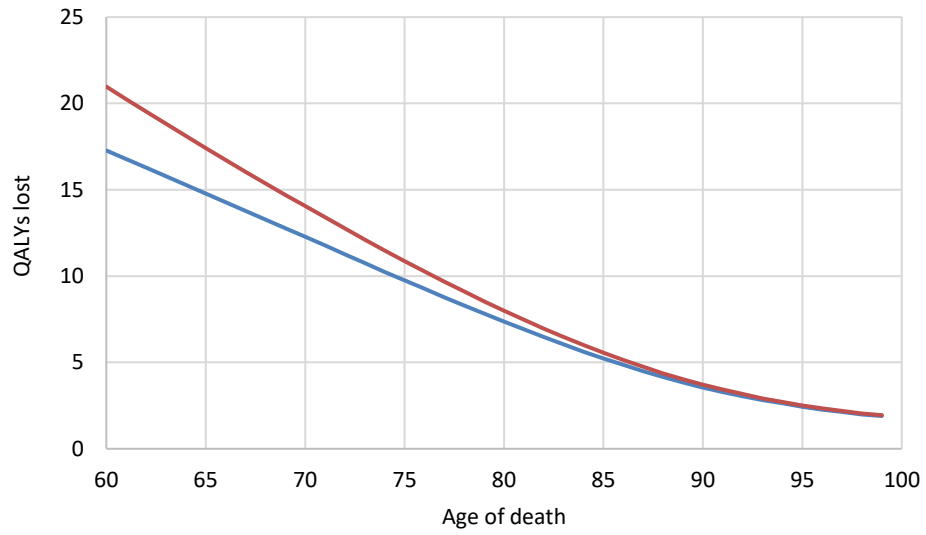


Figure S6: The number of QALYs lost by age of death due to pneumococcal-related premature death. The red line shows the undiscounted QALY loss and the blue line the discounted QALY loss at 1.5% per year. QALY: Quality-adjusted life year

Sensitivity analysis

We performed several one-way sensitivity analyses, in which one parameter was varied while the other parameters were kept fixed. The assumptions are shown in Supplemental Table S5.

Table S5: Parameters varied in the one-way sensitivity analyses and their input values

Parameter	Base case	Sensitivity analysis
% CAP hospitalizations caused by *S. pneumoniae*	22.1%	30%
VE of PCV	Age-specific, mean value	Age-specific, lower bound of 95% confidence interval Age-specific, upper bound of 95% confidence interval
VE of PPV23	Age-specific, mean value	Age-specific, lower bound of 95% confidence interval Age-specific, upper bound of 95% confidence interval
VE against ST3	Equal VE for all serotypes	No VE against serotype 3
VE against hospitalized NIPP	Included	No VE against hospitalized NIPP
Waning of PCV	VE 4 years stable, linear decline to 0% at 15 years after vaccination	VE 4 years stable, linear decline to 0% at 10 years after vaccination* VE 8 years stable, linear decline to 0% at 15 years after vaccination
Waning of PPV23	VE 2 years stable, linear decline to 0% at 5 years after vaccination	VE 5 years stable, and instant to 0% at 5 years after vaccination
QALY loss hospitalized IPD/NIPP	0.706, based on the disease period and one month follow-up	0.15, based on the disease period and one year follow-up [24]
Indirect health care costs	No inclusion of indirect health care costs	Inclusion of indirect health care costs as presented in Table S3
Perspective	Societal perspective	Health care payer's perspective (only including direct medical costs)
Discounting	4%/1.5% per year for costs/QALYs	No discounting 4%/4% per year for costs/QALYs
Administration costs €10	€21	€10 €22.50 (13% discount)
PPV23 price per dose	€25.94	50% discount (possible price reduction following tender [25]) 13% discount, varies per vaccine
PCV price per dose	Varies per vaccine (List price – see Table S3)	50% discount (possible price reduction following tender [25]), varies per vaccine

* For this analysis we reduced the time-horizon from 15 years to 10 years to avoid that a third dose of PPV23 after 10 years is included in the comparison.

IPD: Invasive pneumococcal disease, NIPP: non-invasive pneumococcal pneumonia, PCV: Pneumococcal conjugate vaccine, PPV: pneumococcal polysaccharide vaccine, QALY: Quality-adjusted life year.

Supplementary results

Base case analysis

The reduction in IPD cases and NIPP hospitalizations, the number needed to vaccinate and the Incremental cost-effectiveness ratio (ICER) of the various pneumococcal vaccination strategies in a 65-year-old cohort over a 15-year time-horizon, in case of an unchanged childhood vaccination program, are presented in supplemental Table S6, supplemental Table S7, supplemental Table S8, supplemental Table S9 show the results when a change of PCV10 to PCV13, PCV15 or PCV20, respectively, was assumed.

Table S6: Clinical impact, number needed to vaccinate and cost-effectiveness of different pneumococcal vaccination strategies in a 65-year-old cohort, while continuing PCV10 in children. The analysis assumed an uptake of 70% in elderly.

Outcome	No vaccination	Difference to no vaccination							
		3x PPV23	PCV13	PCV15	PCV20	PCV13 + 3xPPV23	PCV15 + 3xPPV23	PCV20 + 3xPPV23	PCV21
Vaccines administered	-	450,282	159,875	159,875	159,875	603,330	603,334	603,344	159,875
Clinical outcomes									
IPD cases	1,360	-274	-156	-208	-358	-343	-365	-430	-424
NIPP cases	2,281	-227	-161	-214	-369	-309	-335	-413	-437
Deaths	488	-69	-40	-53	-92	-87	-92	-109	-109
Costs									
Vaccination	-	17.75	15.30	15.30	16.62	32.13	32.13	33.45	16.62
Medical costs	35.25	-5.18	-3.25	-4.31	-7.42	-6.64	-7.15	-8.63	-8.80
Patient costs	0.44	-0.06	-0.04	-0.05	-0.09	-0.08	-0.08	-0.10	-0.11
Productivity losses	1.61	-0.22	-0.17	-0.23	-0.39	-0.31	-0.33	-0.42	-0.46
QALY loss									
Illness	205	-30	-19	-26	-44	-39	-42	-51	-53
Mortality	4,130	-633	-402	-533	-918	-801	-864	-1,047	-1,089
Total									
Costs	37	12	12	11	9	25	25	24	7
QALYs	4,336	-662	-421	-559	-963	-840	-906	-1,098	-1,141
Relative to no vaccination									
NNV per IPD case avoided		584	1,022	770	447	466	438	372	377
NNV per NIPP hospitalization avoided		705	991	747	434	518	477	387	366
NNV per death avoided		2,329	3,980	2,999	1,741	1,844	1,730	1,466	1,469
ICER (€/QALY gained)		18,559	28,120	19,162	9,051	29,891	27,128	22,134	6,352

ICER: Incremental cost-effectiveness ratio, IPD: Invasive pneumococcal disease, NIPP: Non-invasive pneumococcal pneumonia, NNV: Number needed to vaccinate, PPV: pneumococcal polysaccharide vaccine, PCV: Pneumococcal conjugate vaccine, QALY: Quality-adjusted life year

Table S7: Clinical impact, number needed to vaccinate and cost-effectiveness of different pneumococcal vaccination strategies in a 65-year-old cohort, while transitioning to PCV13 in children. The analysis assumed an uptake of 70% in elderly.

