National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Pneumococcal vaccination in older adults

Information for the Health Council of the Netherlands

RIVM letter report 2022-0047
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Synopsis

Pneumococcal vaccination in older adults

Information for the Health Council of the Netherlands

Pneumococci can cause severe infections, such as pneumonia, septicaemia and meningitis. Severe pneumococcal disease is most common in people aged 60 and over and in people with certain chronic diseases. There are many types of pneumococcal bacteria and the prevalence of the different types differs per country. Pneumococcal vaccines exist; these prevent against several pneumococcal bacteria types.

Since autumn 2020, individuals aged between 60 and 79 have been invited for pneumococcal vaccination in the Netherlands. The vaccination with the used pneumococcal vaccine must be repeated every five years.

Recently, two new vaccines have been developed and approved for use in adults. Furthermore, two more vaccines are expected (soon). The Dutch Ministry of Health, Welfare and Sport has asked the Health Council of the Netherlands to advise which vaccines can be used for individuals aged 60 and over. To this end, RIVM has collected scientific information about pneumococcal disease and pneumococcal vaccines. It has also collated an overview of the incidence of severe pneumococcal disease in the Netherlands in recent years and of the type of pneumococcal bacteria they have been infected with.

How many cases with pneumococcal disease can be prevented through vaccination depends on several factors. For instance, the new vaccines will most likely provide longer protection than the ones currently used. The new vaccines will likely also provide better protection against pneumococcal disease in people with certain chronic diseases. The number of cases that can be prevented through vaccination also depends on whether the pneumococcal types covered by the vaccine are the same as the types that cause older adults to become ill in the Netherlands.

In line with this, it is important to take into account the effect of childhood vaccination. Children have been vaccinated against pneumococci since 2006. There are also (new) vaccines available for children that cover more types than the one currently used in the Netherlands. If these vaccines are used, fewer individuals in society will be infected by the types of pneumococci covered by the vaccine. Older adults and other high-risk groups can still be infected by other pneumococcal types. For this reason, vaccination against those types remains useful.

Keywords: pneumococcus, pneumococcal disease, vaccination, burden of disease, effectiveness, safety, older adults

Publiekssamenvatting

Pneumokokken vaccinatie in ouderen

Informatie voor de Gezondheidsraad

Pneumokokken kunnen ernstige infecties veroorzaken zoals longontsteking, bloedvergiftiging en hersenvliesontsteking. Ernstige pneumokokkenziekte komt het meeste voor bij mensen van 60 jaar en ouder, en bij mensen met bepaalde chronische ziektes. Er bestaan heel veel typen pneumokokkenbacteriën en het verschilt per land welke typen veel voorkomen. Tegen een deel van de typen bestaan vaccins.

Vanaf het najaar van 2020 worden mensen van 60 tot en met 79 jaar in Nederland uitgenodigd om zich tegen pneumokokken te laten vaccineren. Dit pneumokokkenvaccin moet elke vijf jaar worden herhaald.

Onlangs zijn twee nieuwe vaccins gemaakt en goedgekeurd voor volwassenen. Ook worden er (binnenkort) nog twee nieuw vaccins verwacht. Het ministerie van VWS heeft de Gezondheidsraad daarom gevraagd te adviseren welke vaccins voor mensen van 60 jaar en ouder kunnen worden gebruikt. Daarvoor heeft het RIVM de wetenschappelijke informatie verzameld over pneumokokkenziekte en pneumokokkenvaccins. Het geeft ook een overzicht hoeveel mensen in Nederland de afgelopen jaren pneumokokkenziekte hebben gekregen en door welke type pneumokokken bacteriën zij zijn besmet.

Het hangt van meerdere factoren af hoeveel ernstig zieke mensen de vaccinatie kan voorkomen. Zo beschermen de nieuwe vaccins zeer waarschijnlijk voor meer jaren dan met het vaccin dat nu wordt gebruikt. Ook beschermen de nieuwe vaccins waarschijnlijk beter bij mensen met bepaalde chronische ziektes. Het hangt er ook van af of de typen pneumokokken waar het vaccin tegen beschermt hetzelfde zijn als de typen waar ouderen in Nederland ziek van worden.

In het verlengde daarvan is het belangrijk te kijken naar het effect van de vaccinatie van kinderen. Zij worden sinds 2006 tegen pneumokokken gevaccineerd. Voor kinderen zijn ook (nieuwe) vaccins beschikbaar die tegen meer typen beschermen. Mochten deze vaccins gebruikt gaan worden, dan worden minder mensen in de samenleving besmet met de typen pneumokokken waar die vaccins tegen beschermen. Maar ouderen en risicogroepen kunnen dan nog steeds door andere typen besmet raken. Daarom blijft vaccinatie tegen andere typen nog steeds nuttig.

Kernwoorden: pneumokok, pneumokokkenziekte, vaccinatie, ziektelast, effectiviteit, veiligheid, ouderen

Contents

Summary

The 23-valent pneumococcal polysaccharide vaccine (PPV23) has been offered to older adults in the Netherlands, with estimated vaccine coverages among the first cohorts (born in 1941-1952) of 73-74% and a clear impact on the IPD incidence in the targeted age group.

Higher-valent pneumococcal conjugate vaccines against 15 (PCV15) or 20 (PCV20) serotypes have been licenced for use in individuals aged 18 years or older. Licencing has occurred based on immunogenicity data which have been non-inferior to PCV13 for the overlapping serotypes. The immune response of PCV15 against serotype 3 was superior to PCV13.

Antibody responses to PCV15 in previously PPV23-vaccinated individuals appeared similar to the response in previously pneumococcal vaccine-naïve adults. For PCV20, antibody responses were lower after prior PPV23 vaccination. The clinical effect of the slightly lower response is unknown.

