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Pneumococcal vaccination in older adults

Updated information for the Health Council of the Netherlands

RIVM letter report 2026-0051
A. Steens et al.

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Synopsis

Pneumococcal vaccination in older adults

Updated information for the Health Council of the Netherlands

The bacterium pneumococcus can cause serious infections such as pneumonia, sepsis and meningitis. In the Netherlands, about 1,600 people aged 60 years or older get a serious pneumococcal infection every year. To prevent pneumococcal disease, people in this age group can be vaccinated through the National Pneumococcal Vaccination Programme (NPPV). Children are offered vaccination against pneumococcal disease as part of the National Immunisation Programme (NIP). The vaccines for children and older adults are different, but also protect against some of the same types of pneumococci.

While many types of pneumococci exist, the vaccines focus on those with the highest risk of causing severe illness. Pneumococci are spread primarily by children. Childhood vaccination reduces the prevalence and transmission of the types included in the NIP-vaccine, thereby also indirectly protecting older adults against disease caused by these types. However, types of pneumococci not included in the childhood vaccine may become more common after vaccination and can also cause severe illness. This is known as 'serotype replacement'.

Since autumn of 2025, people aged 60 years or older have been offered a PCV20 vaccine targeting 20 types of pneumococci. Fifteen of these types are identical to those included in the PCV15 vaccine used for children; the other five are not. A new vaccine that protects against 21 types of pneumococci, PCV21, has recently become available. Because PCV21 has less overlap with the PCV15 vaccine used for children, it also protects adults against types of pneumococci that may spread more as a result of childhood vaccination.

This information and more is included in a background document prepared by the National Institute for Public Health and the Environment (RIVM) for the Health Council of the Netherlands. The document supports the Health Council's advice on which vaccine is best suited to the NPPV. The Ministry of Health, Welfare and Sport (VWS) asked the Health Council to advise on this matter.

The RIVM document explains how often serious pneumococcal disease occurs in older adults, how safe PCV21 is and how effective it is. It also describes the chronic diseases that increase people's risk of pneumococcal disease.

Keywords: pneumococcus, pneumococcal disease, vaccination, conjugate vaccines, burden of disease, safety, older adults, risk groups, NPPV

Publiekssamenvatting

Pneumokokken vaccinatie voor mensen van 60 jaar en ouder

Vernieuwde informatie voor de Gezondheidsraad

De pneumokokkenbacterie veroorzaakt ernstige infecties zoals longontsteking, bloedvergiftiging en hersenvliesontsteking. Ernstige pneumokokkenziekte komt in Nederland elk jaar voor bij naar schatting zo'n 1600 mensen van 60 jaar en ouder. Om de ziekte te voorkomen kunnen mensen van deze leeftijd zich laten vaccineren in het Nationaal Programma Pneumokokken Vaccinatie (NPPV). Kinderen worden tegen pneumokokken gevaccineerd via het Rijksvaccinatieprogramma (RVP). De vaccins voor kinderen en ouderen verschillen en werken voor een deel tegen dezelfde typen pneumokokken.

Er zijn veel verschillende pneumokokken. De vaccines richten zich op de typen pneumokokken waar mensen heel ziek van kunnen worden. Pneumokokken worden vooral door kinderen verspreid. Door hen te vaccineren, verdwijnen de typen pneumokokken waartegen kinderen worden gevaccineerd en kunnen deze zich minder verspreiden. Op deze manier worden ouderen indirect ook tegen deze typen beschermd. Wel kunnen de typen pneumokokken die niet in het kindervaccin zitten, na de vaccinaties vaker voorkomen (typeverandering). Van deze typen kunnen mensen soms ook heel ziek worden.

Sinds de herfst van 2025 krijgen 60-plussers een vaccin dat gericht is op 20 typen pneumokokken (PCV20). Daarvan zijn 15 typen hetzelfde als in het vaccin dat bij kinderen wordt gebruikt (PCV15), plus vijf andere. Sinds kort bestaat er een vaccin tegen 21 pneumokoktypen (PCV21). Dit vaccin overlapt veel minder met het PCV15-vaccin voor kinderen. Het beschermt daarom volwassenen ook tegen de typen pneumokokken die als gevolg van kindervaccinatie meer zouden kunnen gaan circuleren.

Dit en meer staat in het achtergronddocument dat het RIVM voor de Gezondheidsraad heeft verzameld. Dit document dient als ondersteuning voor het advies van de Gezondheidsraad over welk vaccin het beste is voor het NPPV. Het ministerie van VWS heeft de Gezondheidsraad gevraagd hierover te adviseren.

Het RIVM beschrijft bijvoorbeeld hoe vaak ernstige pneumokokkenziekte voorkomt bij 60-plussers, hoe veilig PCV21 is en hoe goed het werkt. Daarnaast staat beschreven welke chronische ziektes ervoor zorgen dat mensen sneller pneumokokkenziekte krijgen.

Kernwoorden: pneumokok, pneumokokkenziekte, vaccinatie, ziektelast, veiligheid, ouderen, risicogroepen, NPPV

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1 Background

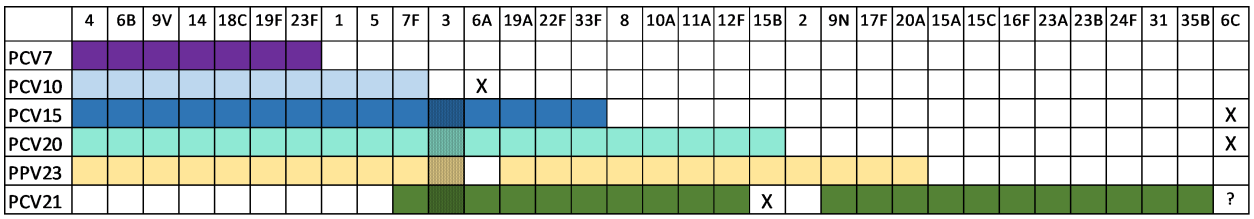
In autumn 2020, vaccination of older adults (aged 60-79 years) through the in the National Programme Pneumococcal vaccination (NPPV) started with the 23-valent pneumococcal polysaccharide vaccine (PPV23). Vaccination was implemented by birth cohort (Table 1). In autumn 2025, PPV23 was replaced with the 20-valent pneumococcal conjugate vaccine (PCV20) and the age range was extended from 60-79 years to everyone aged 60 years or older as advised by the Health Council of the Netherlands in 2023 (1). In March 2025, the 21-valent PCV21, also called V116 or CAPVAXIVE, was licensed for use in adults in the European Union and since April 2026 also for children aged 2 years or older who previously completed a primary paediatric pneumococcal vaccination regimen (2). PCV21 includes 11 serotype antigens that are different from PCV20 (see Figure 1) but does not protect against the PCV10 serotypes (except 7F). It is thus developed for use alongside a comprehensive paediatric national immunisation programme (NIP).

Table 1 Implementation of pneumococcal vaccination in the National Programme Pneumococcal Vaccination for older adults

Year	Vaccine	Birth cohorts	Age of vaccination
2020	PPV23	1941-1947	73-79 years
2021	PPV23	1948-1952	69-73 years
2022	PPV23	1953-1956	66-69 years
2023	PPV23	1957-1960	63-66 years
2024	PPV23	1961-1964	60-63 years
2025	PCV20	≤1947, 1965	≥78, 60 years
2026	PCV20	1948-1952, 1966	74-78, 60 years
2027	PCV20	1953-1956, 1967	71-74, 60 years
2028	PCV20	1957-1960, 1968	68-71, 60 years
2029	PCV20	1961-1964, 1969	65-68, 60 years
2030	PCV20	1970	60 years

As implemented in 2020-2025, and planned in autumn 2026

Figure 1 Serotypes for which antigens are included in indicated vaccines (coloured) and for which cross-protection is expected



Note that PCV7 is no longer available for use. The X indicates cross-protection provided by the vaccine (3) and ? indicates cross-protection assumed for the vaccine. For serotype 15C in PCV21, the deOAc15B polysaccharide is used, of which the molecular structure is shared between 15B and 15C. However, PCV21 cross-protection to 15B is only licensed by the FDA for protection against IPD and not to pneumococcal pneumonia (4) while it is mentioned as cross-reacting in the licensure by the EMA (5). Pattern: While serotype 3 is included in the license for PCV13/15/20/21 and PPV23, its effectiveness is (likely) limited (6-9)

The Health Council of the Netherlands will re-evaluate which vaccine is most appropriate for use in older adults in the Netherlands. This document provides an update of the RIVM letter report on 'Pneumococcal vaccination in older adults' published in 2022 (10) and re-uses information published in the RIVM letter report on 'Higher-valent pneumococcal vaccines for children' published in 2025 (11). It provides an updated overview of information from the literature and from recent Dutch (surveillance) data. The report also covers changes in epidemiology that may be expected due to the recent switch of the vaccine used in the childhood NIP (PCV10 to PCV15 in autumn 2024) and its potential indirect effects on the impact of the NPPV.
Note that, although the focus of this report is on vaccination of older adults through the NPPV, the information will also be relevant for vaccination of (medical) risk groups that are currently not included in the NPPV and that have increased risk for severe pneumococcal disease (12). The report therefore includes a section on medical risk groups.

2 Epidemiology of pneumococcal disease in the Netherlands

2.1 Surveillance data

The surveillance of pneumococcal disease in the Netherlands is mainly directed at invasive pneumococcal disease (IPD) (13). Data on IPD-causing pneumococcal serotypes comes from the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM; Amsterdam UMC) and data on the IPD-cases notified by the municipal health services in OSIRIS. For time trends over a longer period, sentinel data covering approximately 25% of the population is used until 2022, while since 2023, national data is used for all ages. For children <5 years of age, national data has been used from 2008 onwards; sentinel data is used for the period 2004-2008. For this report, data available on April 9th, 2026 is used.

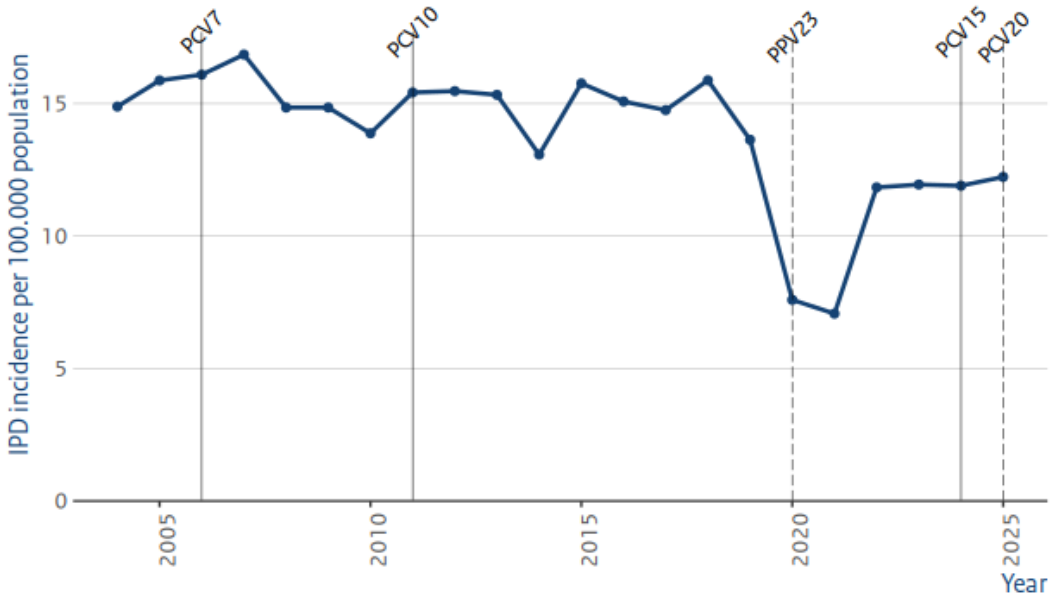
In this report, vaccine serotypes as presented are categorised based on the expected protective effect of the vaccine as presented in Figure 1, e.g., serotype 3 is categorised a non-vaccine serotype. Otherwise, note that, in surveillance, no distinction can be made between the different subtypes (factor-types) of serotype 20, so all serotype 20 IPD cases are included as PPV23 / PCV21 IPD.

We do not have continuous comprehensive insight into the dynamics of pneumococcal carriage and non-invasive pneumococcal disease because these data are dependent on dedicated studies rather than standing routine surveillance. Most recent data on the prevalence and serotype distribution in pneumococcal carriage in children and parents was obtained in the winter of 2022/23 (14) and on non-invasive pneumococcal pneumonia in adults during the winter of 2024/25 (see paragraph 2.5).

2.2 Invasive pneumococcal disease in the general population

The incidence of IPD caused by any serotype in the general population is presented in Figure 2. The incidence fluctuated in the period 2004–2019 between 13.1/100,000 (lowest; in 2014) and 16.8/100,000 (highest; in 2007). The overall incidence was lowest during the COVID years (2020, 7.6/100,000 and 2021, 7.1/100,000) and has been stable at around 12/100,000 in 2022-2025 (approximately n~2150 cases annually). The incidence has been impacted by the implementation of pneumococcal vaccination in the NIP (PCV7 from 2006 onwards, PCV10 from 2011 onwards, PCV15 from 2024 onwards) and in the NPPV (PPV23 from autumn 2020 onwards, PCV20 from autumn 2025 onwards) as well as the preventive measures that were implemented during the COVID years (March 2020 – March 2022 (15)). A more elaborate description of those changes has been published before (10, 11); below we provide preliminary impact estimates of the most recent changes in the NIP and NPPV.

Figure 2 IPD incidence as the number of IPD cases per 100,000 population in the general population (all ages) per calendar year



The straight lines indicate when vaccines were introduced in the NIP; the dashed lines show the timing of vaccine implementation in the NPPV. 3Data are extrapolated from sentinel data in the period 2004-2022 covering ~25% of the population whereas national data are used from 2023 onwards. Only IPD cases diagnosed in blood or cerebrospinal fluid (CSF) samples have been included

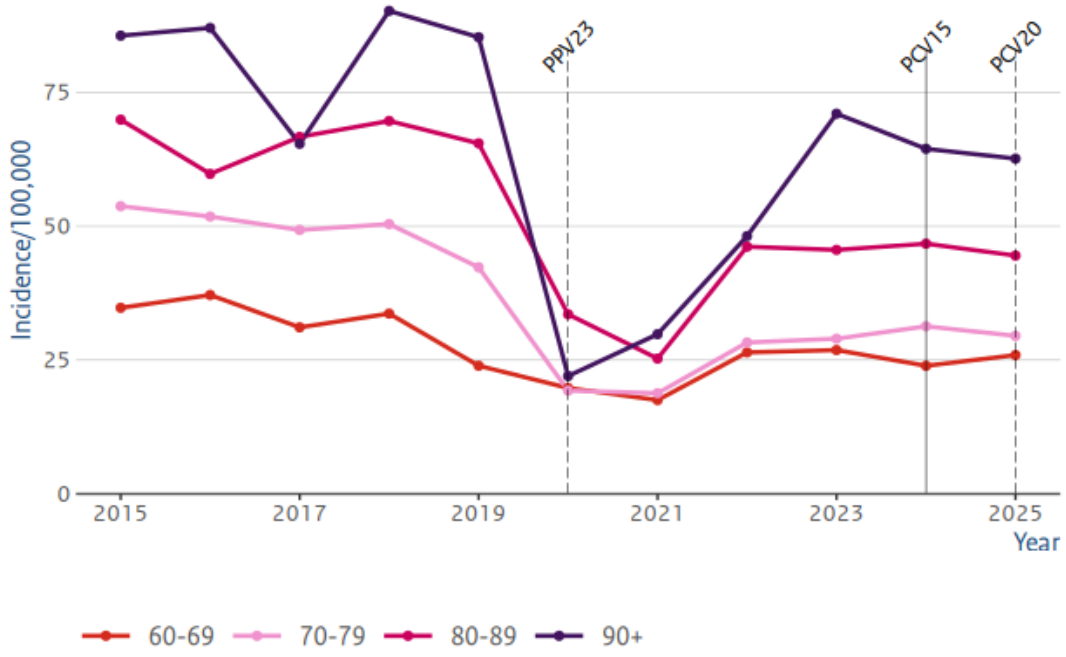
Indirect protection of childhood vaccination and serotype replacement after the changes in the NIP influenced the serotype distribution. In the years 2024-2025, the majority of IPD cases in the Netherlands were caused by serotypes for which protection can be expected by PCV20 (63%, n~1,370 annually) or PCV21 (75%, n~1,640). This information is described in more detail for those aged 60 years and older in the next paragraph.