Outcome	No vaccination	Difference to no vaccination							
		3x PPV23	PCV13	PCV15	PCV20	PCV13 + 3xPPV23	PCV15 + 3xPPV23	PCV20 + 3xPPV23	PCV21
Vaccines administered	-	450,283	159,875	159,875	159,875	603,329	603,332	603,343	159,875
Clinical outcomes									
IPD cases	1,346	-271	-105	-164	-335	-316	-340	-410	-412
NIPP cases	2,263	-224	-104	-165	-344	-275	-305	-393	-426
Deaths	485	-68	-25	-40	-86	-79	-85	-104	-106
Costs									
Vaccination	-	17.75	15.30	15.30	16.62	32.13	32.13	33.45	16.62
Medical costs	34.92	-5.12	-2.18	-3.40	-6.95	-6.03	-6.59	-8.23	-8.56
Patient costs	0.44	-0.06	-0.03	-0.04	-0.09	-0.07	-0.08	-0.10	-0.10
Productivity losses	1.59	-0.22	-0.12	-0.18	-0.37	-0.27	-0.30	-0.40	-0.45
QALY loss									
Illness	203	-29	-13	-20	-42	-35	-39	-48	-51
Mortality	4,091	-625	-266	-417	-859	-723	-793	-997	-1,060
Total									
Costs	37	12	13	12	9	26	25	25	8
QALYs	4,294	-655	-279	-437	-901	-758	-831	-1,045	-1,111
Relative to no vaccination									
NNV per IPD case avoided		591	1,520	977	478	506	470	390	388
NNV per NIPP hospitalization avoided		712	1,540	969	464	581	524	407	376
NNV per death avoided		2,352	6,414	3,961	1,869	2,036	1,881	1,539	1,507
ICER (€/QALY gained)		18,882	46,561	26,730	10,228	33,961	30,258	23,650	6,750

ICER: Incremental cost-effectiveness ratio, IPD: Invasive pneumococcal disease, NIPP: Non-invasive pneumococcal pneumonia, NNV: Number needed to vaccinate, PPV: pneumococcal polysaccharide vaccine, PCV: Pneumococcal conjugate vaccine, QALY: Quality-adjusted life year

Table S8: Clinical impact, number needed to vaccinate and cost-effectiveness of different pneumococcal vaccination strategies in a 65-year-old cohort, while transitioning to PCV15 in children. The analysis assumed an uptake of 70% in elderly.

Outcome	No vaccination	Difference to no vaccination							
		3x PPV23	PCV13	PCV15	PCV20	PCV13 + 3xPPV23	PCV15 + 3xPPV23	PCV20 + 3xPPV23	PCV21
Vaccines administered	-	450,284	159,875	159,875	159,875	603,329	603,331	603,343	159,875
Clinical outcomes									
IPD cases	1,339	-262	-105	-130	-319	-306	-320	-395	-405
NIPP cases	2,254	-217	-104	-127	-327	-267	-282	-377	-418
Deaths	483	-66	-25	-30	-81	-76	-79	-100	-104
Costs									
Vaccination	-	17.75	15.30	15.30	16.62	32.13	32.13	33.45	16.62
Medical costs	34.75	-4.95	-2.18	-2.71	-6.62	-5.86	-6.16	-7.92	-8.42
Patient costs	0.43	-0.06	-0.03	-0.03	-0.08	-0.07	-0.07	-0.09	-0.10
Productivity losses	1.58	-0.21	-0.12	-0.14	-0.35	-0.27	-0.28	-0.38	-0.44
QALY loss									
Illness	202	-28	-13	-16	-40	-34	-36	-47	-50
Mortality	4,070	-604	-266	-328	-817	-702	-738	-959	-1,042
Total									
Costs	37	13	13	12	10	26	26	25	8
QALYs	4,273	-633	-279	-344	-857	-736	-774	-1,006	-1,092
Relative to no vaccination									
NNV per IPD case avoided		611	1,520	1,226	502	522	500	404	395
NNV per NIPP hospitalization avoided		738	1,540	1,254	490	599	568	424	382
NNV per death avoided		2,440	6,414	5,268	1,976	2,103	2,025	1,603	1,533
ICER (€/QALY gained)		19,824	46,561	36,065	11,173	35,228	33,090	24,908	7,007

ICER: Incremental cost-effectiveness ratio, IPD: Invasive pneumococcal disease, NIPP: Non-invasive pneumococcal pneumonia, NNV: Number needed to vaccinate, PPV: pneumococcal polysaccharide vaccine, PCV: Pneumococcal conjugate vaccine, QALY: Quality-adjusted life year

Table S9: Clinical impact, number needed to vaccinate and cost-effectiveness of different pneumococcal vaccination strategies in a 65-year-old cohort, while transitioning to PCV20 in children. The analysis assumed an uptake of 70% in elderly.

Outcome	No vaccination	Difference to no vaccination							
		3x PPV23	PCV13	PCV15	PCV20	PCV13 + 3xPPV23	PCV15 + 3xPPV23	PCV20 + 3xPPV23	PCV21
Vaccines administered	-	450,283	159,875	159,875	159,875	603,327	603,329	603,336	159,875
Clinical outcomes									
IPD cases	1,319	-195	-105	-130	-204	-237	-250	-290	-383
NIPP cases	2,227	-158	-104	-127	-197	-208	-222	-264	-396
Deaths	478	-47	-25	-30	-46	-57	-60	-69	-99
Costs									
Vaccination	-	17.75	15.30	15.30	16.62	32.13	32.13	33.45	16.62
Medical costs	34.25	-3.70	-2.18	-2.71	-4.24	-4.58	-4.89	-5.77	-7.97
Patient costs	0.43	-0.04	-0.03	-0.03	-0.05	-0.05	-0.06	-0.07	-0.10
Productivity losses	1.55	-0.16	-0.12	-0.14	-0.23	-0.21	-0.23	-0.28	-0.42
QALY loss									
Illness	199	-21	-13	-16	-26	-27	-29	-34	-48
Mortality	4,012	-450	-266	-328	-511	-548	-585	-690	-986
Total									
Costs	36	14	13	12	12	27	27	27	8
QALYs	4,211	-471	-279	-344	-537	-575	-613	-724	-1,033
Relative to no vaccination									
NNV per IPD case avoided		818.6267056	1,520	1,226	783	675	639	552	417
NNV per NIPP hospitalization avoided		1,011	1,540	1,254	812	770	720	605	404
NNV per death avoided		3,397	6,414	5,268	3,458	2,797	2,660	2,327	1,622
ICER (€/QALY gained)		29,381	46,560	36,065	22,550	47,408	43,956	37,738	7,876

ICER: Incremental cost-effectiveness ratio, IPD: Invasive pneumococcal disease, NIPP: Non-invasive pneumococcal pneumonia, NNV: Number needed to vaccinate, PPV: pneumococcal polysaccharide vaccine, PCV: Pneumococcal conjugate vaccine, QALY: Quality-adjusted life year

Cost-effectiveness tables, age 65, different childhood vaccines

The QALY losses, costs and ICER of the various pneumococcal vaccination strategies in a 65-year-old cohort over a 15-year time-horizon, in case of an unchanged childhood vaccination program, are presented in supplemental Table S10. Table S11, Table S12, and Table S13 show the results when a change in children from PCV10 to PCV13, PCV15 or PCV20, respectively, was assumed.

Table S10: QALY losses, costs and incremental cost-effectiveness ratio of different vaccination strategies in a 65-year-olds cohort, while continuing PCV10 in children.

Schedule	Total QALY loss	Total costs (€, millions)	Comparator	Incremental QALYs	Incremental costs (€, millions)	ICER (€/QALY gained)
No vaccination	4,336	37.3				
PCV13	3,914	50.5	No vaccination	421	13.16	Dominated
PCV15	3,776	49.3	No vaccination	559	12.03	Dominated
3x PPV23	3,673	49.6	No vaccination	662	12.29	Dominated
PCV13 + 3xPPV23	3,496	63.7	No vaccination	840	26.42	Dominated
PCV15 + 3xPPV23	3,430	63.2	No vaccination	906	25.88	Dominated
PCV20	3,373	46.0	No vaccination	963	8.71	9,051
PCV20 + 3xPPV23	3,238	61.6	PCV20	135	15.59	115,412
*PCV21**	*3,194*	*44.6*	*No vaccination*	*1,141*	*7.25*	*6,352*

* As PCV21 is currently under development, we assumed its vaccine price to be equal to PCV20. Therefore, this strategy was excluded from the incremental comparison and only indicatively compared with no vaccination.
ICER: Incremental cost-effectiveness ratio, PPV: pneumococcal polysaccharide vaccine, PCV: Pneumococcal conjugate vaccine, QALY: Quality-adjusted life year.

Table S11: Incremental cost-effectiveness ratio of different vaccination strategies in a 65-year-olds cohort, while transitioning to PCV13 in children.