Vaccine effectiveness (VE) against vaccine-type IPD of PPV23 and PCV13 (as a proxy for higher-valent PCVs) show overlapping ranges, at around 32%−59% for PPV23 and for PCV13, at 47%−75%.

The VE of PPV23 declines to limited effectiveness 5 years post-vaccination. Waning after PPV23 is specifically apparent in the population aged 70 years and older. For PCV13, no decrease in VE occurred over the studied 4.5 years after vaccination.

Because of waning immunity, PPV23 vaccination should be repeated every 5 years, and no boosting can be expected after a subsequent dose. It is unknown whether PCV vaccination needs to be repeated in the ageing population but likely not before 10- or 15-years post-vaccination; booster responses can be expected.

The serotype coverage of the vaccines is important for the size of the potential public health effect. PPV23, PCV20 and PCV15 covered, respectively, 79%, 74%, and 46% of the serotypes that caused invasive pneumococcal disease (IPD) in individuals aged 60 years and older in 2022.

Because of the substantially lower coverage of disease by PCV15 compared to PPV23 and PCV20, it might be considered to combine PCV15 with PPV23, with PCV15 given first, followed by PPV23 after at least one year. Use of PCV15+PPV23 possibly provides a slightly improved immunological response for some PCV15-serotypes in comparison to PPV23.

Two broad PCVs are in clinical development: PCV21 that covers eight complementary serotypes not covered by PCV13/15/20 or PPV23, and the 24-valent AFX3772 that includes the PPV23 serotypes+6A (Note that the serotype 20 antigen is not identical to the PPV23 serotype 20

antigen). The 24-valent vaccine uses a different technology than the PCVs, and includes a conserved pneumococcal protein. Potential broader protection or universal coverage due to this technology needs to be established.

PCV21 covered 88% and the 24-valent vaccine 79% of the 60+ years IPD cases in 2022.

Several patient groups are at increased risk for IPD even at younger age and can benefit from pneumococcal vaccinations.

The impact of the vaccines and thereby the cost-effectiveness of the programme in older adults will depend on the vaccine choice for the childhood immunisation programme because of the large indirect effects from childhood immunisation.

1 Background

In 2018, the Health Council of the Netherlands advised the implementation of the 23-valent pneumococcal polysaccharide vaccine (PPV23) among older adults (at 60, 65, 70 and 75 years of age) with revaccination every five years up to age <80 years (1). Because of the COVID-19 pandemic and limited vaccine availability, PPV23 was implemented in autumn 2020 among those aged 73-79 years followed by younger age groups in the years after (Table 1) (2).

Table 1 Birth cohorts and age at vaccination with PPV23 in the pneumococcal adult vaccination programme, as being implemented in 2020-2022 and planned for 2023-2025.

(autumn of) year of vaccination	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**
birth cohort, vaccination 1	1941-1947	1948-1952	1953-1956	1957-1960	1961-1964	1965
age of vaccination	73-79 yrs	69-73 yrs	66-69 yrs	63-66 yrs	60-63 yrs	60 yrs
birth cohort, revaccination						1946-1947
age of vaccination						78-79 yrs

Recently, a 15-valent (PCV15) pneumococcal conjugate vaccine and a 20-valent PCV (PCV20) have been authorised for use in adults aged 18 years and older in the European Union (3, 4). For children, PCV15 has recently been authorised (5) and authorisation of PCV20 is expected in 2023.

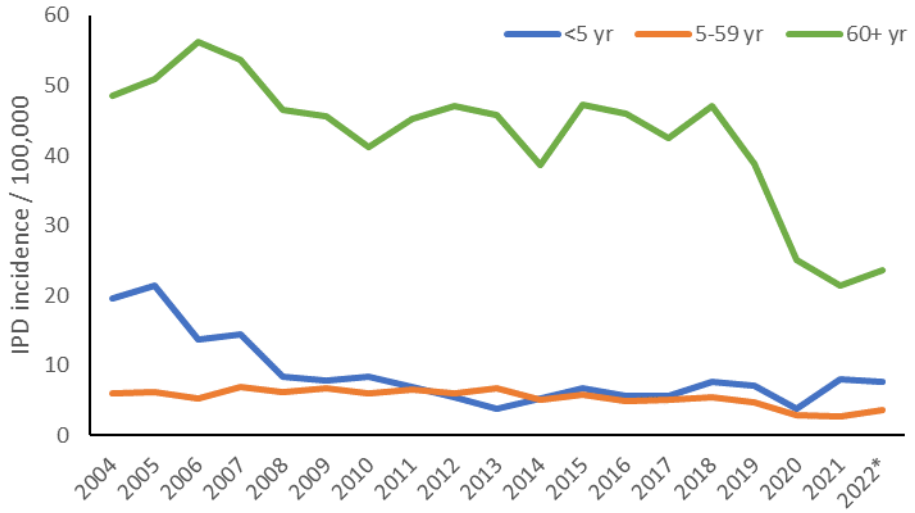
With the availability of these new PCVs, the Health Council will evaluate which vaccine is most appropriate for use in older adults in the Netherlands. This document provides an overview of information that will be useful for that decision, both, from the literature on pneumococcal disease and vaccination and from data on the current epidemiological situation in the Netherlands.

2 Epidemiology of pneumococcal disease

The epidemiology of invasive pneumococcal disease (IPD) among older adults has been strongly affected by the implementation of the 7-valent PCV (PCV7) in the national childhood immunisation programme (NIP) in 2006 and the subsequent switch to 10-valent PCV (PCV10) in 2011. Furthermore, IPD incidences in 2020-2021 were much lower than the previous years (Figure 1). This decrease was very likely related to the non-pharmaceutical interventions against COVID-19, including social distancing and school closures (6, 7).