2.3 Invasive pneumococcal disease in those aged 60 years and older

2.3.1 Incidence by age-group

The average incidence in 2024-2025 in the overall 60+ population was ~30/100,000 (n~1,500 annually). The IPD incidence increases, however, with age. The age-specific incidences in 2024-2025 were 25/100,000 (n~550) in the 60-69yrs olds, 30/100,000 (n~530) in the 70-79yrs olds, 45/100,000 (n~355) in the 80-89yrs olds and 63/100,000 (n~88) in those aged 90+ year olds (Figure 3). These recent incidences are lower than what was observed before the COVID pandemic. The introduction of PPV23 has likely played a role (see also paragraph 2.7.2), as well as other factors, as also the incidence in age groups not eligible for PPV23 vaccination in the NPPV (e.g. those aged 90 years and older) has slightly decreased.

Figure 3 All-serotype IPD incidence by 10-years age groups, for those aged 60 years and older



2.3.2 *Incidence by (vaccine) serotypes in recent years*

The incidence of PCV20-type IPD in 2024-2025 was ~19/100,000 (n~940 annually) and of PCV21-type IPD ~24/100,000 (n~1180) for the 60+ year olds. The vaccine type-coverage per age-group in this period is presented in Table 2. In all age groups, PCV21 covers a larger proportion of cases than PCV20. Maximally 7% of the cases are caused by serotypes for which PCV20 should provide protection while PCV21 does not, and 20-25% of the cases in each 10-years age-group are caused by serotypes against which serotype PCV21 may provide protection while PCV20 does not.

Table 2 Total number of IPD cases per PCV type and 10-year age-group in the two year period 2024-2025 and the percentage that are caused by serotypes for which protection may be expected by PCV20 or PCV21

Age group	**PCV20 n (%)**	**PCV21 n (%)**	**PCV20-nonPCV21 n (%)**	**PCV21-nonPCV20 n (%)**	**Shared serotypes n (%)**
60-69yrs (n=1152)	745 (65)	903 (78)	77 (7)	235 (20)	668 (58)
70-79yrs (n=1081)	630 (58)	811 (75)	77 (7)	256 (24)	554 (51)
80-89yrs (n=721)	415 (58)	553 (77)	43 (6)	182 (25)	372 (52)
90+yrs (n=175)	105 (60)	139 (79)	6 (3)	39 (23)	99 (57)
All 60+ (n=3129)	1895 (61)	2406 (77)	203 (7)	712 (23)	1693 (54)

Note that numbers are extrapolated for cases with missing serotype (n=25) using the vaccine-type proportion observed among those with serotype available.
PCV20-nonPCV21 = PCV20 unique serotypes, i.e., serotype 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F. PCV21-nonPCV20 = PCV21 unique serotypes, i.e., serotype 9N, 17F, 20, 15A, 15C, 16F, 23A, 23B, 24F, 31, 35B. Shared PCV20/21 serotypes are cases infected with a serotype covered by PCV20 and by PCV21, i.e., serotype 6A, 6C, 7F, 8, 10A, 11A, 12F, 15B, 19A, 22F, 33F

The number of cases per serotype that were diagnosed in 2024-2025 in the general 60+ year old population is presented in Table 3. It can be expected that the serotypes covered by PCV15 but not by PCV10 (serotypes 19A, 22F, 6C and 33F) will (slightly) decrease over time due to indirect protection of the recent switch to PCV15 in the NIP; see chapter 6. Note, however, that these PCV15-10 serotypes are covered by both PCV20 and PCV21.

Table 3 Serotype distribution of IPD cases aged 60 years and older, in the Netherlands in the years 2024-2025, ordered by frequency

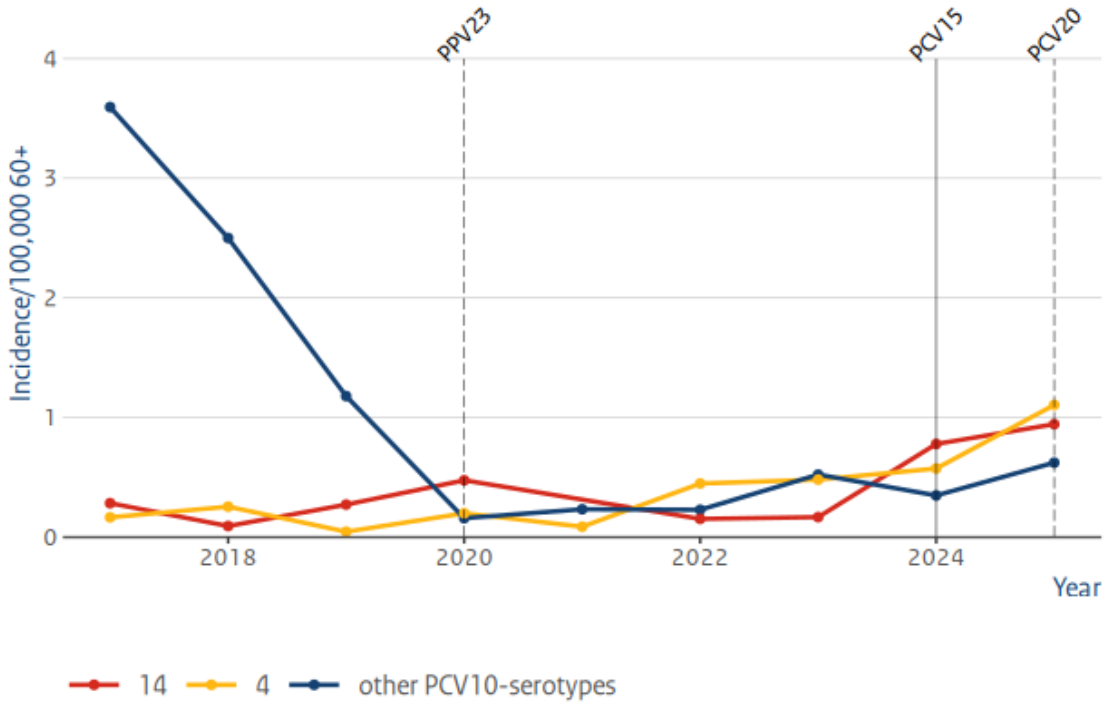
Serotype	Frequency	% of all with known serotype	PCV15	PCV20	PCV21
19A	519	16.7	X	X	X
8	417	13.4		X	X
3	362	11.7	-	-	-
9N	214	6.9			X
22F	163	5.3	X	X	X
12F	155	5		X	X
6C	144	4.6	*	*	*
23B	107	3.4			X
33F	98	3.2	X	X	X
15A	88	2.8			X
4	85	2.7	X	X	
14	84	2.7	X	X	
10A	80	2.6		X	X
23A	79	2.5			X
11A	62	2		X	X
7C	53	1.7			
16F	46	1.5			X
20	40	1.3			X
24F	35	1.1			X

Only cases that covered ≥1% of all 3104 cases with known serotype in the 2-year period are shown. Orange and x indicates which vaccine, if any, covers the serotype. Cross protection is indicated by * and lighter orange. While antigens for serotype 3 are included in the vaccines, real world protection is not expected. indicated by - . See Figure 1.

2.3.3 Increase in some vaccine serotypes

While serotype 4 and serotype 14 antigens have been included in the vaccines used in the NIP since the start (included in PCV7, PCV10 and PCV15), and they are included in PPV23, the incidence of these serotypes has recently increased in adults including the 60+ population (Figure 4). Of those aged 60+ years in this population, most were unvaccinated (75% of those with known vaccination status). No such increase has been observed in the Netherlands for the other PCV10 serotypes. Importantly, these serotypes are covered by PCV20, but not by PCV21. Overall, these two serotypes caused 5.4% of IPD in the 60+ year old population in 2024-2025 (Table 3).

Figure 4 Incidence of IPD in 60+ caused by serotype 4, serotype 14, or the eight PCV10 serotypes pooled together



Note that for serotype 4, national data is used from 2017 onwards as for that serotype, the geographical spread of the cases was not equally distributed and represented by the sentinel data. The surveillance coverage was, however, not yet complete in 2017-2019 (estimated at 62% in 2017, 76% in 2018, 88% in 2019 and ≥96% from 2020 onwards; to be published in October 2026, RIVM report 2026-0117. In those years, the incidence may thus be a slight underestimation

Serotype 4 also increased in (mainly unvaccinated) individuals in Belgium, England and Spain, where PCV13 has been used in the NIP. In Belgium, the increase was mainly seen in vulnerable (young) adults with identified risk factors: unemployment, unstable housing or homelessness, and heavy substance use (smoking, alcohol, hard drugs) (16). Whole genome sequencing (WGS) showed that the increase of serotype 4 infections is driven by the highly dominant lineage Global Pneumococcal Sequencing Cluster (GPSC)162, primarily composed of geographically different sub-lineages within ST801 and ST15063 (Belgium, UK and Netherlands (17)) or ST15063 alone (Spain (18)). In Belgium, UK and Dutch isolates, virulence factors that are involved in (serotype 4-specific) capsular synthesis and two genes associated with adherence were highly prevalent in these STs. In Spain, enhanced infection rates of human lung cells, especially in the presence of cigarette smoke exposure and by influenza H3N2 coinfection were observed. It is unknown whether i) higher levels of antibodies are therefore needed to prevent transmission with the current dominant serotype 4 clone, ii) (also) a different clone of serotype 14 is present, iii) compromised immunogenicity of more-valent vaccines ((19); see Chapter 7) plays a role and/or iv) other reasons may explain the increase, such as reduced natural boosting of immunity among the (unvaccinated) population as a result from decreased exposure to these

vaccine serotypes due to childhood vaccination (i.e., an end of the honeymoon effect).

2.4 Death due to invasive pneumococcal disease in older adults

Information on the outcome of IPD is gathered through the OSIRIS notification system. However, this information is likely not completely correct as the outcome is not always known at the moment of notification and may not be corrected later. Still, as an indication of the serotypes that caused fatal disease in the 60+ year olds in the Netherlands in the period 2024-2025, we analysed death caused by IPD as reported in the notification data.

Of the 2926 notified cases in 2024-2025, an outcome was reported for 2690 (92%). Of these 2690 cases, death was reported for 231 (8.6%). Of the serotypes with more than 5 fatal cases in the 60+ year old population in the two-year period, serotype 3 had the highest case fatality rate (12%), followed by serotype 15A and 23A (each 11%), 12F and 22F (each 10%), and 9N, 23B and 33F (each 9%). As serotypes differ in their incidence, the most commonly reported serotypes causing fatal IPD were serotype 3 (n=39), 19A (n=35), 8 (n=22), 9N (n=16), 22F (n=14), 12F (n=13), 15A (n=9), 23B (n=8) and 6C, 23A and 33F (each n=7). For other serotypes, 5 or less fatal cases were reported.

2.5 Non-invasive pneumococcal disease in older adults

In 2025, the IDS RIVM team, in close collaboration with Spaarne Gasthuis and Streeklab Haarlem, conducted a pilot study to assess the feasibility of surveillance of community acquired pneumonia (CAP) for monitoring the effects of NPPV in the Dutch population. Lower respiratory tract samples (415 sputum samples, 81 bronchial or bronchoalveolar lavage samples, and 30 tracheal aspirates) were collected at a single site (Spaarne Hospital, Haarlem) between January and April from 526 patients hospitalised with respiratory symptoms from whom no pneumococci were cultured from blood. The patients were aged 5–93 years, with a median age of 72 years. Respiratory samples were tested using molecular methods for *Streptococcus pneumoniae* and pneumococcal serotypes.

Samples from 62 individuals (12%) tested positive for pneumococcus. Molecular serotyping revealed infections with multiple serotypes per patient. Overall, a total of 75 serotype detection events were present; in 18 individuals (29% of the pneumococcus-positive individuals) multiple serotypes were detected. In 44 (71%) and 51 (82%) of the cases, a PCV20 or PCV21 serotype was diagnosed, respectively. Compared to the serotype distribution observed among 1,769 adult IPD cases reported in the Netherlands between January and October 2025, serogroup 15 and serogroup 11 serotypes were significantly more frequent in the non-invasive cases in the pilot study, and serotype 8, was significantly more frequent among the IPD cases. These findings suggest that the contribution of certain serotypes to overall (non-invasive + invasive) adult pneumococcal disease may be higher (e.g., serogroup 11 and serogroup 15) or lower (e.g., serotype 8) than anticipated based solely on IPD data, while this is similar for serotype 3 and 19A. Differences in serotype distributions between non-invasive and invasive CAP have

previously been reported (20, 21), underscoring the importance of surveillance of non-invasive pneumococcal disease to inform policy decisions.

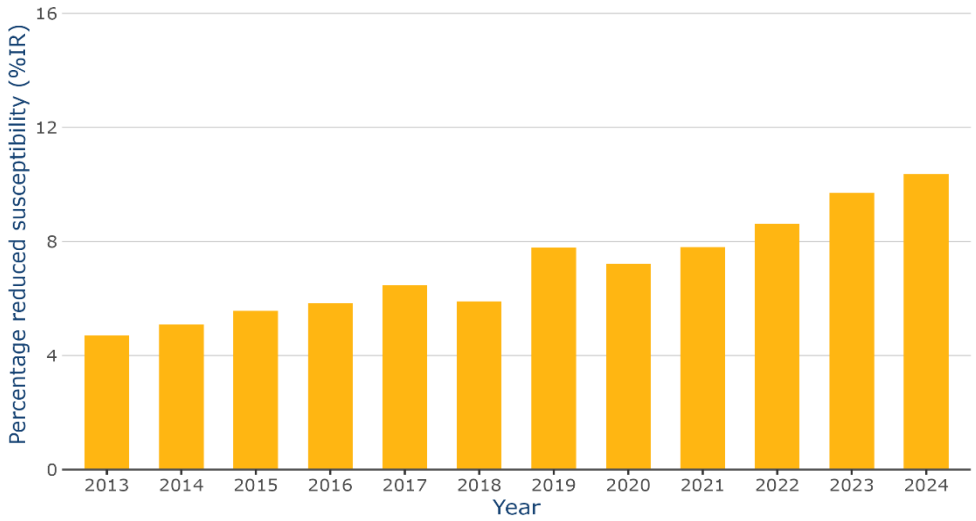
2.6 Antibiotic non-susceptibility over time in older adults

Besides the serotype-specific incidence and case fatality of pneumococcal disease, antimicrobial resistance is also one of the factors to consider when optimizing vaccine policy (22). In the Netherlands, antimicrobial resistance (AMR) among *S. pneumoniae* is monitored by the Dutch surveillance system of antimicrobial resistance (ISIS-AR). Data from ISIS-AR was leveraged to study trends in resistance of pneumococci to antibiotics included in the Dutch treatment guidelines for pneumococcal infections (i.e., (benzyl)penicillin and third-generation cephalosporins). Regarding (benzyl)penicillin resistance and decreased susceptibility, the trend over time was also investigated at a serotype-specific level for serotypes covered by PCV20 and by PCV21, using data of the NRLBM.