Schedule	Total QALY loss	Total costs (€, millions)	Comparator	Incremental QALYs	Incremental costs (€, millions)	ICER (€/QALY gained)
No vaccination	4,294	36.94				
PCV13	4,015	49.92	No vaccination	279	12.98	Dominated
PCV15	3,857	48.63	No vaccination	437	11.69	Dominated
3x PPV23	3,639	49.30	No vaccination	655	12.36	Dominated
PCV13 + 3xPPV23	3,535	62.70	No vaccination	758	25.75	Dominated
PCV15 + 3xPPV23	3,462	62.10	No vaccination	831	25.16	Dominated
PCV20	3,393	46.16	No vaccination	901	9.21	10,228
PCV20 + 3xPPV23	3,248	61.67	PCV20	145	24.72	107,314
*PCV21**	*3,183*	*44.44*	*No vaccination*	*1,111*	7.50	*6,750*

* As PCV21 is currently under development, we assumed its vaccine price to be equal to PCV20. Therefore, this strategy was excluded from the incremental comparison and only indicatively compared with no vaccination.
ICER: Incremental cost-effectiveness ratio, PPV: pneumococcal polysaccharide vaccine, PCV: Pneumococcal conjugate vaccine, QALY: Quality-adjusted life year.

Table S12: Incremental cost-effectiveness ratio of different vaccination strategies in a 65-year-olds cohort, while transitioning to PCV15 in children.

Schedule	Total QALY loss	Total costs (€, millions)	Comparator	Incremental QALYs	Incremental costs (€, millions)	ICER (€/QALY gained)
No vaccination	4,273	36.76				
PCV13	3,994	49.74	No vaccination	279	12.98	Dominated
PCV15	3,928	49.18	No vaccination	344	12.42	Dominated
3x PPV23	3,640	49.30	No vaccination	633	12.54	Dominated
PCV13 + 3xPPV23	3,536	62.70	No vaccination	736	25.94	Dominated
PCV15 + 3xPPV23	3,498	62.38	No vaccination	774	25.62	Dominated
PCV20	3,416	46.33	No vaccination	857	9.57	11,173
PCV20 + 3xPPV23	3,267	61.81	PCV20	149	15.48	103,800
*PCV21**	*3,180*	*44.42*	*No vaccination*	*1,092*	*7.65*	*7,007*

* As PCV21 is currently under development, we assumed its vaccine price to be equal to PCV20. Therefore, this strategy was excluded from the incremental comparison and only indicatively compared with no vaccination.
ICER: Incremental cost-effectiveness ratio, PPV: pneumococcal polysaccharide vaccine, PCV: Pneumococcal conjugate vaccine, QALY: Quality-adjusted life year.

Table S13: Incremental cost-effectiveness ratio of different vaccination strategies in a 65-year-olds cohort, while transitioning to PCV20 in children.

Schedule	Total QALY loss	Total costs (€, millions)	Comparator	Incremental QALYs	Incremental costs (€, millions)	ICER (€/QALY gained)
No vaccination	4,211	36.23	No vaccination			
PCV13	3,932	49.21	No vaccination	279	12.98	Dominated
PCV15	3,866	48.65	No vaccination	344	12.42	Dominated
3x PPV23	3,739	50.08	No vaccination	471	13.85	Dominated
PCV20	3,674	48.33	No vaccination	537	12.10	22,550
PCV13 + 3xPPV23	3,635	63.51	PCV20	575	27.28	Dominated
PCV15 + 3xPPV23	3,597	63.19	PCV20	613	26.96	Dominated
PCV20 + 3xPPV23	3,486	63.56	PCV20	188	15.23	81,193
*PCV21**	*3,177*	*44.37*	*No vaccination*	*1,033*	*8.14*	*7,876*

* As PCV21 is currently under development, we assumed its vaccine price to be equal to PCV20. Therefore, this strategy was excluded from the incremental comparison and only indicatively compared with no vaccination.
ICER: Incremental cost-effectiveness ratio, PPV: pneumococcal polysaccharide vaccine, PCV: Pneumococcal conjugate vaccine, QALY: Quality-adjusted life year.

Cost-effectiveness by time horizon

We evaluated the effect of the time-horizon on the ICER, to indicate how the costs and benefits of the intervention balance over time, with results shown in Figure S7.

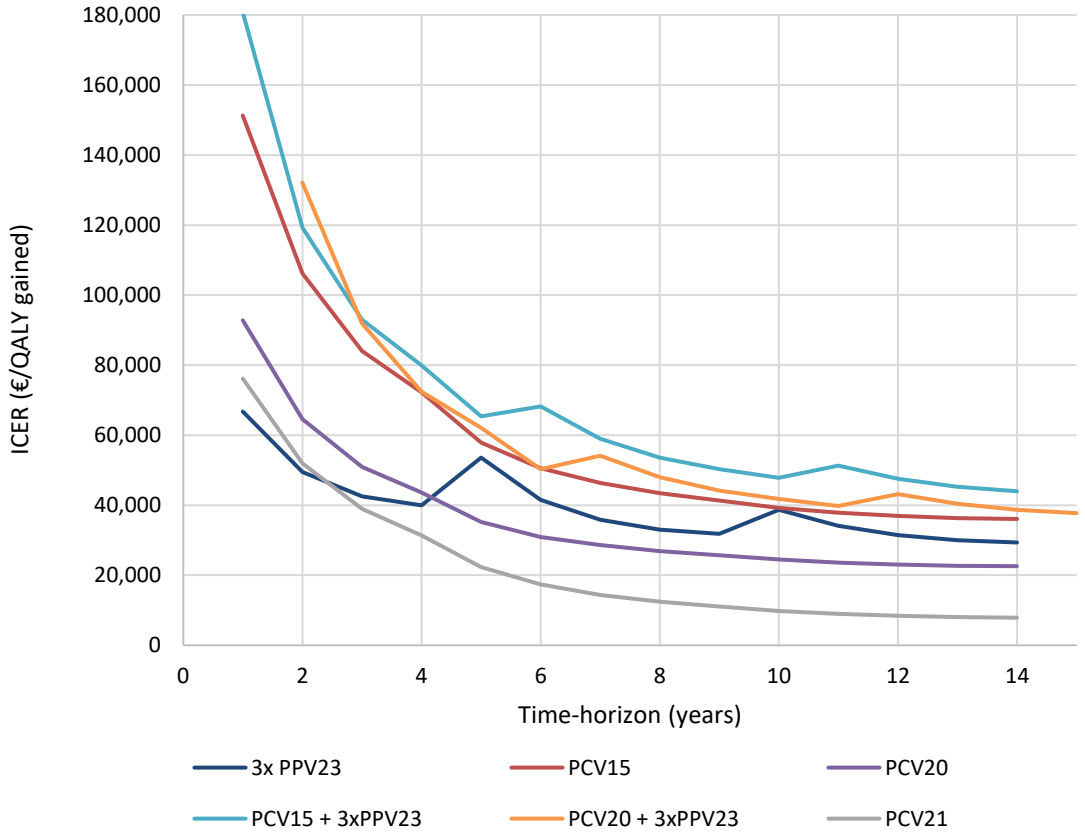
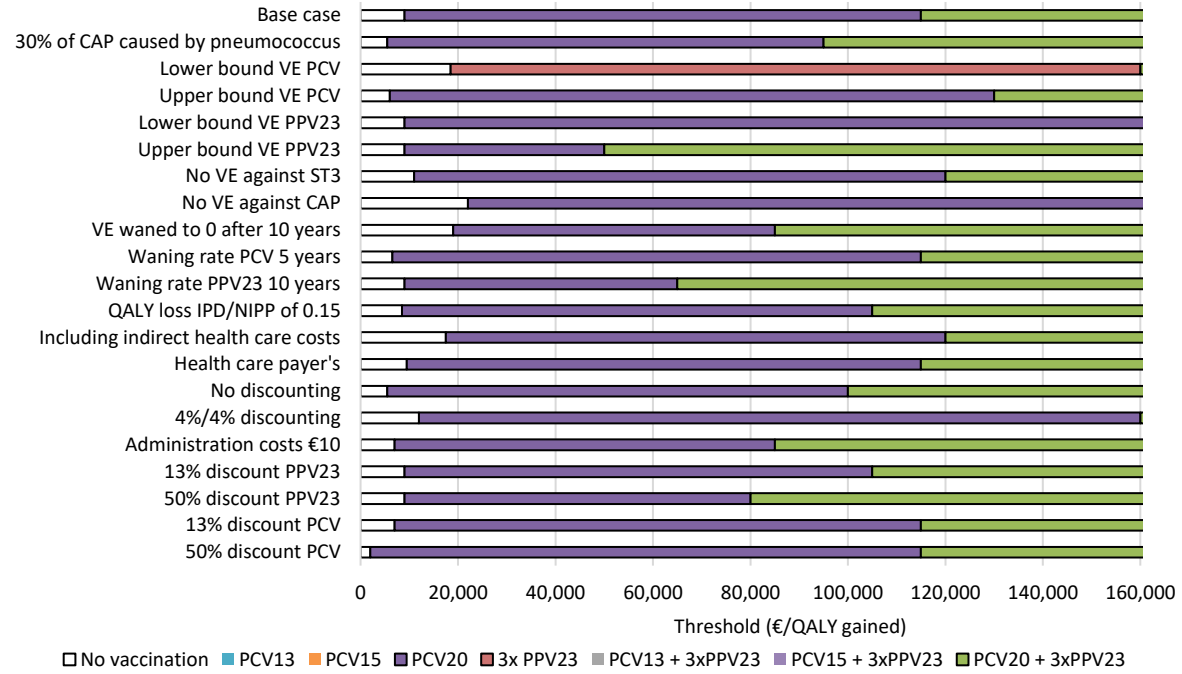