2.1 Incidence of invasive pneumococcal disease

IPD incidence among the 60+ year-old population has been relatively stable in 2012-2019, fluctuating between 39/100,000 and 47/100,000 individuals (Figure 1). This corresponded to 382-510 cases per year as identified by nine sentinel laboratories that, in that period, covered around 25% of the Dutch population. In 2020 and 2021, the incidence decreased to 22/100,000 and 19/100,000, respectively (n=282 and 248 identified by sentinel laboratories that covered 28% of the population). Although the incidence has slightly increased again in 2022 (24/100,000; extrapolated from data up to 31 October), the incidence has not rebounded to the pre-COVID-19 levels.

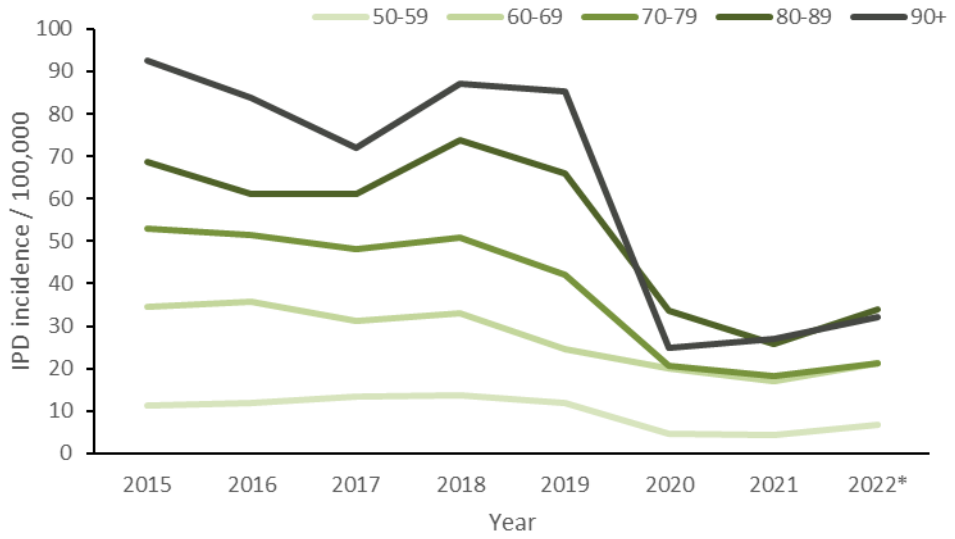


*Note that 2022 is extrapolated from the data up to and including 31 October 2022. For 5–59 years and 60+ year-olds, the data are based on extrapolation from 9 sentinel laboratories that covered between 25-28% of the population. The data for those younger than 5 years of age are since 2008 based on nation-wide data; in 2004-2007, sentinel data was used. Only blood or CSF isolates are included.

Figure 1 The incidence of invasive pneumococcal disease (IPD) per 100,000 population by age group for the period 2004-2022.

As presented in Figure 2, the IPD incidence among those aged 60+ years increases with age, with an incidence almost three times as high among the 90+ compared to those aged 60–69 years. During the COVID-19 years, this difference had decreased, possibly as a result of

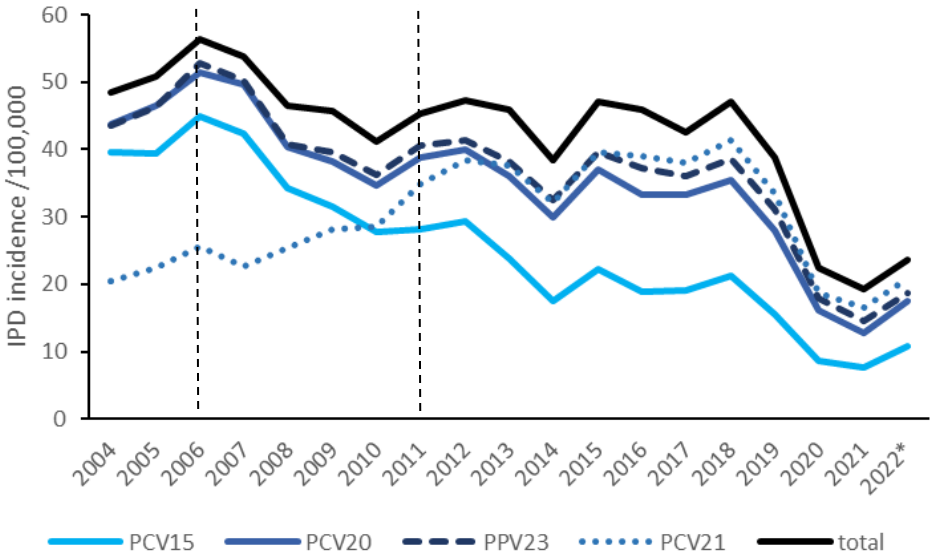
(age-specific adherence to) COVID-19 control measures. The introduction of PPV23 among those born between 1941-1952 may also have affected the numbers in 2021-2022 for the 70-79 age-group (8).



*Note that 2022 is extrapolated from the data up to and including 31 October 2022. Data are based on extrapolation from 9 sentinel laboratories that covered between 25-28% of the population. Only blood or CSF isolates are included.

Figure 2 The incidence of invasive pneumococcal disease (IPD) per 100,000 population per 10-year age-group among those aged 50 years and older, for the period 2015-2022.