For the analysis based on ISIS-AR data, we included routine medical data from 32 clinical microbiology laboratories that provided complete data between 2013 and 2024. We included infection-related pneumococcal isolates of patients aged 60 years or older that were obtained from the lower respiratory tract (and thus were considered to be the causative pathogens of pneumonia). We selected only the first isolate per patient per year (n=23,257). Susceptibility to (benzyl)penicillin and third-generation cephalosporins (i.e. cefotaxime/ceftriaxone) was determined according to the EUCAST 2025 guidelines. The percentage of resistant (%R) and susceptible with increased exposure (%I; i.e., susceptible with higher antibiotic dosages) isolates were calculated per year for each antibiotic. Time-trends of the sum of both percentages (%IR) were analysed with logistic regression.

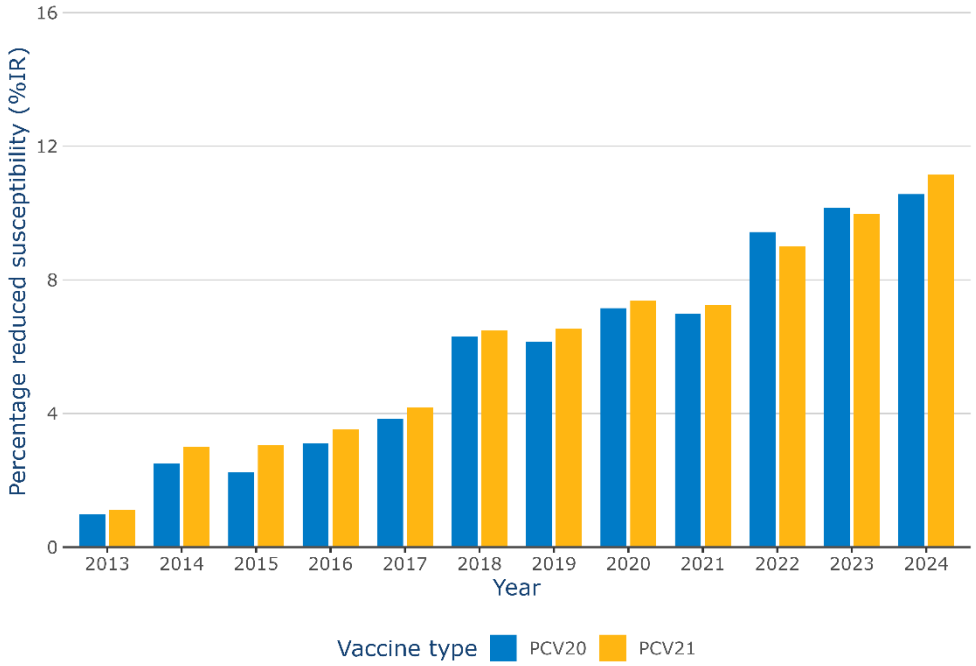
In total 23,239 isolates were included. Resistance levels (%R) in 2024 were low for both (benzyl)penicillin (1.3%) and third-generation cephalosporins (0.1%). Susceptibility to third-generation cephalosporins did not change significantly over time. For (benzyl)penicillin, we found a significant increase in %IR isolates over time (4.8% in 2013 to 11.0% in 2024; odds ratio 1.08 [95%CI 1.06-1.09], $p<0.001$; Figure 5). These results indicate a reduction in (benzyl)penicillin-susceptibility over time.

Figure 5 Percentage of infection-related pneumococci showing resistance or are susceptible with increased exposure (combined; %IR) to (benzyl)penicillin per year, isolated from the lower respiratory tract of patients aged 60 years or older (ISIS-AR) in the time period 2013-2024



Because ISIS-AR does not contain information on serotypes, the NRLBM data of IPD isolates from patients aged 60+ years were used to explore trends in (benzyl)penicillin susceptibility among pneumococcal serotypes covered by PCV20 and PCV21 in the same way as presented above. For PCV20 and PCV21 serotypes, 8001 and 9634 isolates were included, respectively. Overall, the increase in %IR over time was in line with the observation in ISIS-AR data. This trend was similar between PCV20 and PCV21 serotypes (Figure 6). The main serotypes among the IR isolates were serotypes 19A and 23B, where an increase in %IR over time was also observed. The incidence of 19A may decrease in the coming years because of the recent switch to PCV15 in the NIP. With the current serotype and antibiotic non-susceptibility distribution, PCV20 and PCV21 are likely to have similar impact on infections caused by (benzyl)penicillin-IR pneumococci.

Figure 6 Percentage of IPD cases confirmed at NRLBM caused by pneumococci with resistant or susceptible with increased exposure (%IR) to (benzyl)penicillin, per vaccine type (PCV20 and PCV21) per year, 2013-2024



2.7 Summary of the frequency and of severity indicators for the PVC20/PCV21 serotypes

In line with the 'approach to define the optimal immunization strategy' described by De Wals (see (22)), Table 4 summarizes the number of IPD cases, case fatality rate, the proportion of all IPD deaths attributed to a serotype, and (expected) time trend in the 60+ population for serotypes included in PCV20 or PCV21 or both. Data are based on the period 2024-2025, except for the time trend, which includes the period from 2022 onwards. De Wals also included carriage and antibiotic susceptibility data in the approach (22). However, since we do not have recent carriage data (14), we describe the time trend in IPD instead. Furthermore, given the limited penicillin resistance among clinical pneumococcal isolates, we did not include this parameter in our summary.

Table 4 Summary of number of IPD cases, case-fatality, proportion of deaths attributed to a serotype, and time trend per serotype during the period 2024-2025 (for time trend, 2022 onwards) in 60+ year old population

Vaccine type	Serotype	Number of cases	Case fatality rate (%)	% of deaths attributed to the serotype	Time trend*	Comment to trend
PCV20 but not in PCV21						
	14	85	2.5	0.9	↑	Unexpected
	4	84	5.3	1.7	↑	Unexpected
	19F	14	0	0	→	
	6B	8	0	0	→	
	23F	5	0	0	↓/→	↓ expected (covered by PCV15)
	1	2	0	0	→	
	9V	2	0	0	→	
	18C	1	0	0	→	
	5	0	NA	NA	→	
PCV21 but not in PCV20						
	9N	214	8.5	6.9	↑	
	23B	107	8.9	3.5	↑	
	15A	88	11.4	3.9	↑	
	23A	79	10.6	3.0	→	
	16F	46	10.8	1.7	→	
	20	40	3.0	0.4	↑/→	
	24F	35	6.2	0.9	→	
	31	29	12.5	1.3	↑	
	17F	28	23.8	2.2	↓/→	
	35B	22	21.1	1.7	↑/→	
	15C	18	13.3	0.9	→	
PCV20 and PCV21						
	19A	519	7.9	15.2	↓/→	↓ expected (covered by PCV15)
	8	417	6.2	9.5	→	
	22F	163	9.5	6.1	↓	↓ expected (covered by PCV15)
	12F	155	10.3	5.6	↑	
	6C	144	5.7	3.0	↓/→	↓ expected (covered by PCV15)
	33F	98	8.8	3.0	→	↓ expected (covered by PCV15)
	10A	80	7.8	2.2	→	
	11A	62	9.1	2.2	↑/→	
	15B	25	13.0	1.3	→	
	6A	12	0	0	→	
	7F	4	0	0	→	

Data resembles data shown in Table 3; note that we treat serotype 3 as non-vaccine serotype, as described above.
Categorisation for colouring (Dark orange/orange/light orange, and white for values at or below the mean, respectively): Frequency: ≥240 cases in the two-year period / ≥120 cases / ≥60 cases / <60 cases (mean); Case-fatality rate: ≥15 / ≥11 / ≥7 / <7% (mean); Proportion of deaths due to IPD attributed to the serotype: ≥9 / ≥6 / ≥3 / <3% (mean).
Time trend: → stable frequency, ↑ increasing in frequency, ↓ decreasing in frequency, when arrows are combined, the trend is not very clear. *Based on qualitative assessment of 2022-2025. Because of the disruption of numbers during the COVID pandemic, trends are not analytically determined. As it is expected that PCV15 will provide indirect protection, a decreasing time trend is expected for PCV15-covered serotypes that are not covered by PCV10; this is described in the comment column

As shown in Figure 1, all serotypes that are present in PCV20 but not in PCV21 (serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F and 23F) were covered by PCV10 already and are also covered by PCV15, which is currently used in the NIP. Little additional changes in incidence as a result of indirect protection are therefore to be expected. However, serotype 4 and serotype 14 seem to increase in incidence in recent years, despite the fact that these serotypes have been included in the NIP-vaccines from the start of pneumococcal vaccination.

Serotypes 9N, 17F, 20, 15A, 15C, 16F, 23A, 23B, 24F, 31 and 35B are covered by PCV21 but not by PCV20, nor by PCV15. Of these, serotype 9N, 23B and 15A were among the 10 serotypes that caused most IPD in the 60+ population in 2024-2025 and that show a slightly increasing trend. Serotype 23A also caused a substantial burden. These four PCV21-unique serotypes had a case-fatality rate of 9% or higher. Note that isolates belonging to serotype 23B showed a higher percentage of (benzyl)penicillin IR.

The PCV20-PCV21 shared serotypes 6A, 6C, 7F, 8, 10A, 11A, 12F, 15B, 19A, 22F and 33F include the currently most-common serotype 19A and several of the serotypes causing most fatal infections (19A, 8, 22F, 12F). Note that we do not include serotype 3 as shared vaccine-serotype, as PCV20 and PCV21 will likely fail to protect against this serotype. Because of the recent switch to PCV15 in the NIP, it is expected that the incidence of IPD caused by serotype 6C, 19A, 22F and 33F will decrease in the coming years.

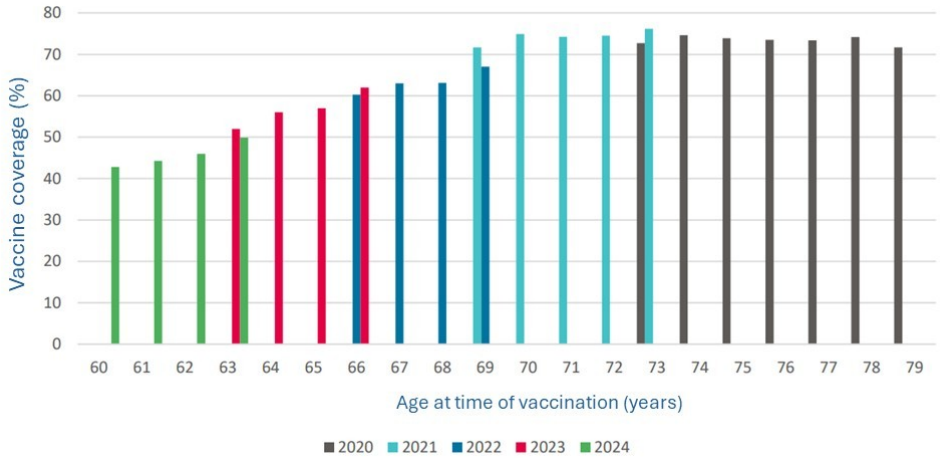
In summary, PCV21 serotypes 9N, 23B, 15A and 23A and shared serotypes 8 and 12F are frequent causes of IPD and show either a high case fatality or a large proportion of attributed deaths. Except serotype 8 and 23A, these serotypes also show an increasing trend in frequency. While serotype 4 and 14 do not appear as virulent, their increase in frequency is unexpected as they are covered by the NIP vaccine.

3 Impact of recent changes in the pneumococcal vaccination programmes

3.1 Vaccination coverage NPPV

As shown in Table 1, different birth cohorts were eligible in different years for the NPPV. The uptake of vaccination differed by age group (Figure 7). Overall, in the first year of the programme, i.e. autumn 2020, the vaccination uptake was estimated at 73% (among 73-76 year olds), the second year, it was 74% (69-73 year olds), in 2022, it was 63% (66-69 year olds), in 2023 56% (63-66 year olds) and in 2024, the uptake was estimated at 45% (60-63 year olds) (23).

Figure 7 PPV23 vaccine uptake (coverage) in the National Programme Pneumococcal Vaccination in older adults. Source: Nivel report (23)



3.2 Impact of NPPV on pneumococcal disease

3.2.1 Impact of PPV23

As described in the NIP annual surveillance report (24), the impact of PPV23 implementation on PPV23-type IPD among adults aged 60–79 years in the first 5 years of the programme ranged from 14% to 43% depending on the age-cohort and year of vaccination. The impact was measured for the entire eligible birth cohorts and is thus affected by the respective vaccination uptakes.

The impact of PPV23 on non-invasive pneumococcal pneumonia (NIPP) was determined for the first 3 years of the NPPV (25). During these first 3 years, the protective effect on NIPP among the eligible birth cohorts was estimated at 20%.

3.2.2 Preliminary impact of PCV20

The PCV20 vaccine has only replaced PPV23 in the NPPV in October 2025. Impact estimates of the switch are thus very preliminary. Still, we determined the proportion of PCV20-type IPD for those who were offered PCV20 but not PPV23 due to age (those aged 85 years old in 2025), for the winter period (November 2025 - March 2026) and

compared that with the same period and same age group in the seasons 2023-2024 and 2024-2025. After PCV20 implementation, 48% of the IPD cases aged 85+ years were caused by a PCV20 serotype, while this was 59% in the two-years before implementation; see Table 5. Of the 38 PCV20-cases in 2025-2026, vaccine history was known for 36. Eight had received PCV20 (22%), two had received PPV23 (6%) and for 26 (72%) it was reported that they had not been vaccinated against pneumococcus. For those with a non-PCV20 serotype in 2025-2026, 51% had been vaccinated with PCV20 (18/35; one was vaccinated but the specific of vaccine was unknown).

To determine whether the preliminary change in PCV20-type IPD was not due to indirect protection of PCV15 in the NIP, we also determined the proportion of PCV20 disease in those aged 74-78 years in the same period. As an indirect effect of PCV15 would be present in all age groups, such effect should also be observed in this age group of almost similar age as the PCV20-targeted age group. The 74-78 years cohort was offered PPV23 in autumn 2021 but did not receive PCV20 yet. In the 74-78 year olds, 58% of the IPD cases in 2025-2026 were caused by a PCV20 serotype while this was 60% in the 2023 and 2024 winters. If PCV15 had already induced any indirect protection, the effect of it seems still small.