Figure S7: Cost-effectiveness of different pneumococcal vaccination strategies in a 65-year-old cohort, while varying the time horizon. Children are vaccinated with PCV10. ICER: Incremental cost-effectiveness ratio, PCV: Pneumococcal conjugate vaccine, PPV: pneumococcal polysaccharide vaccine, QALY: Quality-adjusted life year.

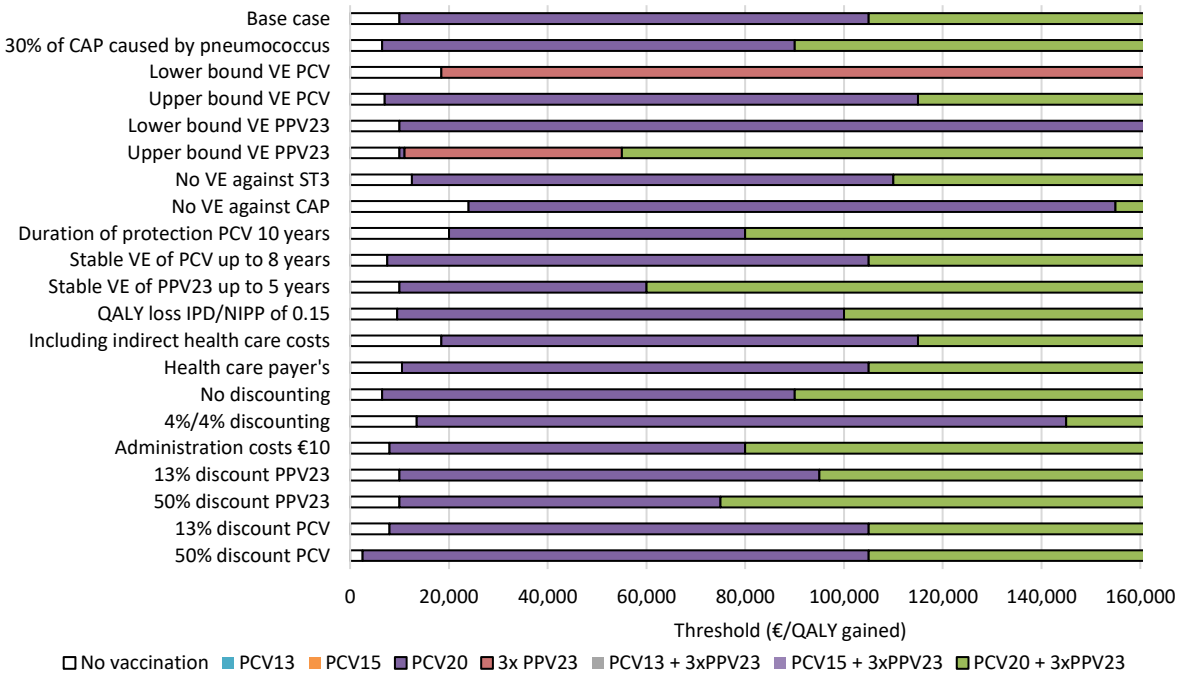
One-way sensitivity analysis, 65 years, various childhood vaccines

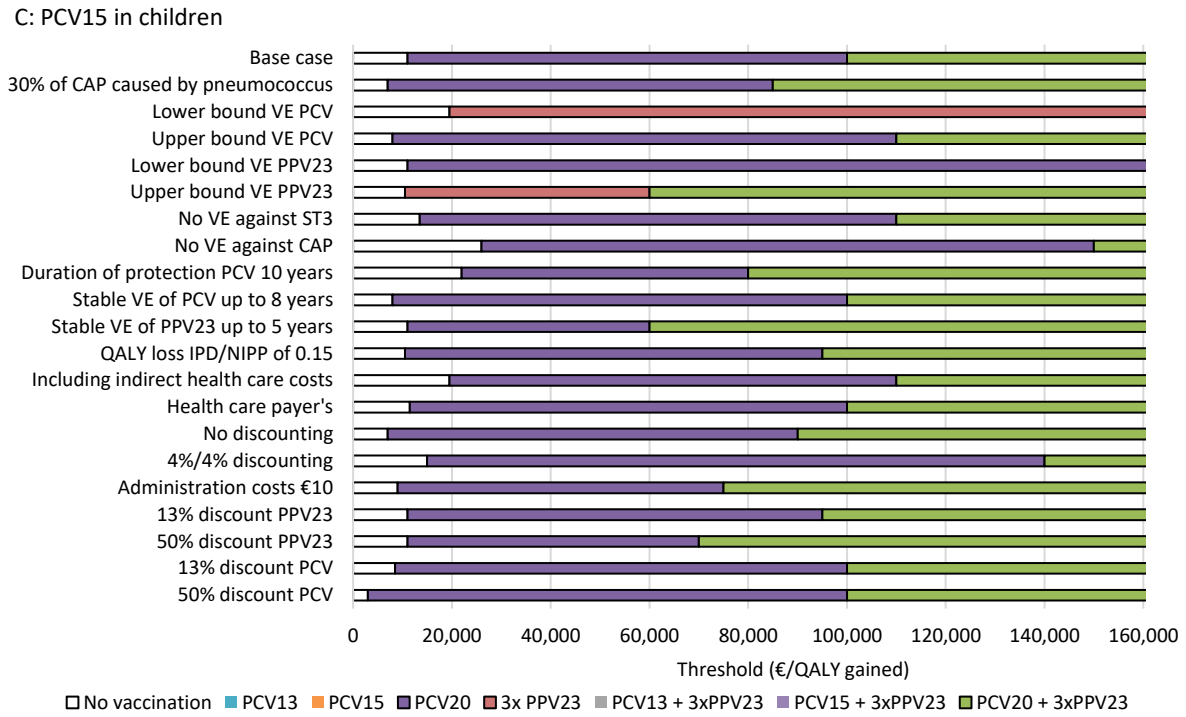
A sensitivity analysis on the time-horizon indicates that the ICER of the more expensive PCV20 becomes favorable compared to 3x PPV23 for time-horizons of 5 years and longer.