In Figure 3, the vaccine-type specific incidences are shown for the 60+ year-old population. Since vaccine introduction in the NIP, the percentage of IPD cases aged 60+ years that were caused by PPV23-serotypes decreased from 94% in 2006 to around 80% since 2018 as a result of herd immunity from childhood vaccination. After re-distribution of the circulating serotypes following the switch in the NIP to PCV10 in 2011, the serotype distribution has stabilised in recent years, even though some serotype-specific changed occurred during the COVID-19 pandemic. During the early pandemic, IPD caused by serotypes 7F, 15A, 12F, 33F, and 8 showed the most pronounced decline (≥76%) (9, 10). The proportion of serotypes covered by the different vaccines (see chapter 3) in recent years are presented in Table 2. In 2022, PPV23 covered 79% of the IPD cases, for PCV20 this was 74% and for PCV15, this was 46%. The vaccines in clinical development, PCV21 and the 24-valent vaccine, covered respectively 88% and 79%.



*Note that 2022 is extrapolated from the data up to and including 31 October 2022. Data are based on extrapolation from 9 sentinel laboratories that covered between 25-28% of the population. Only blood or CSF isolates are included.
Figure 3 Incidence of IPD in adults aged 60 years and older caused by serotypes covered by the different vaccines.

Table 2 Coverage by different vaccines in the years 2019, the COVID-19-years 2020-2021 and in 2022 among IPD cases aged 60 years and older

	Number and percentage of IPD cases infected by vaccine types in 2019	**Percentage of IPD cases infected by vaccine types in 20-21**	**Number and percentage of IPD cases infected by vaccine types in 2022 (data up to October)**
PCV15 (Vaxneuvance / V114)	171 (40%)	40%	117 (46%)
PCV20 (Apexxnar)	309 (72%)	70%	190 (74%)
PPV23 (Pneumovax)	342 (80%)	78%	202 (79%)
PCV21 (V116)	369 (86%)	85%	227 (88%)
24-valent vaccine (AFX3772)	343 (80%)	79%	202 (79%)

In Table 3, the number of IPD cases in 60+ year-olds is presented by serotype (only for those serotypes with at least 10 cases in the selected period). In orange, the serotypes that are covered by the different vaccines are indicated. As shown, the majority of the serotypes causing IPD among the 60+ year-olds are covered by PPV23 and PCV20 as well as the PCVs in development (PCV21 and the 24-valent vaccine). Serotype 8 and serotype 19A were the most common serotypes, causing 41% of the cases in 2019-2022.

Table 3 Serotype distribution of IPD cases aged 60 years and older, in the Netherlands in the years 2019-October 2022, ordered by frequency. Orange indicates which vaccine, if any, covers the serotype. Cross protection is indicated by (x).

serotype	Freq.	% total of all known	PCV15	PCV20	PPV23	PCV21	PCV24
8	315	24		x	x	x	x
19A	225	17	x	x	x	x	x
3	115	9	x	(x)	(x)	x	(x)
22F	91	7	x	x	x	x	x
9N	73	6			x	x	x
6C	70	5	(x)	(x)		(x)	(x)
23B	43	3				x	
12F	41	3		x	x	x	x
10A	29	2		x	x	x	x
23A	29	2				x	
33F	27	2	x	x	x	x	x
15A	26	2				x	
11A	22	2		x	x	x	x
15B	21	2		x	x	(x)	x
20	17	1			x	x	x
14	16	1	x	x	x		x
16F	15	1				x	
17F	11	1			x	x	x
35F	11	1					
7C	11	1					
4	10	1	x	x	x		x

Note that 6C is likely covered by the PCVs through cross-protection by 6A and for PCV21, 15B through cross-protection of 15C. Note that the serotype 20 antigen in PPV23 (20A (11)) and the 24-valent vaccine (serotype 20B) are not identical. In surveillance, no distinction is made between these variants.

2.2 Death due to invasive pneumococcal disease in older adults

Information on survival has been retrieved for the 60+ year-olds that were diagnosed by the sentinel laboratories, and was available for 95% of the cases in 2012-May 2016 (12). Of these, 16% (n=305) of the cases had died. Although information on outcome (survival/death) after IPD is gathered through the notification system, these data are not complete, among others because notification is only done shortly after diagnosis. The serotypes that had the highest case fatality (CF) of those with minimally 20 cases aged 60+ years in the period 2012-2016 were serotypes 19F (n=9 deaths, CF 45%), serotype 17F (n=9, CF=41%), serotype 23A (8, CF=28%) and 35F (n=6, CF=25%). In absolute numbers, serotype 19A (n=45 deaths, CF=19%), serotype 8 (n=41, CF=11%), serotype 3 (n=23, CF=16%) and serotype 7F (n=15, CF=8%) caused most deaths among the 60+ year-olds in this period; all these are covered by PPV23 and PCV20 as well as by PCV21 and the 24-valent vaccine. Note, however, that the numbers per serotype are small and therefore have large uncertainty. Generally, death attributable to pneumococci increases with age (12, 13), with the incidence being more than 10 times higher among the 70+ compared to the 50-69 year olds, independent of comorbidities (14, 15). Mortality is increased after IPD up to (at least) 5-year post-infection, with long-term mortality at 1 and 5

years being 16% and 39% as compared to 3% and 15% in the age- and sex-matched persons (13).

2.3 Pneumonia

Based on hospital discharge data (International Statistical Classification of Diseases and Related Health Problems, ICD10; J13), the number of pneumococcal pneumonia hospitalisations per year among the 50+ year-old population was estimated at around 2500 in pre-COVID-19 years (2015-2018) (8, 16, 17). These numbers will be an underestimation of the real number because of the challenging diagnostics. When looking at community acquired pneumonia (CAP), depending on the method used, about 11-32% of CAP cases can be attributable to pneumococci; when including optimal testing in post-PCV13 countries, this was 17% (95%CI 10-24) (14). Of those pneumococcal CAP cases, 67% (95%CI 62-72) were caused by PPV23 serotypes.