Table 5 Proportion of IPD cases in the winter period (November-March) with PCV20 serotype disease pre- and post-PCV20 implementation for those eligible and not eligible for PCV20

Time period (winter; November-March)	**PCV20 eligible (aged 85+ in 2025)**	**PCV20 non-eligible (74-78 years in 2025)**
Pre-PCV20 (2023/25)	211/356 (**59**%)	148/247 (60%)
Post-PCV20 (2025/26)	38/79 (**48**%)	55/95 (58%)

3.3 Preliminary impact of PCV15 NIP implementation on adults

The epidemiology in older adults depends on the epidemiology of children and thus the vaccine used in the NIP (26). In September 2024, PCV10 was replaced by PCV15 in the NIP. During the first few months, only the booster vaccination at 11 months (12 months from 2025 onwards) was replaced. After PCV10 stores at the municipal health services were consumed (approximately January 2025), PCV15 was also used for the primary series. In practice, this means that birth cohort 2024 was offered PCV15 as booster and birth cohort 2025 was offered PCV15 for the entire series.

We estimated potential initial indirect protection in adults of PCV15 to the additional serotypes included in PCV15 but not in PCV10 (PCV15-10 serotypes). As older individuals were offered PCV20 (see also paragraph 3.2.2), we focused on adults aged 20-59 years. The proportion of PCV15-10 serotypes dropped by 7-percentage points in this age-group from 26% in 2024 (n=124/487 (total)) to 19% in 2025 (n=112/576). It should be noted, however, that a similar, unexplained, decrease of 5 percentage points was observed between 2023 and 2024 (31% (n=153/499) and 26% (n=124/487), respectively. There has been a decreasing trend in this age group since 2021, when PCV15-10 serotype proportions were highest at 36% (n=27/76, sentinel data).

These findings indicate that it is uncertain whether the reduction of PCV15-10 serotypes in 2025 can be attributed to the implementation of PCV15 in the NIP. From earlier PCV introductions in the Netherlands and in other countries, it was shown that indirect protection generally was observed from approximately one year after introduction (27). This (seemingly) absence of indirect protection within the first year of the switch is therefore not unexpected; additional years of surveillance data are needed to assess indirect effects of PCV15.

4 Pneumococcal disease in medical risk groups

4.1 Increased risk to pneumococcal disease for certain medical risk conditions regardless of age

Next to pneumococcal vaccination of infants and older adults, routine vaccination of high-risk groups regardless of age has become a standard preventive strategy in many countries and is supported by retrospective studies. For influenza, such a combined vaccination strategy is already in place in the Netherlands, but not for pneumococcal disease (28). Studies show that the risk of severe pneumococcal disease in individuals with a medical risk condition is increased (12), and that the risk is higher in individuals younger than 65 years with high-risk medical conditions than in older adults (≥65 years) without these risk conditions (29). The risks were consistently higher in individuals with multimorbidity compared to those with a single risk condition (12). In addition to medical risk conditions, certain occupational hazards like welding can increase the risk for severe pneumococcal disease (30, 31); this is not further discussed in this report.

A recent meta-analysis of observational studies in 46 adult populations showed that age 65 years and older, after correction for the presence of other risk conditions, posed a 2.5-3.5 higher risk of IPD compared to adults 18-45 years of age (12). The risk of age alone was lower than that of certain medical conditions with incidence rate ratios (IRR) as high as 18-47: immunocompromising conditions (haematological malignancy, persons living with HIV, transplant recipients and asplenia), chronic kidney disease, compromised blood-brain barrier and Down syndrome. For other chronic conditions (lung, heart and liver disease, diabetes) IRRs for IPD were in the same range as those for smoking, alcoholism and acquired immunodeficiency (IRR 4-6). The latter category included immunocompromising therapies and summarized 11 studies mostly in patients with auto-immune diseases (rheumatoid arthritis (RA), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE)), but also with chemotherapy for cancer and in smaller mixed groups of acquired immunodeficiency. The increased risk differs among immunocompromised patients: a 6-fold increase in patients with chronic inflammatory diseases (such as RA, SLE, IBD), >40 times increase in solid organ transplant recipients and >60 times increase in stem cell transplant recipients (32).

In the Dutch national pneumococcal surveillance system, it was already shown that IPD patients with a high or medium risk condition have a significantly higher case-fatality, similar to Canadian data (33, 34). Whereas risk of IPD has been studied extensively, there is less data on all-cause pneumonia and pneumococcal pneumonia in medical risk groups. In the most recent US retrospective analysis of pneumococcal disease in a large claims-database it was demonstrated that the incidence of CAP in adults aged 18-49 years with at least one immunocompromising condition was higher than that in healthy adults $\geq$ 65 years (this was also shown for the endpoint IPD, similar to what is reported above) (35). In that retrospective analysis the incidence of pneumococcal pneumonia in adults 18-49 years with any immunocompromising condition was similar to that of

healthy adults ≥65 years. In adults 50-64 years with any immunocompromising condition the incidence was more than 2-fold increase compared to healthy adults ≥65 years. Similar trends were also demonstrated for patients with chronic heart and lung disease.

Next to the acute complications of pneumococcal disease, also longer-term complications are common: in patients with underlying comorbidities, healthcare utilisation, costs and mortality are increased for at least 3 years after being hospitalised for CAP (36). Specifically in patients with chronic heart disease, short-term cardiac complications of pneumococcal infection have been demonstrated, showing an increased risk of adverse cardiovascular outcomes such as myocardial infarction. A meta-analysis showed that these cardiovascular events can be reduced by pneumococcal vaccination (37).

4.2 Pneumococcal serotypes in medical risk groups

Several studies have documented that there is a higher susceptibility to a wider variety of serotypes in the medical risk groups compared to the general population, including a higher susceptibility to replacing serotypes (34, 38). In Norway as well as in Sweden, it was shown that, after PCV13 introduction in the NIP, non-PCV13 IPD was substantially higher in those with high-risk medical conditions (immunocompromising conditions, heart, lung, liver, kidney disease) compared to lower risk groups, both for adults below and above 65 years of age (29, 39). Similarly, a higher proportion of non-PCV7 IPD after PCV7 introduction was demonstrated in Canada among the immunocompromised: 36% vs 23% in immunocompetent individuals (34). Serotypes associated with the highest risk were 16F, 15C, 35F, 19F, and 23A (odds ratios of 3–5 for chronic medical conditions and >10 for immunocompromised). From these serotypes, 16F, 15C and 23A are unique serotypes included in PCV21, whereas only 19F is exclusive to PCV20 (see Figure 1). It was also shown that mortality due to non-PCV13 serotypes was increased in medical high-risk individuals, but that it remained stable in persons without comorbidities.

For the Netherlands, no data are currently available on the serotype distribution in (medical) risk groups. As proxy, we use the vaccine-type percentages of IPD in the total population aged 20-59 years in the years 2024-2025. Among the 1063 cases with serotype information in these two years, 69% was caused by a PCV20 serotype, 70% by a PCV21 serotype, 16% by a PCV21 type that is not covered by PCV20 and 15% by a PCV20 type that is not covered by PCV21.

Concluding, currently, PCV20 and PCV21 cover a similar percentage of IPD cases in the age group 20-59 years (independent of medical risk condition). These percentages may however change depending on the amount and kind of serotype replacement that may occur as a result of PCV15 introduction in the NIP. After NIP vaccine introductions, in general, larger increases in IPD due to non-vaccine serotypes have been observed in adults with chronic conditions and/or immunocompromised conditions. These non-NIP-vaccine serotypes in medical risk groups cause more complications including death. Complementary PCVs to the vaccine used in the NIP may thus be beneficial for medical risk groups.

5 PCV21 for use in adults

5.1 Product description of PCV21

PCV21 (Capvaxive) is a pneumococcal conjugate vaccine licensed by the European Medicines Agency (EMA) in April 2025 to protect adults against pneumonia and invasive diseases caused by the bacterium *Streptococcus pneumoniae*. The vaccine includes antigens of 21 pneumococcal polysaccharide capsules (Figure 1; serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B/C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B). All individual polysaccharides are conjugated to CRM197, the nontoxic form of diphtheria toxin, expressed recombinantly in *Pseudomonas fluorescens*. Unlike the earlier licensed PCVs (PCV7-PCV20), PCV21 does not contain an adjuvant, i.e., it is not adsorbed on aluminium phosphate. PCV21 is licensed for use in individuals aged 18 years of age and older and can be used in a one-dose schedule. Since April 2021, PCV21 is also licensed for children and adolescents aged 2 to <18 years who completed primary paediatric pneumococcal vaccination (2).

5.2 Safety / reactogenicity of PCV21

As known for the other PCVs, PCV21 has been shown to have an acceptable safety profile across all studies within clinical trial development programme. The most common adverse reactions after administration of PCV21 are injection-site pain (53%), fatigue (25%), headache (18%), and myalgia (10%); most were mild or moderate and of short duration (≤3 days) (2). In older adults (≥75 years), a lower frequency of local injection-site reactions was observed compared to participants aged 65-74 years. Also for individuals with medical risk conditions and in special populations, the safety profile of PCV21 was generally comparable to what was seen in the PCV15 + PPV23 group. A more comprehensive description can be found in the product information at EMA website (2).

5.3 Immunogenicity of PCV21

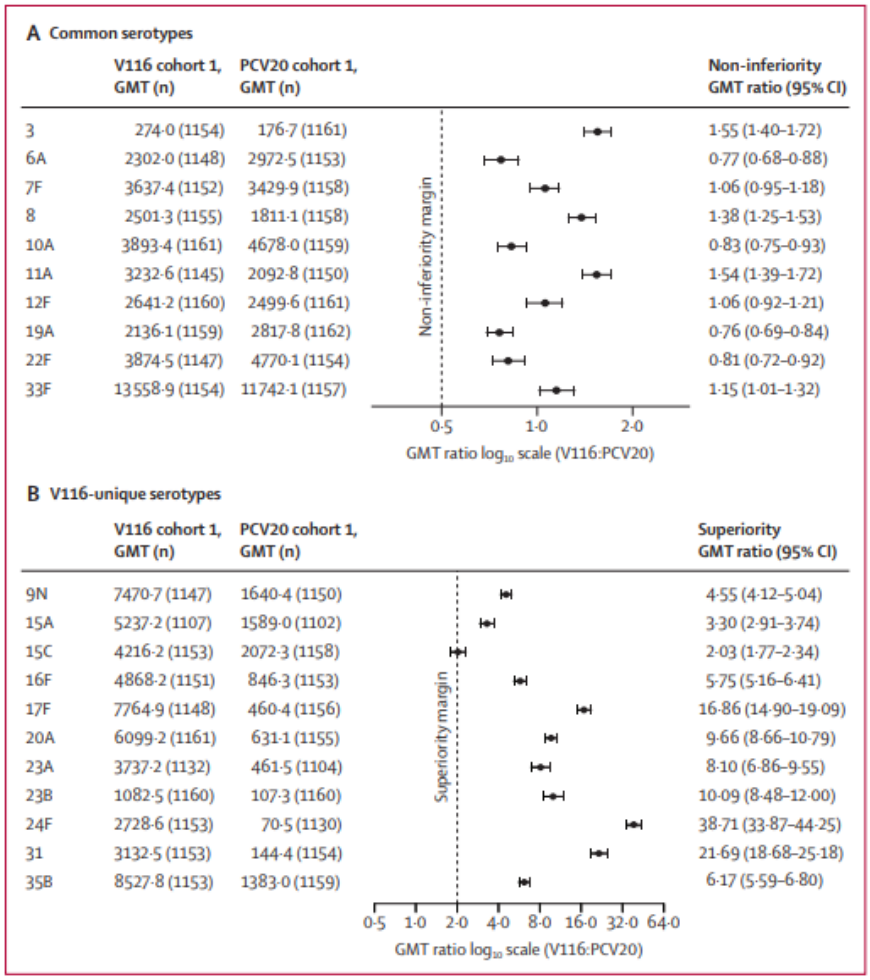
Currently, no clinical effectiveness data are available yet.
As for other PCVs, PCV21 has been licensed for use in adults based on the induction of functional antibodies through a T-cell dependent immune response. These antibodies enhance opsonisation, phagocytosis and killing of pneumococci. Opsonophagocytic activity (OPA) is considered an important immunologic surrogate measure of protection against severe pneumococcal disease. For adults, unlike for children, no correlates of protection (per serotype) have been defined, making it difficult to determine whether the PCV21 induced level of immunity is sufficient to provide clinical protection. However, to get an indication of its added value, PCV21-induced serotype-specific IgG antibody concentrations and OPA have been compared with the responses induced by the already licensed PCV20 and PPV23 vaccines, as well as with sequential PCV15 and PPV23 vaccination.

The STRIDE studies (Safety, Tolerability, and Robust Immunogenicity of a 21-valent Vaccine for Adults), performed by the pharmaceutical

company that developed and produces PCV21 (MSD), evaluated PCV21 in different target populations including the following populations relevant for this report: STRIDE-3 focusses on pneumococcal vaccination in pneumococcal vaccination naïve adults aged 50+ or 18-49 years comparing PCV21 with PCV20 (40), STRIDE-6 in adults aged ≥50 years with previous pneumococcal vaccination (PPV23 and/or PCV13 and/or PCV15) (41), STRIDE-8 in vaccine-naïve adults aged 18-64 years with medical risk conditions (42) and STRIDE-10 in naïve adults ≥50 years comparing PCV21 with PPV23 (43). In general, non-inferiority for shared serotypes was assessed by comparing serotype-specific OPA geometric mean titres (GMTs) at day 30. The lower bound of the two-sided 95%CI of the OPA GMT ratio (i.e., PCV21:PCV20 or PCV21:PPV23) had to be more than 0.5 to show non-inferiority. Superiority for serotypes unique to PCV21 was shown if the lower bound of the two-sided 95%CI of the OPA GMT ratio at day 30 was higher than 2.

STRIDE-3 was performed in adults aged 50 years and older (stratified by age 50-64, 65-74, 75-84, and ≥85 years; cohort 1), as well as those aged 18-49 years (cohort 2). PCV21, (n=1,179 and n=200) was compared to PCV20 (n=1177 and n=100) for cohort 1 and 2 respectively (40). PCV21 met non-inferiority criteria for serotypes common to both vaccines using serotype-specific OPA GMT ratios measured in cohort 1 at 30 days post vaccination (Figure 8). As expected, in the same cohort both the OPA GMT ratios as well as the proportions of participants with a four-fold or greater rise in OPA responses from day 1 to day 30 were superior for PCV21 to PCV20 for 10 of the 11 serotypes that are unique for PCV21, except for serotype 15C. The 15C immune response after PCV21 was, however, numerically higher when compared with the response after PCV20 (1.7 times). For 4 shared serotypes (6A, 10A, 19A and 22F), however, OPA GMTs were lower for PCV21 compared with PCV20. Immunogenicity may still be sufficient for protection against IPD but could become insufficient for protection against (non-invasive) disease and/or carriage. Immune responses in adults 18-49 years of age were non-inferior to the responses measured in adults of 50 years and older. There was a trend towards lower serotype-specific OPA GMTs in older adults, aged 65–74 years and ≥75 years, compared with adults 50–64 years of age for PCV21 as well as for PCV20.

Figure 8 Analysis of OPA GMTs on day 30 in cohort 1 (adults ≥50 years) (A) Non-inferiority analysis for the ten serotypes in both PCV21 and PCV20 (B) Superiority analysis for the 11 serotypes unique to PCV21



PCV21=V116, OPA=opsonophagocytic activity. GMT=geometric mean titre. Figure from STRIDE-3 (40).

PCV21 immune responses have also been directly compared to PPV23 induced responses in adults of 50 years and older (n=1484, 46% 50-64 yrs, 10% 75 yrs and older) (STRIDE-10 study (43)). PCV21 induced OPA GMTs were non-inferior compared with PPV23 (based on PCV21/PPV23 GMT ratios) for the 12 shared serotypes and superior for the 9 unique serotypes at day 30 post vaccination.