A: PCV10 in children



B: PCV13 in children





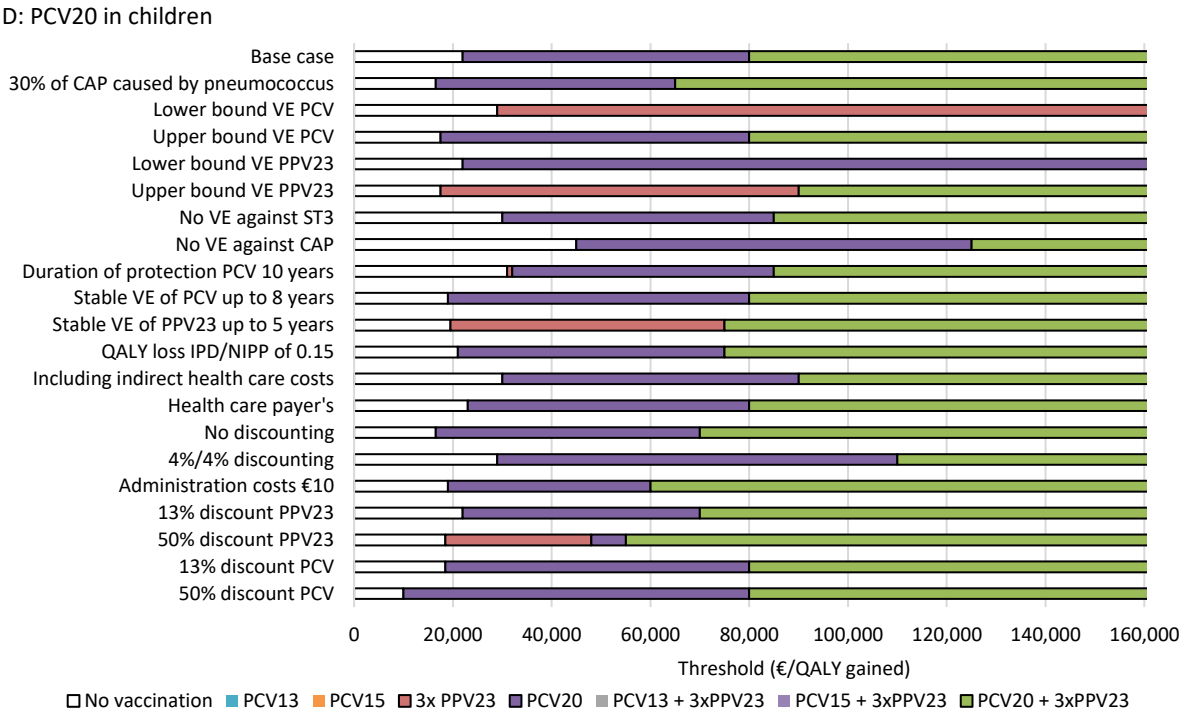


Figure S8: One-way sensitivity analysis of the cost-effectiveness of pneumococcal vaccination in a 65-years-old cohort while continuing PCV10 in children (panel A), or with a transition to PCV13 (Panel B), PCV15 (Panel C) and PCV20 (Panel D). The bars show the cost-effective strategy across a range of cost-effectiveness thresholds. CAP: Community-acquired pneumonia, ICER: Incremental cost-effectiveness ratio, IPD: Invasive pneumococcal disease, NIPP: Non-invasive pneumococcal pneumonia, PCV: Pneumococcal conjugate vaccine, PPV: pneumococcal polysaccharide vaccine, QALY: Quality-adjusted life year. VE: Vaccine effectiveness, ST: Serotype

Effect of age at vaccination on the results

While the main manuscript and abovementioned results were obtained for a cohort vaccinated at 65 years of age, we determined the effect of age at time of vaccination on the ICER (Figure S8). The effect of vaccination age on clinical impact, number needed to vaccinate and the cost-effectiveness is shown for vaccination age 60 years (Table S14), 70 years (Table S15), 75 years (Table S16), 80 years (Table S17) and 85 years (Table S18). The incremental cost effectiveness for different vaccination ages are presented in tables S19-S23 for vaccination ages 60-85 years. The effect of different vaccines used in childhood vaccination on the scenario's with different ages at vaccination are presented in Figure S8.

Cost-effectiveness by vaccination age, PCV10 in children

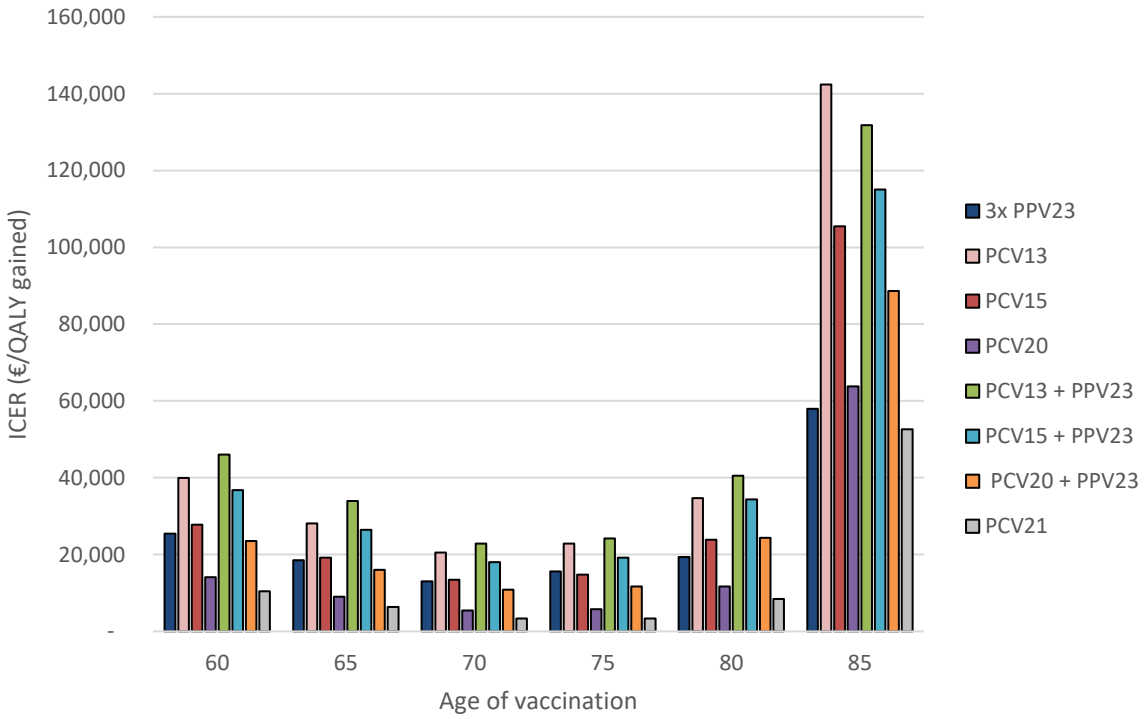


Figure S9: Cost-effectiveness of various vaccination pneumococcal vaccination strategies compared to no vaccination by vaccination age, while PCV10 is continued in children. ICER: Incremental cost-effectiveness ratio, PCV: Pneumococcal conjugate vaccine, PPV: pneumococcal polysaccharide vaccine, QALY: Quality-adjusted life year.

Table S14: Clinical impact, number needed to vaccinate and cost-effectiveness of different pneumococcal vaccination strategies in a 60-year-old cohort, while remaining PC10 in children. The analysis assumed an uptake of 70% in elderly.