2.4 Carriage

High density pneumococcal carriage is most common among children. Hence children are considered the main reservoir of pneumococci and the primary driver of pneumococcal transmission in the population (18). In line with this, pneumococcal carriage in older adults is associated with exposure to young children (19, 20). Carriage rates in older adults are assumed to be low (19), but there is ample evidence that the low-density asymptomatic carriage prevalence is underestimated in older adults (21, 22). This is because the 'paediatric approach' of culturing nasopharyngeal swab is not sensitive enough for carriage studies in adults; pneumococcal detection in this population requires extensive testing of additional respiratory samples and combining conventional diagnostics with molecular methods in order to pick up also low density carriage (22). With the combined approach, it was found that 22% of the asymptomatic community-dwelling 60+ year-old population in the Netherlands carried pneumococci in 2007-2008 (23). In the 2011-2012 respiratory infection season, 1/3 of older adults with symptoms of influenza-like illness carried pneumococci (24). In the latter study, the serotype distribution of carriege isolates resembled that in (PCV7)-vaccinated infants in the Netherlands in 2010/2011 (25). In the SARSliva study performed in the Netherlands in October 2020-January 2021 among SARS-CoV-2 positive households, serotype 8 was the 3rd prevalent serotype in adults while this was the 9th in children; overall 121 pneumococcal carriers were observed in this study. Serogroup 15 was relative more prevalent in adults than in children (26).

2.5 Severe pneumococcal disease in medical risk groups

After infancy and early childhood, IPD incidence in adults becomes high again in the 60+ year-old population and increases further with age, even in the absence of medical risk conditions (27). However, it has been shown that the risk for IPD is about similar for older adults (here defined as those aged ≥65 years) as for younger individuals with a medical risk condition (27, 28). The actual risk at IPD differs between medical risk groups (28-30); overall with e.g. a more than 10-fold increased IPD incidence in immunocompromised compared to immunocompetent persons; a 6-fold increase compared to healthy controls was found in those with chronic inflammatory diseases, in solid organ transplant

recipients the incidence was >40 times increased and in stem cell transplant recipients >60 times according to a systematic review and meta-analysis (30). A Norwegian population-based study including 257,924 individuals compared older individuals (65+) with younger individuals. They showed that among individuals aged 5-64 years old *with* a high-risk medical condition, the incidence of IPD was (much) higher than the incidence among older adults *without* medical risk conditions (27). The high-risk conditions included immunodeficiency, HIV, asplenia, chronic kidney disease, nephrotic syndrome, haematologic malignancies, generalised malignancies and transplantation. For (younger) adults with medium risk conditions (CSF leakage, cochlear implant, chronic heart disease, chronic lung disease, diabetes mellitus, chronic liver disease, other malignancies or alcoholism but no immunosuppressive condition), the IPD incidence was only slightly below that for older adults without medical risk conditions (27). About similar results have been shown in the US (28). So, apart from age, individuals with these medium and high risk medical conditions are at equal or higher risk than older adults. Those with highest risk of IPD are susceptible for a wider group of serotypes including those that are known to, generally, have a lower invasive capacity in the general population (27, 31, 32). Otherwise, apart from severe illness requiring hospitalisation, healthcare utilisation and mortality remain increased for at least 3 years in patients with underlying medical conditions after being hospitalised with CAP (33).
See below for an overview of the chronic medical conditions that are generally seen as being risk conditions for IPD regardless of age and for which many countries have pneumococcal vaccine recommendations (34-38):

- Chronic heart disease
- Chronic liver disease
- Chronic respiratory disease
- Chronic kidney disease
- Congenital or acquired immunodeficiencies
- CSF leakage
- Cochlear implant
- Diabetes mellitus
- (Functional) asplenia
- Haematological cancer
- Generalised malignancy
- HIV infection
- Iatrogenic immunosuppression
- Solid organ transplantation
- Stem cell transplantation

Note that in the Netherlands, pneumococcal vaccination is advised for several medical risk groups (38) but currently only covered by health insurance for a limited number of high risk groups (39, 40). This will likely be addressed in the coming years (41).

3 Pneumococcal vaccination

Several pneumococcal vaccines are available (Table 4): a 23-valent polysaccharide vaccine (PPV23; Pneumovax) as well as conjugate vaccines with a different number of largely overlapping serotypes. PCV7 (Prevnar) was the firstly available conjugate vaccine, and introduced in the Netherlands for infants in 2006, but this vaccine has been replaced on the market by the more valent PCV13 vaccine (Prevnar 13) and is therefore no longer available. PCV13 is licenced for all aged (starting from 6 weeks (42)). PCV10 (Synflorix) is used in the childhood vaccination programme in the Netherlands since 2011, but is not licensed for use in adults. Recently PCV15 (V114, Vaxneuvance) and PCV20 (Apexxnar) have been licensed for use in all 18+ adults including elderly. These PCVs share the same serotypes, but in the higher-valent vaccines, more serotypes are included. Note that PCV15 is also licenced for younger age groups (from 6 weeks onwards (43). PPV23 includes most serotypes; it includes all PCV20 serotypes except for serotype 6A, and additionally serotypes 2, 9N, 17F and 20. Note that the PCVs that include 6A (PCV13, PCV15, PCV20) likely also cover 6C, through cross-protection of the 6A antigen (44, 45). PPV23 does not cover 6A.