5.3.1 *PCV21 immune response after previous pneumococcal vaccination*

Study STRIDE-6 was performed in adults aged ≥50 years who previously received pneumococcal vaccination (41). Overall, 717 adults were included of which cohort 1 is relevant for the situation in the Netherlands since it includes n=350 individuals who previously received PPV23 ≥1 year before enrolment and received either PCV21 (n=229) or PCV15 (n=119) during the study. The PCV21 group included 181 participants of 65 years and older of which only a limited percentage was 80 years or older (8% of all phase 3 study participants were 75 years or older, 14% had received other prior pneumococcal vaccine).

Data showed that vaccination with PCV21 induced serotype-specific (functional) antibodies measured as IgG GMCs as well as IgG and OPA GMFRs (functional) antibodies were independent of the pneumococcal vaccine received previously, being PPV23, PCV13, PCV15 or PCV20 (data on PCV15 and PCV20 come from cohort 3 of the STRIDE-6 study). Serotype-specific OPA GMTs and IgG GMCs 30 days post-vaccination were in general comparable for the PCV15 and PCV21 group for shared serotypes and higher for serotypes unique for PCV21. OPA GMTs in older adults ≥65 years of age were in general lower than in adults 50–64 years of age for the majority of PCV21 serotypes for PPV23 as well as PCV13 primed cohorts.

5.3.2 PCV21 in medical risk groups

STRIDE-8 evaluated safety and immunogenicity of PCV21 in pneumococcal vaccine-naive adults 18–64 years of age with at least one condition associated with increased risk of pneumococcal disease (diabetes mellitus or kidney, heart, liver, or lung disease) (42). The majority of participants (84%) had one condition associated with increased pneumococcal disease risk (see also chapter 4). The most common single increased-risk conditions were diabetes mellitus (38%), chronic lung disease (19%), and chronic heart disease (16%). PCV21 was immunogenic for all serotypes in medical risk groups. Serotype specific OPA GMTs and IgG GMCs at day 30 post (last) vaccination were in general comparable for PCV21 (n=372) and for the group that received PCV15 and 8 weeks later PPV23 (n=129) for the 13 common serotypes, and higher for the eight serotypes unique to PCV21. In addition, subgroup analyses determining serotype-specific OPA GMTs for one and ≥2 concurrent medical risk conditions were generally consistent with the results observed in the overall population.

Immunogenicity data on PCV21 are not (yet) available for individuals in immunocompromised groups including those receiving immunosuppressive therapy. However, based on the experience of other PCVs, immunocompromised individuals may have a reduced immune response (2).

6 Cost-effectiveness of PCV21 in older adults and the potential role of indirect effects of childhood vaccination

6.1 Methods

We aimed to estimate the cost-effectiveness of PCV21 in older adults. Specifically, we evaluated the costs and quality adjusted life years (QALY) losses associated with vaccinating cohorts aged ≥60 years with PCV21 versus PCV20. To assess the cost-effectiveness of the overall NPPV, we also compared vaccination with either PCV20 or PCV21 against a hypothetical scenario in which older adults were not vaccinated.

We updated a previous cost-effectiveness analysis of different pneumococcal vaccination strategies for older adults in the Netherlands (44). This analysis used a static multi-cohort Markov model to estimate the impact of pneumococcal vaccination on the clinical burden, costs from a societal perspective, and QALY losses of pneumococcal diseases among older adults aged ≥60 years. Vaccination reduced disease rates caused by vaccine serotypes based on age-specific uptake rates and age- and outcome-specific vaccine effectiveness (VE). The model accounted for (projected) indirect protection and serotype replacement in disease among older adults resulting from the change from PCV10 to PCV15 in the Dutch NIP for infants. Given the static nature of the model, these indirect effects were incorporated using correction factors applied to the serotype-specific disease incidences.

In this analysis, all cohorts aged ≥60 years were assumed to be vaccinated once at the start of the analysis instead off a phased roll out as was actually done in the Netherlands (Table 1), and were subsequently followed over a 15-year time horizon. The analysis included only the impact on severe disease outcomes, i.e. IPD and hospitalized NIPP. Outpatient pneumococcal disease was excluded because its burden and the impact of PCVs on it are uncertain, and a previous cost-effectiveness analysis showed that the impact of outpatient NIPP on the overall cost-effectiveness outcomes was minor (45).

The model was parameterized using the following key inputs:

- Age-specific IPD incidence by serotype was derived from Dutch national surveillance data collected between May 2022 and April 2024. At that time, PCV10 was used in the NIP and a PPV23 program was being rolled out among adults aged 60-79 years, following its introduction in the NPPV in 2020. The incidence rates in adults aged ≥60 years were first converted to a "no-vaccination" setting before the impact of the PCV20 or PCV21 program was modelled. This conversion included the inflation of the IPD incidence of PPV23 serotypes based on the actual Dutch PPV23 uptake rates by age (46), and VE estimates of PPV23 from the literature (47), accounting for waning immunity (48). Note that, while PCV15 has since been introduced into the Dutch NIP for infants in the autumn of 2024, an (initial) effect on

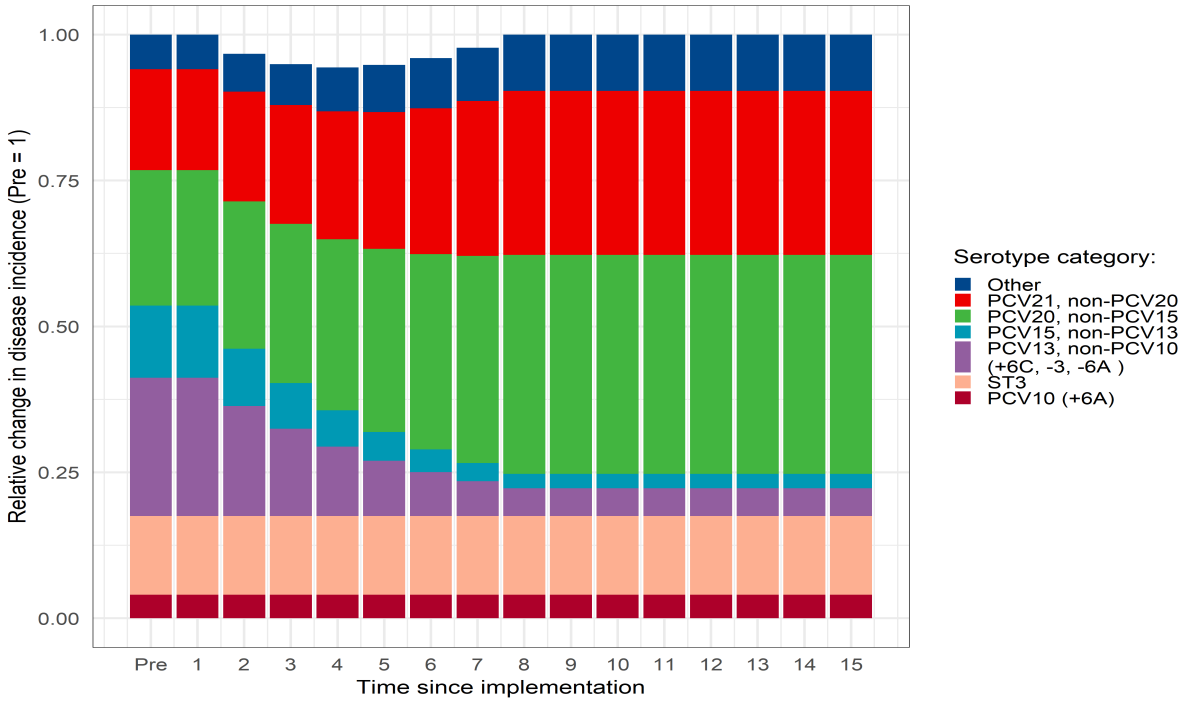
pneumococcal epidemiology of this program change (see also chapter 3.3) has not been taken into account.
- Hospitalized NIPP incidence was based on the incidence of clinical admission rates for pneumonia during the calendar years 2015-2019 (before the introduction of the PPV23 program for older adults), derived from Dutch Hospital Data. Of these cases, 22.1% were attributed to pneumococcus, as observed in the placebo group of the Dutch CAPITA trial for PCV13 in older adults (49). In the absence of serotype distribution data for NIPP, we applied the IPD serotype distribution to hospitalized NIPP cases as well.
- Case-fatality rates, disease-related costs from a societal perspective (2025 price year), and QALY losses were based on various Dutch sources (details are provided in (44)).
- Vaccination uptake was assumed to be 50% in cohorts aged 60-64 years, 65% in cohorts aged 65-69 years and 75% in cohorts aged ≥70 years, similar to the PPV23 uptake in the NPPV during the period 2020-2024 (46).
- VE against vaccine-type IPD and vaccine-type hospitalized NIPP was based on PCV13 data (49), and was extrapolated to all serotypes included in PCV20 and PCV21. VE was modelled to decrease with increasing age (50); at age 65, the VE was 54% against vaccine-type IPD and 27% against vaccine-type hospitalized NIPP (44). Note that, in this analysis, serotype 3 was treated as a vaccine serotype for adults, based on the CAPITA study (49), in contradiction to what is otherwise presented in this report. As the serotype 3-antigen is included in PCV15, PCV20 and PCV21, in- or exclusion as vaccine-serotype will not affect the comparison. Cross-protection against 6C (via 6A) was included, as well as PCV21 protection against serotype 15B (see Figure 1).
- In the absence of data on the duration of protection, the VE of PCVs was assumed to remain constant for the first 4 years after vaccination (as was observed during the trial period), and then to decline linearly to 0% by 15 years after vaccination (51).
- Vaccine prices were based on Dutch list prices for private purchase: €82.95 for PCV20 and €99.54 for PCV21 (i.e., a price premium of €16.59) (52, 53). Administration costs were set at €21 per dose.

We accounted for indirect effects associated with the change in the NIP from PCV10 to PCV15. In this analysis, the introduction of PCV15 was assumed to occur at the start of the analysis. Under the hypothetical scenario of continued PCV10 use, pneumococcal disease incidence by serotype was assumed to remain constant, as the serotype distribution data were derived from a period more than 10 years after the introduction of PCV10 into the NIP. The magnitude and time course of the indirect effects of PCV15 implementation were informed by IPD trends observed internationally following the introduction of PCV13 into national immunization programs (27, 54):
- Indirect protection: Over the period of 1–8 years following PCV15 introduction, IPD incidence caused by "PCV15, non-PCV10" serotypes was assumed to decrease by 80%, following an exponential decay function. Cross-protection against serotype 6C was included. No indirect protection was assumed for serotype 3.

- Serotype replacement: Over the period of 1-8 years following PCV15 introduction, IPD incidence caused by non-PCV15 serotypes was assumed to increase until pre-PCV15 introduction incidence levels were reached again (i.e., full serotype replacement in disease), using a linear function. During this period, the relative contribution of non-vaccine serotypes was assumed to remain constant.

After year 8, a new steady state was assumed to be reached, with the resulting IPD incidence per serotype carried forward for the remaining time horizon. The temporary reduction in incidence can be explained by the faster exponential decrease in PCV15 serotypes compared to the linear increase of non-PCV15 serotypes. A visualization of changes in projected IPD incidence due to indirect effects of the NIP (in the absence of PPV23, PCV20, or PCV21 vaccination of older adults) is provided in Figure 9. The same indirect effects were also applied to the incidence of hospitalized NIPP.

Figure 9 Modelled relative changes in pneumococcal disease (IPD and NIPP) incidence as compared to the mature PCV10 period by serotype category in the population aged ≥60 years following the introduction of PCV15 into the NIP for infants over a 15-year time horizon.



The used model input is explained in the text. Note that this figure does not consider an NPPV with PPV23, PCV20 or PCV21; the data therefore show the changing incidence used to model the impact of introduction either PCV20 or PCV21 into the NPPV. Y-axis: pre-PCV20 incidence=1

For the cost-effectiveness analysis, clinical cases, costs and QALY losses were accumulated over the time horizon for the different strategies. Costs were discounted at 3% per year and QALY losses at 1.5% per year. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in total costs between two strategies by the

difference in QALY losses, and is expressed as euros (€) per QALY gained. We also provide net monetary benefits (NMBs), an alternative measure of cost-effectiveness that expresses health gains in monetary terms using a predefined willingness-to-pay (WTP) threshold. NMBs were calculated using the formula: QALYs gained * WTP threshold – Net costs. There is no official cost-effectiveness threshold for preventive interventions in the Netherlands. Historically, a threshold of €20,000/QALY gained has often been used by the Health Council, while more recently, a threshold of €50,000/QALY gained has been advised in the absence of a defined threshold, based on the threshold commonly used by the National Health Care Institute for curative interventions. In this analysis, we used the conservative threshold of €20,000/QALY gained to calculate the NMBs. A positive NMB indicates that the intervention is cost-effective at the €20,000 per QALY gained threshold, whereas a negative NMB indicates that the intervention is not cost-effective.

We conducted several sensitivity analyses. Given that the projected impact on hospitalized NIPP is more uncertain as we based the serotype distribution and indirect effects on IPD data, we also showed a conservative scenario in which only the impact on IPD was considered. A probabilistic sensitivity analysis (PSA) using 1000 simulations was performed, in which multiple parameters were varied simultaneously within their uncertainty distributions. Structural uncertainty was explored by varying parameters one by one (a 'one-way scenario analysis'), including the proportion of NIPP caused by pneumococcus, the vaccine price, discount rates and magnitudes of indirect protection and serotype replacement in disease. We also showed results from a health care payer perspective, which included only vaccination and health care treatment costs. Finally, we conducted a scenario analysis to compare the cost-effectiveness of PCV21 with no (additional) vaccination in the presence of immunity from a previous PCV20 dose, while varying the interval between PCV20 and PCV21 administration. This analysis was conducted among individuals aged ≥60 years, with the age distribution of vaccinees based on the age structure and uptake rates used in the analysis.

6.2 Results

6.2.1 Clinical impact

Without a pneumococcal vaccination in the NPPV for older adults, a total of 32,155 IPD cases, 109,385 NIPP hospitalizations and 24,005 deaths were expected among those aged ≥60 years over the 15-year time horizon (Table 6). Vaccination with PCV20 was estimated to prevent 4,784 IPD cases (14.9% reduction), 7,816 NIPP hospitalizations (7.1% reduction) and 1,966 deaths (8.2% reduction). Compared with PCV20, vaccination with PCV21 could prevent an additional 1,516 IPD cases (5.5% further reduction), 2707 NIPP hospitalizations (2.7% further reduction) and 707 deaths (3.2% further reduction).

6.2.2 Cost-effectiveness

Vaccination with PCV20 in the NPPV was estimated to cost €337.5 million, while saving €176.1 million on disease-related societal costs and gaining 16,720 QALYs over the 15-year time horizon compared with no

NPPV (Table 6). With net costs of €161.4 million, the cost-effectiveness was estimated at €9,653 per QALY gained, and the NMB was estimated at €173 million using a WTP-threshold of €20,000 per QALY gained. Compared with PCV20, PCV21 would increase the vaccination costs by €53.9 million, but would save an additional €54.4 million on disease-related societal costs and gain an additional 5,383 QALYs. With net savings of €0.5 million while resulting in QALY gains, PCV21 would dominate PCV20, with an estimated NMB of €108 million. Compared with no NPPV, the ICER of PCV21 was estimated at €7,277 per QALY gained, with an NMB of €281 million.