Outcome	No vaccination	Difference to no vaccination							
		3x PPV23	PCV13	PCV15	PCV20	PCV13 + 3xPPV23	PCV15 + 3xPPV23	PCV20 + 3xPPV23	PCV21
Vaccines administered	-	514,586	178,444	178,444	178,444	688,218	688,221	688,229	178,444
Clinical outcomes									
IPD cases	1,290	-263	-144	-191	-328	-328	-348	-406	-389
NIPP cases	1,633	-171	-113	-150	-259	-230	-248	-301	-307
Deaths	342	-52	-27	-36	-62	-64	-68	-79	-73
Costs									
Vaccination	-	20.22	17.08	17.08	18.55	36.35	36.36	37.82	18.55
Medical costs	27.13	-4.19	-2.59	-3.44	-5.92	-5.39	-5.79	-6.96	-7.02
Patient costs	0.35	-0.05	-0.03	-0.04	-0.07	-0.07	-0.07	-0.09	-0.09
Productivity losses	4.55	-0.73	-0.61	-0.81	-1.40	-1.06	-1.18	-1.51	-1.66
QALY loss									
Illness	166	-26	-16	-21	-36	-33	-36	-43	-43
Mortality	3,525	-573	-331	-439	-756	-713	-764	-913	-896
Total									
Costs	32	15	14	13	11	30	29	29	10
QALYs	3,691	-599	-346	-460	-792	-747	-800	-956	-939
Relative to no vaccination									
NNV per IPD case avoided		609	1,113	839	487	488	460	393	411
NNV per NIPP hospitalization avoided		937	1,413	1,064	618	696	645	531	521
NNV per death avoided		3,086	5,937	4,472	2,597	2,494	2,356	2,028	2,191
ICER (€/QALY gained)		25,449	39,961	27,805	14,085	39,961	36,647	30,602	10,423

ICER: Incremental cost-effectiveness ratio, IPD: Invasive pneumococcal disease, NIPP: Non-invasive pneumococcal pneumonia, NNV: Number needed to vaccinate, PPV: pneumococcal polysaccharide vaccine, PCV: Pneumococcal conjugate vaccine, QALY: Quality-adjusted life year

Table S15: Clinical impact, number needed to vaccinate and cost-effectiveness of different pneumococcal vaccination strategies in a 70-year-old cohort, while remaining PC10 in children. The analysis assumed an uptake of 70% in elderly.

Outcome	No vaccination	Difference to no vaccination							
		3x PPV23	PCV13	PCV15	PCV20	PCV13 + 3xPPV23	PCV15 + 3xPPV23	PCV20 + 3xPPV23	PCV21
Vaccines administered	-	372,049	137,480	137,480	137,480	500,058	500,063	500,077	137,480
Clinical outcomes									
IPD cases	1,356	-262	-153	-203	-349	-325	-346	-409	-414
NIPP cases	2,849	-237	-175	-232	-399	-313	-341	-424	-473
Deaths	721	-86	-53	-70	-121	-107	-115	-138	-143
Costs									
Vaccination	-	14.76	13.16	13.16	14.29	27.01	27.01	28.14	14.29
Medical costs	42.18	-5.56	-3.57	-4.74	-8.16	-6.98	-7.52	-9.10	-9.67
Patient costs	0.52	-0.06	-0.04	-0.05	-0.09	-0.08	-0.08	-0.10	-0.11
Productivity losses	1.46	-0.17	-0.14	-0.19	-0.33	-0.24	-0.27	-0.34	-0.39
QALY loss									
Illness	237	-30	-20	-27	-46	-38	-42	-51	-54
Mortality	4,833	-659	-438	-581	-1,000	-826	-897	-1,104	-1,186
Total									
Costs	44	9	9	8	6	20	19	19	4
QALYs	5,070	-689	-458	-607	-1,046	-865	-939	-1,155	-1,240
Relative to no vaccination									
NNV per IPD case avoided		610	1,047	789	458	492	462	391	386
NNV per NIPP hospitalization avoided		676	916	690	401	511	468	377	338
NNV per death avoided		1,858	3,025	2,279	1,323	1,491	1,391	1,162	1,116
ICER (€/QALY gained)		13,012	20,553	13,462	5,459	22,793	20,393	16,106	3,323

ICER: Incremental cost-effectiveness ratio, IPD: Invasive pneumococcal disease, NIPP: Non-invasive pneumococcal pneumonia, NNV: Number needed to vaccinate, PPV: pneumococcal polysaccharide vaccine, PCV: Pneumococcal conjugate vaccine, QALY: Quality-adjusted life year

Table S16: Clinical impact, number needed to vaccinate and cost-effectiveness of different pneumococcal vaccination strategies in a 75-year-old cohort, while remaining PC10 in children. The analysis assumed an uptake of 70% in elderly.

Outcome	No vaccination	Difference to no vaccination							
		3x PPV23	PCV13	PCV15	PCV20	PCV13 + 3xPPV23	PCV15 + 3xPPV23	PCV20 + 3xPPV23	PCV21
Vaccines administered	-	310,369	123,391	123,391	123,391	420,206	420,210	420,222	123,391
Clinical outcomes									
IPD cases	1,264	-219	-133	-177	-304	-235	-257	-320	-360
NIPP cases	3,282	-164	-164	-218	-375	-258	-292	-390	-445
Deaths	855	-72	-54	-72	-124	-90	-100	-130	-147
Costs									
Vaccination	-	12.45	11.81	11.81	12.83	23.30	23.30	24.31	12.83
Medical costs	42.48	-4.55	-3.43	-4.55	-7.83	-5.87	-6.47	-8.22	-9.28
Patient costs	0.57	-0.05	-0.04	-0.05	-0.09	-0.06	-0.07	-0.09	-0.10
Productivity losses	0.97	-0.05	-0.05	-0.07	-0.11	-0.08	-0.09	-0.12	-0.14
QALY loss									
Illness	259	-24	-18	-24	-42	-31	-34	-44	-50
Mortality	4,486	-476	-345	-458	-789	-582	-644	-826	-935
Total									
Costs	44	8	8	7	5	17	17	16	3
QALYs	4,745	-501	-363	-482	-831	-613	-678	-870	-985
Relative to no vaccination									
NNV per IPD case avoided		732	1,202	905	526	679	622	499	443
NNV per NIPP hospitalization avoided		973	973	733	426	619	548	410	359
NNV per death avoided		2,218	2,943	2,217	1,287	1,770	1,592	1,231	1,086
ICER (€/QALY gained)		15,573	22,827	14,814	5,770	28,209	24,576	18,250	3,355

ICER: Incremental cost-effectiveness ratio, IPD: Invasive pneumococcal disease, NIPP: Non-invasive pneumococcal pneumonia, NNV: Number needed to vaccinate, PPV: pneumococcal polysaccharide vaccine, PCV: Pneumococcal conjugate vaccine, QALY: Quality-adjusted life year

Table S17: Clinical impact, number needed to vaccinate and cost-effectiveness of different pneumococcal vaccination strategies in a 80-year-old cohort, while remaining PC10 in children. The analysis assumed an uptake of 70% in elderly.

Outcome	No vaccination	Difference to no vaccination							
		2x PPV23	PCV13	PCV15	PCV20	PCV13 + 2xPPV23	PCV15 + 2xPPV23	PCV20 + 2xPPV23	PCV21
Vaccines administered	-	156,561	89,009	89,009	89,009	236,650	236,652	236,658	89,009
Clinical outcomes									
IPD cases	855	-110	-81	-108	-186	-122	-140	-192	-220
NIPP cases	2,509	-63	-83	-110	-190	-116	-136	-195	-225
Deaths	744	-38	-36	-48	-83	-52	-61	-86	-98
Costs									
Vaccination	-	6.78	8.52	8.52	9.25	14.68	14.68	15.42	9.25
Medical costs	28.49	-2.11	-1.73	-2.30	-3.96	-2.70	-3.06	-4.11	-4.69
Patient costs	0.43	-0.02	-0.02	-0.03	-0.05	-0.03	-0.04	-0.05	-0.06
Productivity losses	0.76	-0.02	-0.03	-0.03	-0.06	-0.04	-0.04	-0.06	-0.07
QALY loss									
Illness	199	-12	-10	-14	-24	-15	-18	-25	-28
Mortality	3,162	-228	-184	-244	-421	-279	-319	-436	-499
Total									
Costs	30	5	7	6	5	12	12	11	4
QALYs	3,360	-240	-194	-258	-444	-294	-336	-460	-527
Relative to no vaccination									
NNV per IPD case avoided		1,453	1,966	1,481	860	1,315	1,146	831	725
NNV per NIPP hospitalization avoided		2,536	1,923	1,449	841	1,378	1,174	819	710
NNV per death avoided		4,202	4,399	3,314	1,925	3,064	2,634	1,868	1,624
ICER (€/QALY gained)		19,333	34,678	23,872	11,676	40,513	34,319	24,322	8,421

ICER: Incremental cost-effectiveness ratio, IPD: Invasive pneumococcal disease, NIPP: Non-invasive pneumococcal pneumonia, NNV: Number needed to vaccinate, PPV: pneumococcal polysaccharide vaccine, PCV: Pneumococcal conjugate vaccine, QALY: Quality-adjusted life year

Table S18: Clinical impact, number needed to vaccinate and cost-effectiveness of different pneumococcal vaccination strategies in a 85-year-old cohort, while remaining PC10 in children. The analysis assumed an uptake of 70% in elderly.