At least two higher-valent pneumococcal vaccines, PCV21 (V116) and a 24-valent vaccine (AFX3772), are in clinical development. PCV21 covers quite different serotypes compared to the other PCVs and PPV23 (see Table 4). This complementary range of serotypes aims to cover present residual disease in the adult population in settings with a well-established childhood vaccination programme. The 24-valent vaccine covers the PPV23 serotypes, except that the serotype 20 antigen is not identical to PPV23 (Table 4), as well as serotype 6A. Furthermore, it uses a different technology called MAPS (multiple antigen-presenting system (46)) to fuse the serotypes with a genetically conserved pneumococcal surface protein. The pneumococcal protein may provide additional, non-serotype-specific protection but clinical effects are still to be determined. A phase 3 clinical development program with 6 RCTs randomised clinical trial (RCT) for PCV21 has started in July 2022 (5); MSD cannot yet say when licencing of PCV21 may be expected. For the 24-valent vaccine, phase-1/2 RCTs have been performed but phase 3 has not yet started (47). GSK hopes that the 24-valent vaccine may be on the European market in 2026-2028.

Serotype independent vaccines such as protein vaccines, recombinant vaccines and inactivated whole cell vaccines are being developed but still face considerable challenges and will not be available on the market in the near future (48).

Table 4 Serotypes that are covered by each of the licenced vaccines. Note that PCV7 is no longer on the market, and that PCV10 is licenced for children but not for adults. PCV21 and the 24-valent vaccine are not available on the market yet.

	4	6B	9V	14	18C	19F	23F	1	5	7F	3	6A	19A	22F	33F	8	10A	11A	12F	15B	2	9N	17F	20*	15A	15C	16F	23A	23B	24F	31	35B
PCV7	X	X	X	X	X	X	X																									
PCV10	X	X	X	X	X	X	X	X	X	X																						
PCV13	X	X	X	X	X	X	X	X	X	X	X	X	X																			
PCV15	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																	
PCV20	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X												
PPV23	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X								
PCV21										X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X
24-valent vaccine	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								

*The serotype 20 antigen in PPV23 (20A (11)) and the 24-valent vaccine (serotype 20B) are not identical. In surveillance, no distinction is made between these variants.

3.1 Vaccine uptake among older adults in the Netherlands

Between fall 2020 and beginning of 2022, PPV23 has been offered via the general practitioner (GP) to adults born between 1941–1952. Among these first vaccinated cohorts the vaccine coverage was estimated to be 73–74% based on sentinel GPs, but with substantial variation between GP practices: generally the coverage was between 65–85% (49, 50). Note that only about half of the sentinel GPs could be included in the analyses because of the selection criteria for registration of the vaccines. The estimates may therefore be a slight overestimation. Otherwise, it is unknown whether the vaccine coverage has been affected by the fact that vaccination was offered during the COVID-19 pandemic. Use of pneumococcal vaccination among medical risk groups is low (~20%) based on (yet) unpublished data on vaccine history of COVID-hospitalised immunocompromised patients (51).

3.2 Impact of PPV23 implementation in the Netherlands

The introduction of PPV23 vaccination during the COVID-19 pandemic complicates the evaluation of the impact as IPD incidences generally decreased as a result of the COVID-19 control measures (6, 7). Still, after the first year of PPV23 vaccination (October 2020 up to and including May 2021), an estimation of the impact of the programme was made using a controlled pre-post design (8). For those that had been invited for vaccination, 60% of IPD cases were caused by PPV23-serotypes, while among 60+ olds that were not yet invited for vaccination, this was 75%. This resulted in an odds ratio (OR) of 0.49 (95%CI: 0.30–0.84). When the estimation was corrected for the OR in the previous four seasons (1.06, 95%CI: 0.88–1.29), the impact of vaccination on PPV23-type IPD was estimated at 53% (95%CI: 18–73), showing the substantial impact of the campaign in the targeted age-group. An updated analysis of the impact over the period November 2020-September 2021 covered 445 IPD cases aged 60 years or older; 102 cases had been eligible for vaccination (52). The proportion of IPD cases caused by vaccine serotypes was 67% among the targeted age group and 76% among the 60+ year-olds that were not eligible for vaccination (born before 1941 or between 1947-1960). The resulting OR was 0.65 (95%CI: 0.41–1.0). When corrected for the OR in previous seasons, the impact was estimated at 36% (95%CI: -1–60%).

No data on the impact of PPV23 use in the Netherlands on CAP are available yet.

3.3 Immunogenicity and vaccine effectiveness in older adults

The WHO Strategic Advisory Group of Experts (SAGE) has recently summarised the most recent literature on pneumococcal vaccination in older adults in the Yellow Book (14), which was based on a systematic review done by the Scandinavian countries (53, 54). A group from CDC Atlanta used the same search but updated the information (55). The information presented here is mostly based on those documents. Although PCV15 and PCV20 were included in the immunogenicity data presented by SAGE, data of PCV7/PCV13 and PPV23 contributed most to the results described in the Yellow Book. Additional immunogenicity data therefore supplements the information for higher-valent vaccines. There is no information on vaccine effectiveness or efficacy (VE) of the higher-

valent vaccines yet. The lack of a clear correlate of protection for adults makes it more difficult to compare potential protection of the different vaccines based on immunogenicity data. Overall there seems to be a trend of slightly lower immunogenicity for PCVs including more serotypes (56), but it is unknown how this will affect the VE.

3.3.1 *Immunogenicity of PCV15*

A validated multiplex opsonophagocytic assay (MOPA) was used in clinical trials to measure serotype-specific OPA geometric mean titres (GMT) for PCV15 serotypes, at one month after vaccination (43). In previously vaccine-naïve adults aged 50 years or older, functional antibody responses to PCV15 were compared to PCV13. For 12 of the 13 serotypes that are shared between PCV15 and PCV13, PCV15 showed non-inferior responses compared to PCV13, while for serotype 3, PCV15 elicited a superior antibody response compared to PCV13 (GMT ratio between PCV15 versus PCV13: 1.60, 95%CI 1.38–1.85). The GMT ratio of the other 12 overlapping serotypes varied between 0.68 (serotype 4) and 1.23 (serotype 6B). PCV15 also elicited superior responses for the additional serotypes 22F and 33F (GMT ratio ≥7). Note that serotype 3 and serotype 22F are ranked the third and fourth serotypes causing IPD in older adults, with respectively 9% and 8% of the 60+ year-old IPD cases in the Netherlands (Table 3).