About 60% of the total QALY gain and 55% of the total disease-related cost savings were due to the prevention of hospitalized NIPP and its resulting deaths. In the conservative scenario that considered only the impact on IPD, the ICER of PCV21 compared with PCV20 was estimated at €13,561 per QALY gained, with an NMB of €14 million. Compared with no NPPV, the ICER of PCV21 was estimated at €30,999 per QALY gained, with an NMB of −€101 million.

Table 6 Clinical and economic outcomes of severe pneumococcal disease, and cost-effectiveness of a National Programme for Pneumococcal Vaccination (NPPV) with PCV20 or PCV21, compared with no NPPV, and of PCV21 compared with PCV20, in older adults aged ≥60 years

				Difference		
Outcome	**No NPPV**	**PCV20**	**PCV21**	**PCV20 vs. No NPPV**	**PCV21 vs. No NPPV**	**PCV21 vs. PCV20**
Clinical cases						
IPD	32,155	27,371	25,855	-4,784	-6,300	-1,516
Hospitalized NIPP	109,385	101,569	98,862	-7,816	-10,523	-2,707
Deaths IPD only	5,442	4,645	4,372	-798	-1,070	-273
Deaths IPD + NIPP	24,005	22,040	21,332	-1,966	-2,673	-707
Costs (€, millions)						
Vaccination	-	337.5	391.4	+337.5	+391.4	+53.9
Disease IPD only	517.1	434.2	409.3	-83.0	-107.8	-24.8
Disease IPD + NIPP	1,664.6	1,488.5	1,434.1	-176.1	-230.5	-54.4
Net costs IPD only	517.1	771.7	800.7	+254.5	+283.5	+29.0
Net costs IPD + NIPP	1,664.6	1,826.0	1,825.5	+161.4	+160.8	-0.5
QALY loss						
IPD only	43,850	36,843	34,703	-7,007	-9,147	-2,140
IPD + NIPP	164,029	147,309	141,926	-16,720	-22,103	-5,383
ICER (€/QALY gained)						
IPD only	NA	NA	NA	36,325	30,999	13,561
IPD + NIPP	NA	NA	NA	9,653	7,277	PCV21 dominant[b]
NMB (€, millions)[a]						
IPD only				-114	-101	+14
IPD + NIPP				+173	+281	+108

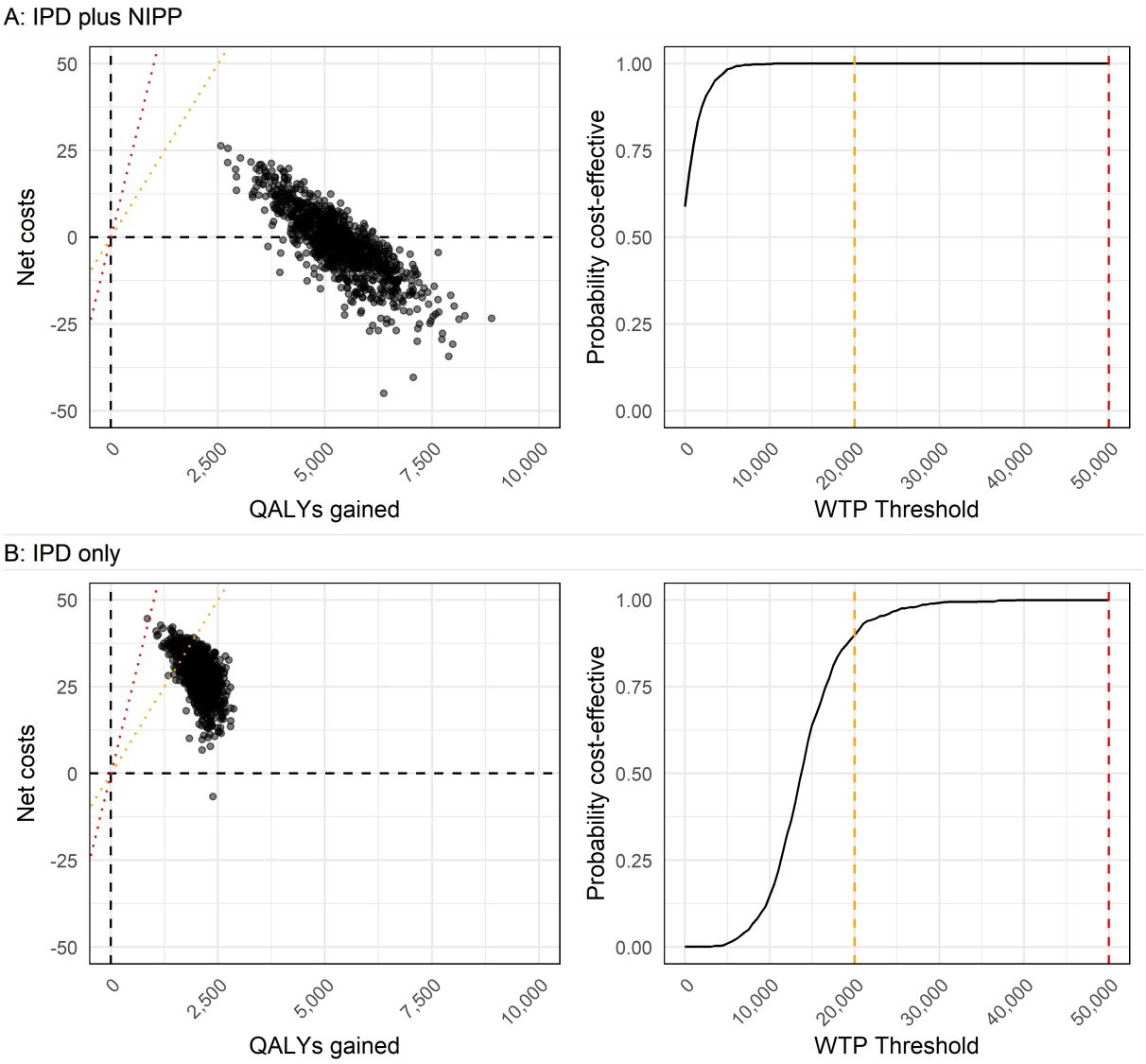
ICER: Incremental cost-effectiveness ratio, IPD: Invasive pneumococcal disease, NIPP: Non-invasive pneumococcal pneumonia, NMB: Net monetary benefit, NPPV: National pneumococcal vaccination program (for older adults), PCV: Pneumococcal conjugate vaccine, QALY: Quality-adjusted life year, National Programme for Pneumococcal Vaccination (NPPV), NA = Not applicable.
[a]: the net monetary benefit (NMB) is calculated as QALYs gained * WTP threshold – Net costs, using a willingness-to-pay threshold of €20,000/QALY gained. A positive NMB indicates that the intervention is cost-effective to the €20,000/QALY threshold, and a negative that the intervention is not cost-effective.
[b]: dominant means that the intervention strategy results in net QALY gains and net cost savings compared to the reference strategy

6.3 Sensitivity analysis

6.3.1 Probabilistic sensitivity analysis

The multivariable PSA using 1000 simulations showed that, compared with PCV20, PCV21 was cost-saving in 58.8% of the simulations, and cost-effective at a threshold of €20,000 per QALY gained in 100% of the simulations (Figure 10). When considering only the impact on IPD, PCV21 was cost-saving in 0.1% of the simulations and cost-effective at a threshold of €20,000/QALY gained in 89.9% of the simulations.

Figure 10 Multivariable probabilistic sensitivity analysis using 1000 simulations when comparing the cost-effectiveness of PCV21 versus PCV20 in the NPPV for older adults aged ≥60 years when (A) including an effect against both IPD and hospitalized NIPP, and (B) including an effect against IPD only. The left plot shows the net costs and effects of PCV21 versus PCV20 (reference) of the 1000 simulations in a cost-effectiveness plane, and the right graph shows the proportion of simulations in which PCV21 was cost-effective compared to PCV20 over a range of willingness-to-pay thresholds (WTP)



The orange dashed line represents a WTP threshold of €20,000/QALY gained, and the red dashed line a WTP threshold of €50,000/QALY gained

6.3.2 *One-way scenario analysis*

When comparing PCV21 with PCV20, scenarios with alternative price differences between PCV21 and PCV20 and alternative proportions of hospitalized pneumonia cases attributable to pneumococcus resulted in the largest changes in cost-effectiveness (Table 7). When comparing PCV21 with no NPPV, a reduction in the duration of protection of PCVs from 15 years to 10 years also had a significant impact. However, in all scenarios, the ICER remained below the €20,000/QALY gained

threshold, and in many scenarios PCV20 was dominated by PCV21. Regarding indirect effects of the NIP, the cost-effectiveness of PCV21 versus no NPPV diminished when reducing the magnitude of serotype replacement in disease from 100% to 50%; however, it had only a minor effect the cost-effectiveness of PCV21 versus PCV20, because the impact of both programs was diminished by this variation.

Table 7 One-way scenario analysis of different parameters for the analysis in which including both IPD and NIPP outcomes

Scenario	**PCV21 vs. No NPPV**		**PCV21 vs. PCV20**	
	ICER (€/QALY)	**NMB (€, millions)**	**ICER (€/QALY)**	**NMB (€, millions)**
Base case	7,277	281	PCV21 dominant	108
PCV21 price equal to PCV20[a]	4,840	335	PCV21 dominant	162
PCV21 price premium of €30 vs. PCV20[a]	9,247	238	7,987	65
30% of hospitalized pneumonia attributable to pneumococcus[b]	3,785	452	PCV21 dominant	150
15% of hospitalized pneumonia attributable to pneumococcus[b]	12,437	128	2,741	71
10-year duration of PCV protection[c]	13,109	112	4,226	57
50% serotype replacement in disease[d]	8,925	223	1,781	82
40% indirect protection[d]	6,616	307	1,781	82
40% indirect protection and 50% serotype replacement in disease[d]	7,341	278	3,030	69
No discounting	4,757	402	PCV21 dominant	140
Healthcare payer perspective	8,498	254	894	103

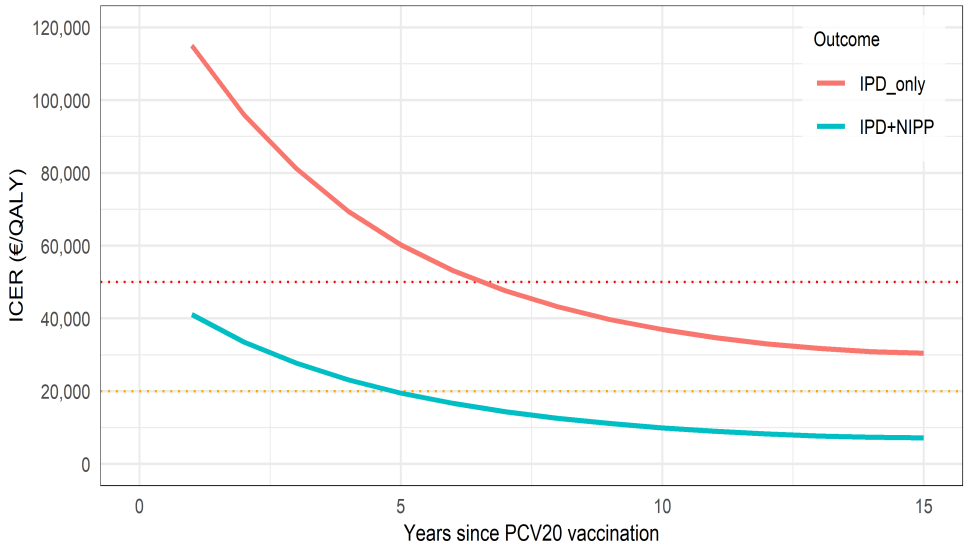
[a]: price premium of €16.59 in base case
[b]: 22.1% attributable to pneumococcus in base case
[c]: 15 year duration of protection in base case
[d]: 100% serotype replacement in disease and 80% indirect protection in base case
[e]: The NMB is calculated as: QALYs gained * WTP threshold – Net costs, using a willingness-to-pay threshold of €20,000/QALY gained

6.3.3 *Vaccination of PCV20-vaccinated individuals with PCV21*

We also explored the cost-effectiveness of vaccinating PCV20-vaccinated individuals with PCV21 by looking at the cost-effectiveness of PCV21 versus no vaccination in individuals aged ≥60 years, while taking into account protection provided by a previous PCV20 dose over time (Figure 11). We found that a previous PCV20 dose strongly diminished the cost-effectiveness of PCV21, showing an ICER of approximately €40,000 per QALY gained one year after PCV20 administration, while without a previous PCV20 dose, the ICER was estimated at €7,277 per QALY gained (Table 6). After 5 years following PCV20 administration, the ICER of PCV21 vaccination fell below a €20,000 per QALY gained threshold (Figure 11). When considering only the impact on IPD, vaccination with PCV21 became cost-effective at the €50,000 per QALY gained threshold

after 7 years following PCV20 administration but did not fall below the €20,000 per QALY gained threshold.

Figure 11 The cost-effectiveness of PCV21 vaccination among PCV20-vaccinated individuals aged ≥60 years over time since PCV20 vaccination

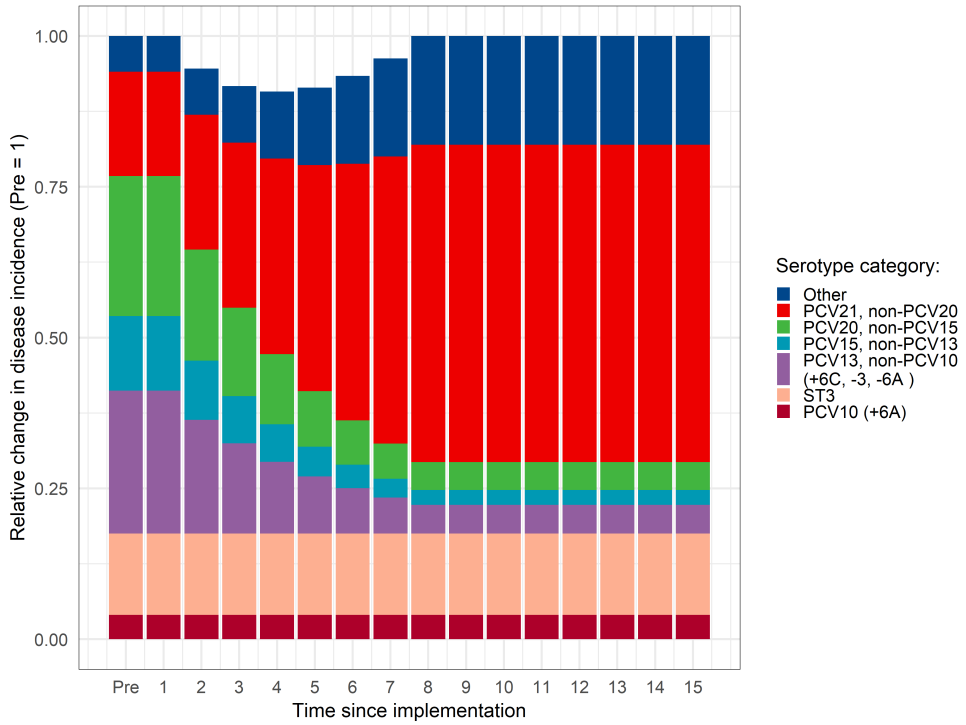


For this analysis, we compared the cost-effectiveness of PCV21 versus no vaccination, taking into account the protection provided by a previous PCV20 vaccination

6.3.4 *Scenario PCV20 in infant vaccination program*

Despite PCV20 not currently being recommended for infants (55), we explored how the cost-effectiveness of PCV20 and PCV21 for older adults could potentially change due to indirect effects resulting from the implementation of PCV20 in the NIP for infants. In this scenario, indirect effects as described for PCV15 were also applied to the "PCV20, non-PCV15" serotypes from the start of the analysis, with the change in IPD incidence per serotype category as illustrated in Figure 12. Although this scenario is a simplification because it assumes immediate implementation of PCV20 and therefore does not account for the period during which PCV15 has been implemented and is generating indirect effects, the results provide useful insights into how the cost-effectiveness of PCV20 and PCV21 for older adults could potentially be affected if PCV20 were introduced into the NIP in the future.