Outcome	No vaccination	Difference to no vaccination							
		1x PPV23	PCV13	PCV15	PCV20	PCV13 + 1xPPV23	PCV15 + 1xPPV23	PCV20 + 1xPPV23	PCV21
Vaccines administered	-	55,006	55,006	55,006	55,006	105,774	105,774	105,775	55,006
Clinical outcomes									
IPD cases	427	-34	-29	-38	-66	-47	-52	-69	-78
NIPP cases	1,362	0	-5	-7	-12	-5	-7	-12	-14
Deaths	422	-8	-9	-11	-20	-13	-15	-20	-23
Costs									
Vaccination	-	2.58	5.27	5.27	5.72	7.56	7.56	8.01	5.72
Medical costs	12.21	-0.28	-0.25	-0.34	-0.58	-0.39	-0.45	-0.60	-0.69
Patient costs	0.24	-0.00	-0.00	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01
Productivity losses	0.42	0.00	-0.00	-0.00	-0.00	-0.00	-0.00	-0.00	-0.00
QALY loss									
Illness	111	-2	-2	-3	-5	-3	-4	-5	-6
Mortality	1,410	-37	-33	-44	-75	-51	-58	-78	-89
Total									
Costs	13	2	5	5	5	7	7	7	5
QALYs	1,521	-40	-35	-47	-80	-54	-62	-83	-95
Relative to no vaccination									
NNV per IPD case avoided		4,672	5,529	4,165	2,419	3,426	3,055	2,320	2,041
NNV per NIPP hospitalization avoided		-1,335,632	30,947	23,314	13,538	31,304	23,473	13,550	11,422
NNV per death avoided		20,116	18,665	14,061	8,166	12,523	10,897	7,896	6,889
ICER (€/QALY gained)		57,957	142,362	105,432	63,749	131,782	115,071	88,632	52,623

ICER: Incremental cost-effectiveness ratio, IPD: Invasive pneumococcal disease, NIPP: Non-invasive pneumococcal pneumonia, NNV: Number needed to vaccinate, PPV: pneumococcal polysaccharide vaccine, PCV: Pneumococcal conjugate vaccine, QALY: Quality-adjusted life year

Cost-effectiveness by age, PCV10 in children

Table S19: Incremental cost-effectiveness ratio of different vaccination strategies in a 60-year-olds cohort, while remaining PC10 in children. The analysis assumed an uptake of 70% in elderly.

Schedule	Total QALY loss	Total costs (€, millions)	Comparator	Incremental QALYs	Incremental costs (€, millions)	ICER (€/QALY gained)
No vaccination	3,691	32.03				
PCV13	3,344	45.88	No vaccination	346	13.85	Dominated
PCV15	3,231	44.82	No vaccination	460	12.79	Dominated
3x PPV23	3,092	47.28	No vaccination	599	15.25	Dominated
PCV13 + 3xPPV23	2,944	61.87	No vaccination	747	29.84	Ext.Dominance
PCV20	2,899	43.18	No vaccination	792	11.15	14,085
PCV15 + 3xPPV23	2,891	61.35	PCV20	8	18	Dominated
*PCV21**	*2,752*	*41.81*	*No vaccination*	*939*	*9.78*	*10,423*
PCV20 + 3xPPV23	2,735	61.29	PCV20	164	18	110,264

* As PCV21 is currently under development, we assumed its vaccine price to be equal to PCV20. Therefore, this strategy was excluded from the incremental comparison and only indicatively compared with no vaccination.
ICER: Incremental cost-effectiveness ratio, PCV: Pneumococcal conjugate vaccine, PPV: pneumococcal polysaccharide vaccine, QALY: Quality-adjusted life year.

Table S20: Incremental cost-effectiveness ratio of different vaccination strategies in a 70-year-olds cohort, while remaining PC10 in children. The analysis assumed an uptake of 70% in elderly.

Schedule	Total QALY loss	Total costs (€, millions)	Comparator	Incremental QALYs	Incremental costs (€, millions)	ICER (€/QALY gained)
No vaccination	5,070	44.16				
PCV13	4,612	53.56	No vaccination	458	9.41	Dominated
PCV15	4,462	52.33	No vaccination	607	8.18	Dominated
3x PPV23	4,380	53.12	No vaccination	689	8.97	Dominated
PCV13 + 3xPPV23	4,205	63.87	No vaccination	865	19.71	Dominated
PCV15 + 3xPPV23	4,131	63.29	No vaccination	939	19.14	Dominated
PCV20	4,024	49.87	No vaccination	1,046	5.71	5,459
PCV20 + 3xPPV23	3,915	62.75	PCV20	108	12.88	118,765
*PCV21**	*3,830*	*48.28*	*No vaccination*	*1,240*	*4.12*	*3,323*

* As PCV21 is currently under development, we assumed its vaccine price to be equal to PCV20. Therefore, this strategy was excluded from the incremental comparison and only indicatively compared with no vaccination.
ICER: Incremental cost-effectiveness ratio, PCV: Pneumococcal conjugate vaccine, PPV: pneumococcal polysaccharide vaccine, QALY: Quality-adjusted life year.

Table S21: Incremental cost-effectiveness ratio of different vaccination strategies in a 75-year-olds cohort, while remaining PC10 in children. The analysis assumed an uptake of 70% in elderly.

Schedule	Total QALY loss	Total costs (€, millions)	Comparator	Incremental QALYs	Incremental costs (€, millions)	ICER (€/QALY gained)
No vaccination	4,745	44.02				
PCV13	4,382	52.32	No vaccination	363	8.30	Dominated
PCV15	4,263	51.17	No vaccination	482	7.15	Dominated
3x PPV23	4,244	51.82	No vaccination	501	7.80	Dominated
PCV13 + 3xPPV23	4,104	61.15	No vaccination	641	17.13	Dominated
PCV15 + 3xPPV23	4,042	60.55	No vaccination	703	16.53	Dominated
PCV20	3,914	48.81	No vaccination	831	4.79	5,770
PCV20 + 3xPPV23	3,859	59.81	PCV20	55	11.00	198,264
*PCV21**	*3,760*	*47.32*	*No vaccination*	*985*	*3.30*	*3,355*

* As PCV21 is currently under development, we assumed its vaccine price to be equal to PCV20. Therefore, this strategy was excluded from the incremental comparison and only indicatively compared with no vaccination.
ICER: Incremental cost-effectiveness ratio, PCV: Pneumococcal conjugate vaccine, PPV: pneumococcal polysaccharide vaccine, QALY: Quality-adjusted life year.

Table S22: Incremental cost-effectiveness ratio of different vaccination strategies in a 80-year-olds cohort, while remaining PC10 in children. The analysis assumed an uptake of 70% in elderly.

Schedule	Total QALY loss	Total costs (€, millions)	Comparator	Incremental QALYs	Incremental costs (€, millions)	ICER (€/QALY gained)
No vaccination	3,360	29.68				
PCV13	3,166	36.42	No vaccination	194	6.74	Ext.Dominance
2x PPV23	3,121	34.31	No vaccination	240	4.63	Dominated
PCV15	3,102	35.84	No vaccination	258	6.16	Dominated
PCV13 + 2xPPV23	3,045	41.45	No vaccination	316	11.77	Dominated
PCV15 + 2xPPV23	3,007	41.11	No vaccination	353	11.43	Dominated
PCV20	2,916	34.87	No vaccination	444	5.19	11,676
PCV20 + 2xPPV23	2,897	40.85	PCV20	19	5.98	309,958
*PCV21**	*2,834*	*34.11*	*No vaccination*	*527*	*4.44*	*8,421*

* As PCV21 is currently under development, we assumed its vaccine price to be equal to PCV20. Therefore, this strategy was excluded from the incremental comparison and only indicatively compared with no vaccination.
ICER: Incremental cost-effectiveness ratio, PCV: Pneumococcal conjugate vaccine, PPV: pneumococcal polysaccharide vaccine, QALY: Quality-adjusted life year.