3.3.2 *Immunogenicity of PCV + PPV23*

In a study with 652 individuals aged 50+, PCV15 or PCV13 was followed by PPV23 administered at least 1 year later. For all 15 serotypes, the OPA GMTs were at least similar between groups after PPV23 vaccination despite the fact that PCV15 covers more serotypes than PCV13 (43). The results for serotypes 22F and 33F therefore indicate that sequential use of PCV15 and PPV23 with an interval of one year provides limited boosting of the PCV-induced memory B cells. The Advisory Committee on Immunization Practices (34) interpreted the serotype-specific data as higher OPA GMTs and higher percentage of seroresponders for PCV15+PPV23 compared to PCV13+PPV23. Numerically these were higher for serotypes 1, 14, 22F and 23F (57). PPV23 was administered at two, six or 12 months post-PCV (PCV15 and PCV13) and OPA GMTs were measured one month after PPV23 administration.

3.3.3 *Immunogenicity of PCV20*

In a phase-III RCT, PCV20 followed by saline placebo one month later was compared to PCV13 followed by PPV23 one month later (56). GMTs at one month after PCV13 or PCV20, but before PPV23 or placebo, measured with the opsonophagocytic activity (OPA) assay, were compared between the groups for the PCV13-serotypes. For the additional seven PCV20 serotypes, OPA GMTs at one month post-PCV20 were compared with GMTs taken one month post-PPV23. Overall, PCV20 GMTs were defined non-inferior to PCV13. OPA GMTs after PCV20 were numerically slightly lower for the PCV13 serotypes except serotypes 9V and 14 than after PCV13 in the 60+ year-old population (56). Whether the numerically lower responses have any clinical effect is currently unknown. The GMT ratio (PCV20 group versus PCV13 group) for the overlapping PCV13 serotypes varied between 0.76 (serotype 6A) and 1.0 (serotype 14) but was for most serotypes between 0.80–0.85. Except for serotype 8 (GMT ratio 0.55, 95%CI 0.49–0.62), the

additional serotypes in PCV20/PPV23 that are not in PCV13 had a GMT ratio of above 1 indicating higher GMTs after PCV20. Despite the slightly lower response for serotype 8 after PCV20 compared to PPV23, participants receiving PPV23 had higher GMTs and pre-PCV20, with 78% of participants achieving a ≥4-fold rise 1 month post-PCV20. Note that serotype 8 is the most common serotype found in IPD patients aged 60+ years in 2019-2021. Overall, PCV20 was found to be non-inferior to PCV13+PPV23 for all shared serotypes.

3.3.4 *Immunogenicity of PCV15 and PCV20 after prior pneumococcal vaccination*

The response to PCV15 in individuals that have received prior PPV23 vaccination (at least 1 year before) appeared similar to the response in previously pneumococcal vaccine-naïve adults (43). This was investigated in 253 individuals aged 65 years or older.

Serotype specific OPA GMTs after PCV20 vaccination were compared among individuals aged 65+ years that had previously been vaccinated with PPV23 (≥1 to ≤5 years) and/or PCV13 (no prespecified interval, but the most likely interval was <5 years). PCV20 elicited immune responses to all 20 vaccine serotypes, but functional antibody responses were numerically lower in participants with PPV23 or with PCV13+PPV23 prior to PCV20 compared to PCV13 only prior to PCV20 (56).

If PCV is given ≤1 year after prior PPV23 vaccination, reduced responses have been observed but the clinical significance of this is unknown (43).

3.3.5 *Immunogenicity of PPV23 versus PCV+PPV23*

SAGE compared immunogenicity data for PPV23 only versus PCV+PPV23. An interval of 1 year and of 4 years between PCV and PPV23 vaccinations were described. Immune response with four years between PCV13 and PPV23 appeared better than after a one year interval, but no direct comparison had been made (34). The US CDC recommends an interval of ≥1 year between PCV15+PPV23 in their recommendation as a shorter interval may lead to a weaker immune response and more side-effects (34). SAGE concluded that there appeared to be no general immunological advantage at 1-2 months post-vaccination for the shared serotypes of combining PCV with PPV compared to using PPV alone (14). Still, for some serotypes (differing between studies but including serotypes 19F, 23F, 3, 5, 6B and 9V), there appeared to be a superior response indicative of boosting (14). Similar data were observed in a Korean test-negative study (58). Combining the two different types of vaccines might still be relevant for PCV15+PPV23 to broaden the serotype coverage compared to PCV15 alone and the possibly slightly improved response for some serotypes in comparison to PPV23 alone. Such combination has been advised as alternative to PCV20, among others, in the US (34).

3.3.6 *Immunogenicity of higher-valent pneumococcal vaccines in clinical development*

The higher-valent PCV21 and 24-valent vaccine are still in clinical development but available results look promising. A phase-1/2 RCT (phase 2 for those aged 50 years or older) compared PCV21 with PPV23 (59). In the phase-2 RCT in ≥50 year olds, 520 participants were

included. Compared to PPV23, PCV21 showed non-inferiority for the 12 shared serotypes and superiority for the nine serotypes that are unique for PCV21.