Figure 12 Modelled relative changes in pneumococcal disease (IPD and NIPP) incidence as compared to the mature PCV10 period by serotype category in the population aged ≥60 years following the introduction of PCV20 into the NIP for infants over a 15-year time horizon



The used model input is explained in the text.. Note that this figure does not take into account an NPPV with PPV23, PCV20 or PCV21; the data therefore show the changing incidence used to model the impact of introduction either PCV20 or PCV21 into the NPPV. Y-axis: pre-PCV20 incidence=1.

The cost-effectiveness results indicate that the introduction of PCV20 in the NIP would substantially improve the cost-effectiveness of PCV21 for older adults compared with PCV20 (Table 8; NMB increasing from €108 million to €215 million). However, compared with no vaccination, the cost-effectiveness of PCV21 decreases (NMB decreasing from €281 million to €231 million). Thus, the improved cost-effectiveness of PCV21 versus PCV20 is driven by a much stronger reduction in the cost-effectiveness of PCV20 (NMB decreasing from €173 million to €16 million) than in that of PCV21. This is explained by indirect effects of PCV20 in the infant NIP, which lead to a shift in pneumococcal disease from PCV20 serotypes to non-PCV20 serotypes, thereby strongly reducing the impact of PCV20 in the NPPV. For PCV21, this reduction is minor because it covers 11 non-PCV20 serotypes that are expected to increase in incidence due to serotype replacement.

Table 8 Impact of the introduction of PCV20 into the children's NIP on the cost-effectiveness of PCV20 versus no vaccination and PCV21 versus no vaccination, and of PCV21 versus PCV20, in the NPPV for adults aged ≥60 years

Infant vaccine	PCV20 vs. no NPPV		PCV21 vs. no NPPV		PCV21 vs. PCV20	
	ICER[a]	NMB[b]	ICER[a]	NMB[b]	ICER[a]	NMB[b]
PCV15	9,653	173	7,277	281	PCV21 dominant[c]	108
PCV20	18,604	16	8,683	231	PCV21 dominant[c]	215

[a]: Incremental cost-effectiveness ratio (ICER), expressed in € per QALY gained.
[b]: Net monetary benefit (NMB), expressed in millions of euros. The NMB is calculated as: QALYs gained * WTP threshold – Net costs, using a willingness-to-pay threshold of €20,000/QALY gained
[c]: In these scenario's, PCV21 had lower costs and higher QALY gains compared to PCV20

6.4 Discussion cost-effectiveness

We found that both PCV20 and PCV21 in the NPPV would prevent substantial disease burden compared with no NPPV. Moreover, both were expected to be cost-effective at a €50,000/QALY gained threshold, and also at a €20,000/QALY gained threshold provided that the impact against hospitalized NIPP is included. PCV21 was projected to result in a roughly 30% higher QALY gain than PCV20, compared with no NPPV, and was expected to dominate PCV20 (being more effective at lower total costs) at the current difference in vaccine list prices of €16.59 per dose. Previous vaccination with PCV20 strongly diminished the cost-effectiveness of PCV21. PCV21 remained cost-effective at a €50,000/QALY threshold, however, at a €20,000/QALY threshold, PCV21 was only cost-effective if administered at least five years after the PCV20 dose.

The cost-effectiveness of PCV21 relative to PCV20 was generally robust across sensitivity analyses. This robustness is partly explained by the fact that, in our analysis, the vaccines only differ in the selection of serotypes they cover, while having identical VE over time against included vaccine serotypes. The results were most sensitive to the difference in vaccine price. Note that the present analysis was based on Dutch list prices for private purchase, which may not reflect prices obtained through national procurement. Moreover, list prices are subject to change, and, if applicable, tendering procedures could also alter the relative cost-effectiveness of the two vaccines.

Due to indirect effects, the cost-effectiveness of adult vaccination programs is influenced by the vaccine type used in infants, with the impact depending on the extent of overlap between serotypes covered by childhood and adult vaccines. With the introduction of PCV15 in the infant NIP, the cost-effectiveness of PCV21 versus PCV20 was only marginally affected by alternative assumptions regarding the magnitude of indirect effects and serotype replacement, as indirect effects take time to be fully realized and both PCV20 and PCV21 cover serotypes not included in PCV15. If PCV20 were to be introduced in the infant program in the future, however, we expect the cost-effectiveness of PCV21 relative to PCV20 to improve further, because indirect protection would reduce the disease burden caused by serotypes included in PCV20,

increasing the relative contribution of the eleven non-PCV20 serotypes included in PCV21. Note, however, that a switch to PCV20 in infants could diminish the cost-effectiveness of PCV21 compared to no NPPV, as replacement is also expected to partly occur with non-PCV21 serotypes. Such diminishment in cost-effectiveness could become larger in a scenario where no full serotype replacement in disease was assumed.

Several assumptions introduce uncertainty into our estimates. First, VE for all serotypes included in PCV20 and PCV21 was extrapolated from PCV13 data. Although both newer vaccines have demonstrated non-inferior immunogenicity compared with PCV13, real-world evidence on their effectiveness against clinical disease, and particularly on their comparative effectiveness, is not yet available. Second, projections of indirect effects following a switch from PCV10 to PCV15 in the infant NIP were informed by international observations after the introduction of PCV13. Although the specific serotypes that will emerge following serotype replacement remain uncertain, when simulating an infant PCV13 program, our model reproduced serotype distributions that were similar to those observed in countries that implemented PCV13 (56). Third, we assumed complete replacement in disease and did not account for differences in serotype invasiveness. This assumption was based on observations following PCV10 introduction in the Netherlands and PCV13 introduction in countries where the preceding PCV7 program had substantially reduced vaccine-type disease (26, 54, 57). While in children and younger adults persistent reductions in IPD were observed following PCV7/10/13 programs, presumably due to replacement with less invasive serotypes, such reduction was not observed in older adults possibly due to host factors such as immunosenescence and comorbidities (38, 58). Finally, we made some simplifications, such as ignoring the fact that PCV15 was already implemented in the NIP for infants in autumn 2024, and assuming an instant implementation of PCV20/PCV21 in the NPPV instead of a phased rollout. However, since we expect the indirect effects of PCV15 on the proportion of IPD cases covered by PCV20 and PCV21 to be minor, we also expect that the simplifications related to PCV15 implementation will not substantially alter the final results.

In conclusion, both PCV20 and PCV21 are likely to be cost-effective vaccines for older adults. However, because PCV21 is expected to prevent more pneumococcal disease through its broader serotype coverage, it is projected to be more effective and cost-saving relative to PCV20 at the current difference in vaccine list prices.

7 Novel pneumococcal vaccine concepts under clinical development

Current PCVs successfully protect against pneumococcal disease caused by vaccine serotypes. Their aim is to reduce severe pneumococcal disease as well as carriage and transmission of serotypes in the paediatric population and to prevent disease in older risks groups. To address the observed ongoing replacement by non-vaccine serotypes, a series of PCVs with increasing serotype valencies has been marketed over the past decades (from PCV7 to PCV10, PCV13, PCV15, PCV20, and PCV21) and more-valent PCVs are in development (e.g. PCV25 (PG4) for children – phase 3 planned, PCV35 (PG5) for adults - clinical development planned). These latter new PCV candidates will not only be optimized by expanded serotype coverage but also by next generation proprietary conjugation technology to elicit a more robust immune response against serotype 3 (59). The mechanistic correlate of protection of all these PCVs is the induction of long-term antibody responses against specific capsular polysaccharide serotypes. Antibody-binding to pneumococci in the upper respiratory tract can lead to bacterial agglutination, promoting removal of bacterial clumps from the niche via ciliary clearance. More importantly, serotype-specific antibodies can opsonize bacteria for uptake and killing by local phagocytes. Further expansion of PCV valency, however, has several immunological limitations, prompting for novel approaches in pneumococcal vaccine development.

In present PCVs, serotype-specific polysaccharide are conjugated via classical conjugation chemistry to heterologous carrier proteins. This modification turn pneumococcal polysaccharide-specific B cell responses into T-cell dependent responses, leading to class switching and affinity maturation of the produced antibodies. However, current conjugation practice may compromise immunogenicity and potentially the effectiveness of PCVs. First, current classical conjugation chemistry induces covalent, random linkages between carrier protein and polysaccharide chains along their full lengths, possibly causing loss of B and T cell immunogenicity of the conjugate. Novel conjugation approaches are under development (60). In clinical stage are 24-valent (phase 2) and 31-valent (phase 3) candidate PCVs of Vaxcyte (Vax-24 and Vax-31, respectively; Table 9). These products employ an enhanced version of the heterologous CRM197 carrier protein (eCRM), with engineered amino acid alterations outside T-cell epitope regions. These mutations facilitate site-specific conjugation with reduced structural heterogeneity and preserved T-cell immunogenicity (61-64).

Second, all carrier proteins used in current PCVs represent a limited set of heterologous proteins, i.e. diphtheria toxoids (CRM197 and DT), tetanus toxoid (TT), and *H. influenzae* Protein D (PD). CD4 T cells induced by these (non-pneumococcal) carrier proteins help to initiate and differentiate the pneumococcal polysaccharide-specific B cell response after vaccination. However, using the same carrier proteins to conjugate an increasing number of polysaccharide serotypes in higher

valency PCVs increases the total amount of carrier protein per vaccine dose. Also, these proteins are mostly vaccine antigens by themselves in other vaccines. This may lead to so-called Carrier-Induced Epitope Suppression (CIES) of serotype-specific B cell responses after PCV vaccination. Mechanisms of suppression can include competition for carrier-specific T cell help between serotype-specific B cells and increasingly induced carrier-specific B cells, masking of polysaccharide epitopes on conjugate antigens by excess of carrier-specific antibodies, and the induction of carrier protein-specific regulatory T cell responses after repeated exposure (65).

To tackle the above limitations of the PCV expansion approach the current clinical pneumococcal vaccine development pipeline contains various novel approaches (Table 10). These include the use of the so-called Multiple Antigen Presenting System (MAPS) technology in MAPS-conjugated candidate Pn-MAPS30plus, not only applying a more efficient, controlled, highly stable and affine non-covalent conjugation chemistry via biotin-rhizavidin dimeric bonds, but also using pneumococcal-specific carrier proteins, avoiding CIES (66, 67). Of the involved serotypes, 24 are publicly disclosed: all PCV20 serotypes as well as the PPV23-serotypes 2, 9N, 17F and 20B. Additional serotypes in Pn-MAPS30plus are still confidential. Development of the 24-valent MAPS vaccine Pn-MAPS24v for adults is discontinued (68).

Other approaches abandon the serotype-dependent vaccine design altogether, being based on selected pneumococcal protein candidates only, or on inactivated whole-cell concepts. The advantage of these concepts is their induction of pneumococcal-protein specific antibodies as well as CD4 T cells. The latter not only critically provide help to antibody responses but also, when recognizing their protein antigens during infections, enhance the opsonophagocytic killing and clearance of bacteria by phagocytes. Specifics, clinical trial numbers and expected timelines of these most promising pneumococcal protein-containing pneumococcal vaccine candidates in clinical development are summarized in Table 10.

As can be observed in Table 10, none of these vaccine candidates in clinical development are close to registration. The same holds true for the Vaxcyte concepts (Table 9). It will thus likely take a while before alternatives to serotype specific vaccines will be available for use in national immunisation programmes.

Table 9 Site-specific conjugation technology for multivalent PCVs in clinical development

		Design phases (Left to right)				
		Phase 1	**Phase (1b)/2**	**Phase 3**	**Registration**	**Approved**
i) Novel conjugation technology						
• *Vaxcyte*	• *Site-specific eCRM conjugation technology*		• *Vax-24*[69),(70),(71] • *Vax-31*[72),(73]	• *Vax-31*[74),(75),(70]		

Study populations per trial: (69). healthy infants, (70-Vax24). adults, (71). older adults, (72). adults, (73). healthy infants & dosing, (74). healthy adults 18-49 yrs, (75). adults >50 yrs of age with prior Sp vaccination, (70-Vax31). adults >50 yrs of age with flu vaccine. Trials as found in March 2026.

Table 10 Current clinical pipeline of pneumococcal protein-containing pneumococcal vaccine candidates by concept of design

		Design phases (left to right)				
Pharmaceutical company	**Proteins**	***Phase 1***	***Phase (1b)/2***	***Phase 3***	***Registration***	***Approved***
i) SELECTED SP PROTEINS						
• CanSino Biologics Inc	• pneumococcal surface protein A (PspA)-RX1, PspA-3296, PspA-5668 and dPly protein	• PBPV[76],[77]				
ii) WHOLE CELL-BASED						
• PATH SII (with Serum Life Science Europe/NIAID)	• betapropiolactone-killed unencapsulated RX1E, PdT ΔlytA (RM200)	• PATH-RM200[78],[79] • wSp005[80]	• PATH-RM200[81] • wSp005[82]			
• GPN Vaccines	• g-irradiated nonencapsulated Rx1, dPly, ΔlytA, ΔpsaA	• Gamma-PN3[83],[84]				
• Recipharm (with ImmBio and iiCON)	• multi-antigen lysate of heat-stressed unencapsulated TIGR4 cells, dPly	• PnuBioVax[85],[86]	• underway			
iii) PNEUMOCOCCAL PROTEIN CARRIERS IN (ADAPTED) CONJUGATE VACCINES						
• GSK	• Pn-MAPS30 plus: confidential	• Pn-MAPS30 plus[87-90]	• planned	• planned		
• Pfizer	• new multivalent PCV (Sp carrier protein(s)?) PG4=PCV25 (for infants)		• PG4[91],[92]	• PG4[93]		
• Matrivax	• Protein Capsular Matrix Vaccine (PCMV) technology (carrier dPly, CbpA ?)	• MVX-01[94]				

Study populations per trial: (76). ☐50 yrs, (77). 18-50 yrs, (78). toddlers, (79). adults, (80). adults, (81). toddlers and adults, (82). young pcv20+ children, (83). some participants, (84). 50-69 yrs, (85). tox GMP lot, (86). 18-40 yrs, (87). 50-64 yrs, (88). toddlers, (89). 12-15M, (90). 50-64 yrs, (91). infants +/- pcv, (92). toddlers, (93). infants, (94). 18-50 yrs. Trials as found in March 2026.