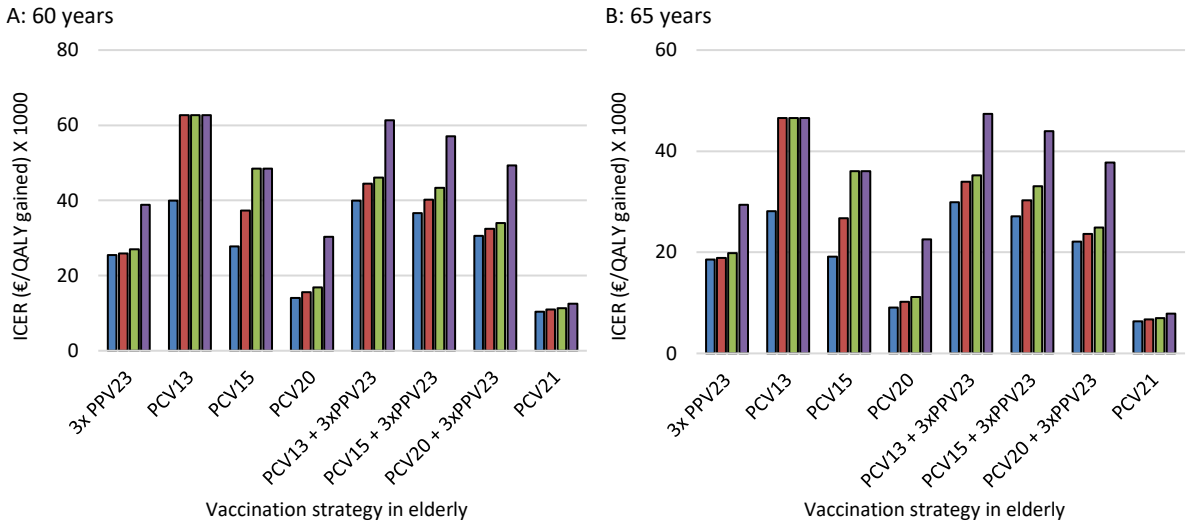
Table S23: Incremental cost-effectiveness ratio of different vaccination strategies in a 85-year-olds cohort, while remaining PC10 in children. The analysis assumed an uptake of 70% in elderly.

Schedule	Total QALY loss	Total costs (€, millions)	Comparator	Incremental QALYs	Incremental costs (€, millions)	ICER (€/QALY gained)
No vaccination	1,521	12.87				
PCV13	1,486	17.87	No vaccination	35	5.00	Dominated
PPV23	1,481	15.17	No vaccination	40	2.30	57,957
PCV15	1,474	17.79	PPV23	7	2.62	Dominated
PCV13 + PPV23	1,467	20.02	PPV23	15	4.86	Dominated

PCV15 + PPV23	1,459	19.97	PPV23	22	4.80	Dominated
PCV20	1,441	17.99	PPV23	41	2.82	69,392
PCV20 + PPV23	1,438	20.26	PCV20	3	2.27	746,328
*PCV21**	*1,426*	*17.88*	*No vaccination*	*95*	*5.01*	*52,623*

* As PCV21 is currently under development, we assumed its vaccine price to be equal to PCV20. Therefore, this strategy was excluded from the incremental comparison and only indicatively compared with no vaccination.
ICER: Incremental cost-effectiveness ratio, PCV: Pneumococcal conjugate vaccine, PPV: pneumococcal polysaccharide vaccine, QALY: Quality-adjusted life year.

Cost-effectiveness by vaccination age, various childhood vaccines



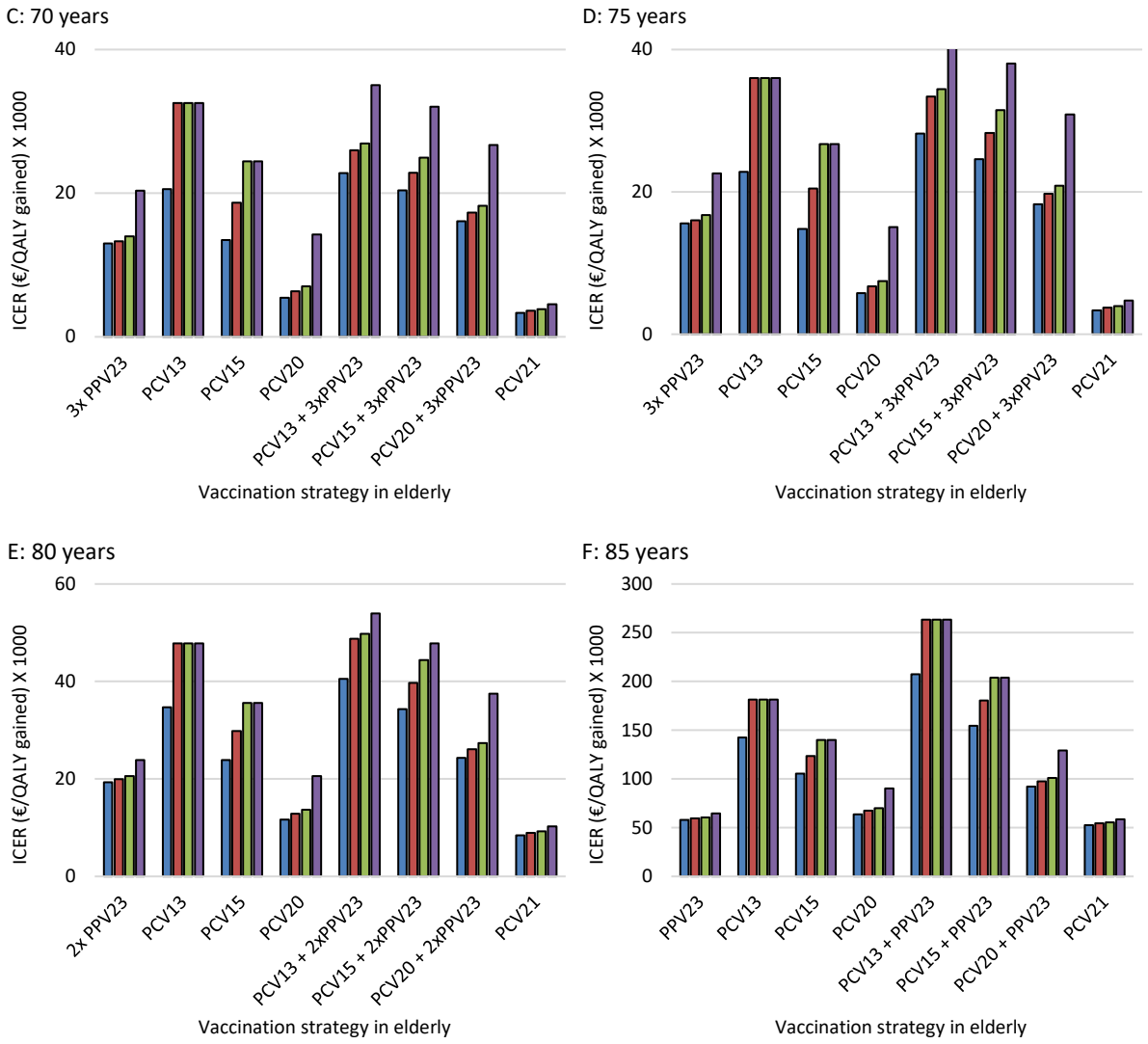


Figure S10: Cost-effectiveness of different pneumococcal vaccination strategies in elderly for different vaccination ages in the age-range 60 to 85 years (Panel A-F), while varying the childhood vaccine between PCV10 (blue bars), PCV13 (red bars), PCV15 (green bars), and PCV20 (purple bars). The results present the ICERs compared to no vaccination. We assumed no PPV23 vaccination above the age of 86 years. ICER: Incremental cost-effectiveness ratio, PCV: Pneumococcal conjugate vaccine, PPV: pneumococcal polysaccharide vaccine, QALY: Quality-adjusted life year.

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