8 Aspects of a vaccine change

8.1 Concomitant administration

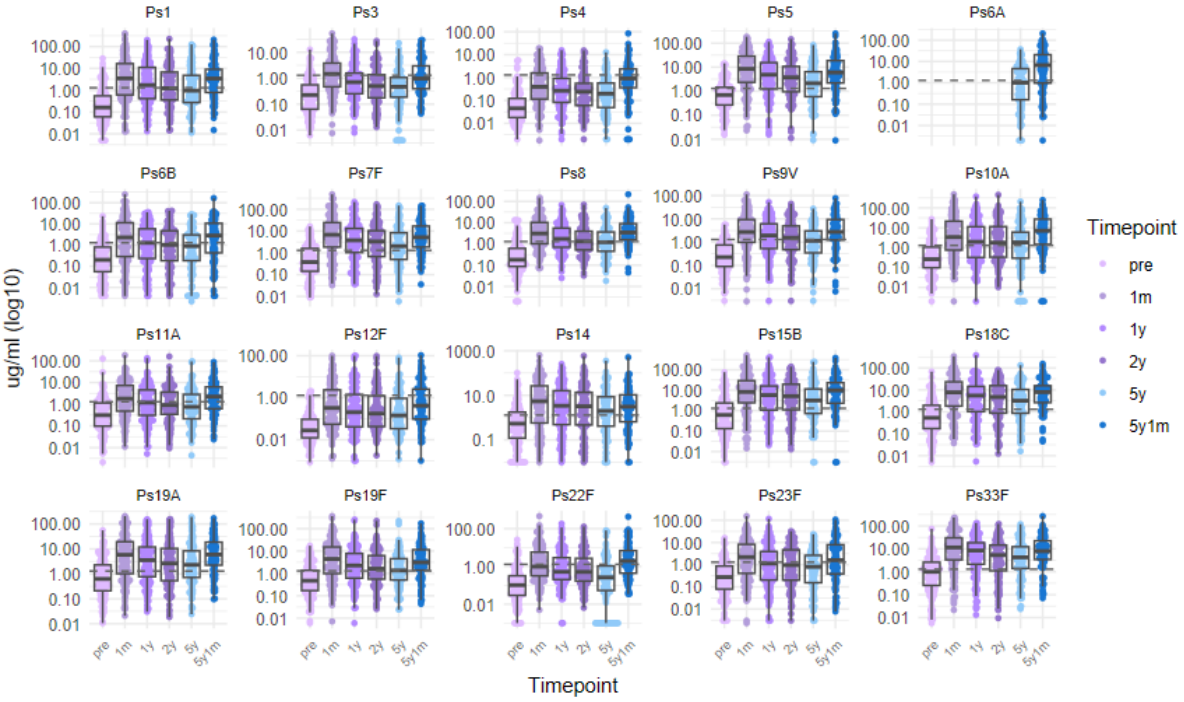
PCV21 can be administered concomitantly with influenza vaccination (2, 95). There is no data on concomitant administration with other vaccines.

8.2 PCV20 as booster after PPV23 primary vaccination

Between fall 2020 and fall 2025 5-year cohorts of older adults aged 60-79 years were eligible for PPV23 vaccination in the Netherlands (Table 1). The cohort that had been vaccinated with PPV23 in 2020 was the first cohort eligible for PCV20 immunisation according to the NPPV, 5 years later, when they were 80-84 years old. In this group the serotype specific IgG antibody responses after the PCV20 booster vaccination given in 2025 were evaluated (Doetinchem study; (96)). Data of this study provides information on the presence of serotype-specific antibody levels 5 years after PPV23 as well as PCV20 induced booster responses in this old age group thereby supplementing data from the STRIDE-6 study (see above; just 8% of all phase 3 study participants were 75 years or older, 14% had received other prior pneumococcal vaccine) in which the older adults were on average younger this in the Doetinchem study.

PCV20 induced a booster response, defined as a 2-fold increase in GMCs pre- versus post-PCV20 vaccination, in most participants but with considerable individual variation (Figure 13). The response was significant for all serotypes except serotype 3 and 14. One month after PCV20 61% of the participants had antibody concentrations above the threshold for protection (1.3 ug/ml) for 70% of the vaccine serotypes. Waning during time after booster vaccination is currently under investigation (autumn 2026)

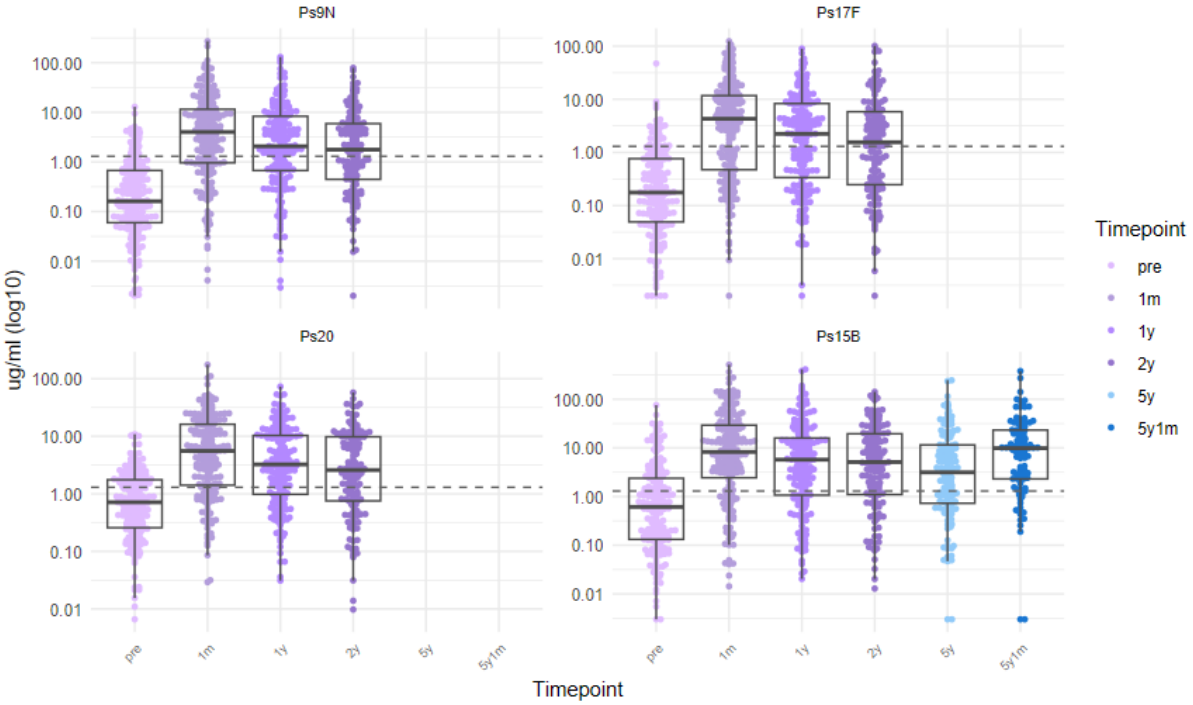
Figure 13 Pneumococcal serotype (Ps)-specific IgG concentrations IgG concentrations (ug/ml) at baseline in 2020 (pre), at a month (1 m) one year (1 y) and two years (2 y) after PPV23 vaccination (purple), as well as 5 years (5 y) post vaccination=pre-PCV20 vaccination in 2025 (light blue) and a month (5 y 1m) post-PCV20 vaccination (dark blue) in older adults



Participants were 73-79 years old pre-PPV23 vaccination and 78-83 years old pre-PCV20 vaccination. The horizontal dashed line indicates a pneumococcal-specific IgG concentration of 1.3 µg/ml

However, antibody concentrations against the PPV23-vaccine serotypes that are not covered by PCV20 will not have been boosted but continued to wane and may have reached levels below the threshold correlated with protection at 5 years post PPV23. Some of these serotypes are included in PCV21, and for those serotypes, vaccination with PCV21 after initial PPV23 vaccination will most likely result in an increase in antibody titers comparable to the increase seen for serotype 15B, a serotype with similar antibody kinetics as for 9N, 17F and 20 (figure 14).

Figure 14 Pneumococcal IgG concentrations (ug/ml) for serotypes 9N (Ps9N), 17F and 20 (all covered by PPV23 but not PCV20) and 15B (covered by PPV23 and PCV20) at baseline (pre), at 1 month (1 m) one year (1 y) and two years (2 y) after PPV23 vaccination of older adults



The horizontal dashed line indicates a pneumococcal-specific IgG concentration of 1.3 µg/ml. The IgG patterns resemble that of serotype 15B-specific IgG showing a response after PCV20 vaccination 5 years post-PPV23

IgG values against serotype 4, a serotype with increased IPD incidence that is not present in PCV21, were significantly higher a month after the PCV20 booster compared to one month after PPV23 primary series vaccinations (Figure 14), geomean values of 5.29 ug/ml and 0.42 ug/ml respectively.

8.3 Revaccination

There is no effectiveness data yet and limited (longitudinal) immunogenicity data. It is thus unknown how fast antibodies wane after vaccination with PCV20 or PCV21. Such information would be helpful to consider whether revaccination would be relevant to stay protected against vaccine-type disease.

8.4 Selecting birth cohorts for PCV21 vaccination

In case of a vaccine change to PCV21 in the NPPV, prioritisation may be needed in case not all birth cohorts can be offered vaccination at once. Vaccination with PCV20 started in autumn 2025 with the 60-year olds, those for whom PPV23 was offered 5 years earlier and the older cohorts that had not yet been eligible for vaccination due to their age (born before 1941; see Table 1). It is currently planned to offer PCV20 to all PPV23 eligible birth cohorts 5 year after PPV23-eligibility (Table 1) as well as those aged 60 years. (Re)vaccination 5 years after PPV23 will

(still) be needed because of waning immunity after PPV23. Revaccination after PCV20 with PCV20 is possibly not needed before 10 years after vaccination based on extrapolation of results of the PCV13 trial in older adults (49), though, no VE data are available yet and clinical decrease in VE needs thus to be followed up. Note, however, that each birth cohort will likely benefit from PCV21 because of the additional serotype coverage (Table 11); around 25% of all IPD cases in 60+ year olds in 2024-2025 were caused by serotypes covered by PCV21 but not PCV20. See also paragraph 6.3.3 (Vaccination of PCV20-vaccinated individuals with PCV21) for the cost-effectiveness analysis. The model projected that the ICER of PCV21 is below the €50,000 per QALY gained threshold independent of time since previous PCV20 vaccination.

Table 11 Total number of IPD cases per PCV type in 2024-2025 and the percentage that are caused by serotypes for which protection may be expected by PCV20 or PCV21, for the birth cohorts that were eligible for PPV23 over time

Birth cohort	PCV20 n (%)	PCV21 n (%)	PCV20-nonPCV21 n (%)	PCV21-nonPCV20 n (%)	Shared serotypes n (%)
<1941	356 (57)	490 (78)	31 (5)	165 (26)	325 (52)
1941-1947	283 (60)	342 (73)	39 (8)	99 (21)	244 (52)
1948-1952	317 (60)	407 (77)	35 (7)	125 (24)	282 (53)
1953-1956	290 (62)	375 (80)	23 (5)	107 (23)	267 (57)
1957-1960	311 (62)	382 (77)	34 (7)	105 (21)	277 (56)
1961-1964	258 (66)	306 (78)	28 (7)	77 (20)	229 (51)

As data comes from 2024-2025 and PCV20 was introduced in autumn 2025, this data likely covers very limited PCV20 impact yet. Note that numbers are extrapolated for cases with missing serotype (n=25) using the vaccine-type proportion observed among those with serotype available.
PCV20-nonPCV21 = PCV20 unique serotypes, i.e., serotype 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F. PCV21-nonPCV20 = PCV21 unique serotypes, i.e., serotype 9N, 17F, 20, 15A, 15C, 16F, 23A, 23B, 24F, 31, 35B. Shared PCV20/21 serotypes are cases infected with a serotype covered by PCV20 and by PCV21, i.e., serotype 6A, 6C, 7F, 8, 10A, 11A, 12F, 15B, 19A, 22F, 33F

8.5 Recommendations in other countries

Most European countries offer PCVs to adults; only a minority offers PPV23. Recommendations are for medical risk groups up to a certain age, and to all persons from that age onwards (97).

In December 2025, Belgium published their recommendation for adults; they recommend either PCV20 or PCV21 for all adults aged ≥65 years as well as for adults aged 50-64 years with risk conditions (98). Note, however, that PCV21 was not yet available on the Belgian market and thus not yet implemented. Risk conditions can be summarised as: immunocompromising conditions, anatomical risk factors, chronic heart disease, chronic lung disease, chronic liver disease, chronic kidney disease, neurological conditions, metabolic disorders, environmental/occupational risk factors. In Austria, persons aged 60 years and older are offered a single dose of PCV21, even if they have received pneumococcal vaccinations before, for broader serotype coverage (97). France offers PCV20 or PCV21 to risk groups aged 18-64 years and all persons aged 65 years and older (97). Likewise, in Norway, a single dose of PCV20 or PCV21, or PPV23 every 6 years, is

recommended for everyone aged 65 years and older and to persons with medical risk conditions (99).

In the United States, all adults aged 50 years and older are recommended a single dose of PCV20 or PCV21 as are persons aged 19-49 years with medical conditions, without previous pneumococcal vaccination (100). Alternatively, PCV15 is used in combination with PPV23. In certain geographical areas in the United States, serotype 4 IPD is more prevalent which may indicate more public health benefit of PCV20 or PCV15+PPV23 compared to PCV21. In Quebec, Canada, PCV21 is recommended for individuals aged ≥65 years, independent of any previous pneumococcal vaccination. For adults (≥18 years) with medical risk conditions posing them at very high risk of pneumococcal disease, PCV20 and administration of PCV21 with an interval of 1 month is recommended (101, 102).

Risk groups that are often included in national guidelines are presented in Table 12.

8.6 Vaccination of medical risk groups

In the Netherlands, pneumococcal vaccination is advised by various professional societies for the different risk groups. The medical indications have been summarized in the LCI-factsheet (103). Uptake among immunocompromised patients has been low (104). PCV21 is not (yet) covered by health insurance. PCV20 is covered by health insurance for certain medical high risk groups since June 2025 (105), if the vaccination is administered by a general practitioner (GP) (106).

GPs are primarily responsible for the vaccination of older adults (NPPV), but not for vaccination of high-risk groups. Responsibility for the selection and vaccination of medical risk groups (with reimbursement via health insurance) usually lies with medical specialists in the hospital (107). Vaccinations administered in the hospital are reimbursed by all health insurers, predominantly for organ transplant patients and those with asplenia. For other medical risk groups it depends on the individual yearly arrangements between hospital and health insurers whether the vaccination administered in the hospital will be reimbursed (108). Moreover, hospital vaccination hubs have capacity constraints and administrative hindrances imposed by health insurance companies to vaccinate all medical risk groups. Currently, vaccinations for medical risk groups administered by the GGD are not reimbursed by health insurances (106). A national programme for pneumococcal vaccination in risk groups, possibly combined with the NPPV as is the case for influenza vaccination (107), might lead to equal access, a better coverage and thereby impact the disease burden in at-risk adults (109-111).

Table 12 Chronic medical conditions that most national guidelines include in their recommendation for pneumococcal vaccination regardless of age

Medical risk condition
Chronic heart disease
Chronic liver disease
Chronic respiratory disease including asthma
Chronic kidney disease
Congenital and acquired immunodeficiencies, including the use of immunosuppressive agents
Cerebrospinal fluid leakage
Cochlear implant
Diabetes mellitus
(Functional) asplenia
Haematological cancer and stem cell transplantation
Solid tumours
HIV infection
Solid organ transplantation
Other risk conditions included in guidelines
Homelessness
Welding

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