In a phase-1/2 RCT among 18-64 (phase I) and 65-85 (phase II) year olds, the 24-valent vaccine but with three different polysaccharide (serotype) concentrations, was compared to PCV13 (47). Additionally, a non-randomised group of previously PCV13-vaccinated individuals aged 65-85 years old received PPV23 and was compared with the arms receiving the 24-valent vaccines. Approximately 100 older adults were included in each arm. Compared to PCV13 and PPV23, the 24-valent vaccine had higher OPA GMTs for the 24 unique serotypes, and OPA GMTs were non-inferior to PCV13 or PPV23 for the shared serotypes (47).

3.3.7 *Vaccine effectiveness of PCV versus PPV23*

For the comparison of the VE of PCV13 and PPV23, SAGE used the systematic review by Berild and colleagues, which has been updated in 2021 (53, 54). This review presents the data of a systematic search for clinical trials and observational studies published between January 1 2016 and February 2021, which resulted in nine studies on PCV13 and 22 on PPV23. Berild *et al*. referred to earlier reviews that estimated a pooled VE of PPV23 against (all-type) IPD of 73% in RCTs and of 45–59% in observational studies. However, as they stated, those pooled results were based on heterogeneous results of studies with varied designs and populations. In the updated systematic review, the estimated VE of PPV23 against all-type IPD ranged from 43% (95%CI 21–60) to 72% (95%CI 37–76), depending on the study design. The VE against vaccine-type IPD was estimated at 32% (26–38) to 59% (4–82). The lower point estimates for vaccine-type IPD than for all-type IPD can be explained by the different study settings. A more recently published Danish nationwide database study including 948,263 individuals between June 2020, and September 2021 on the effectiveness of PPV23 on IPD showed results in the same range, but as expected, the serotype-specific VE (58%, 95%CI: 21-78%) was higher than the all-type VE (42%, 95%CI: 9-63%) (60). These Danish estimates are based on short follow-up (vaccination took place during the study period).

The VE estimates for PCV13 against IPD that were presented earlier (61) were only based on the large Dutch RCT CAPiTA. This RCT included older adults without immunocompromising conditions, though including those with common comorbidities like COPD or diabetes. A VE against all-type IPD of 52% (95%CI 22-71; per protocol analysis) and of 75% (95%CI 41–91) against vaccine-type IPD (VT-IPD) were found (62). A recent non-peer reviewed meta-analysis refers to additional studies evaluating the VE of PCV13 in older adults in the US (55). They found VEs against VT-IPD ranging between 47%–68%. These estimates are slightly lower than found in CAPiTA. Overall, SAGE concluded that the evidence supports the effectiveness of both PCV13 and PPV23 against IPD in adults ≥50 years and that the VE estimates (on the short term, red.) appeared similar (14).

When looking at the serotype-specific VE against IPD, different results may be expected for the different PCVs, especially for serotype 3. Generally, the VE against serotype 3 has been lower compared to other vaccine serotypes. PPV23 has not been effective in preventing IPD caused by serotype 3 in older adults (63). Of PCV13, according to a summary of the CAPiTA papers written by the producers of the vaccine, the VE against serotype 3 pneumonia was around 60% in older adults (64). Data presented in the abovementioned meta-analysis (55) reported a VE against serotype 3 IPD of 53% (95%CI -10–80%) among PPV23-naïve adults 65+ enrolled in Kaiser Permanente Northern California insurance. Based on *in vitro* and immunogenicity studies, PCV15 is more immunogenic against serotype 3 compared to other PCVs; it is not yet known whether the increased response will have a clinical impact, i.e., whether the VE will be higher compared to PCV13 and PCV20 (43). In the Netherlands in 2019-2021, 9% of IPD cases aged ≥60 years were caused by serotype 3 (Table 3). Data of the 6A-containing PCV13 indicate that the vaccine effectively protects against serotype 6C through cross-protection (65). No age-specific VE estimates are yet available for this serotype. It can be expected that the same will be the case for the higher-valent vaccines. PPV23 does not cross-protect against serotype 6C disease.

On the VE of PPV23 against pneumonia, several reviews have been published but with different conclusions. The systematic review of Berild *et al*. and its update (54), report a protective effect of PPV23 against pneumonia. Based on trials, they reported a pooled VE against pneumococcal pneumonia of 64% (95%CI 35−80), but this was mainly driven by a Japanese trial in nursing home residents. Observational studies found diverse VE estimates, ranging from no effect to 51% (95%CI 16−71) against pneumococcal pneumonia. The VE against vaccine-type pneumonia depended on the age groups that were included in the analysis and the study design, but ranged from 0% (with the oldest individuals included) to 36% (95%CI 7−40). Since the systematic review by Berild et al., several new studies have been published. A US study investigated the VE of PPV23 against vaccine-type CAP using the urinary-antigen detection assay in a test-negative case-control study (66). They included 3686 patients. The VE estimate that they presented (14%, 95%CI -17–38) fell within the estimates presented by Berild *et al*. Similarly, a recent study in the UK using the test-negative design on the VE of PPV23 against CAP (diagnosed on urine samples) found a VE within the estimate range presented by Berild *et al*. (VE in 65+ was 20%; 95%CI -5–40) (67). Interestingly, that study found a significant VE after 5 years post-vaccination, in contradiction to other studies and to what SAGE concluded (see below). In the Republic of Korea, a multicentre test-negative case control study among 65+ studied the VE of PPV23, PCV13 and sequential PCV13+PPV23 on non-bacteraemic pneumococcal CAP (58). For PPV23 for all 65+ together, they found no effect of PPV23 against nonbacteraemic CAP (VE was 0%, (95%CI -44-30)). Note that many individuals had underlying medical conditions (80%) and/or were 75 years or older (41%).

The VE of PCV13 against all-type pneumonia, as presented in the Yellow book, ranged between 6% to 11%. The VE of PCV13 against pneumococcal pneumonia ranged from a negative VE (potentially due to

residual confounding of medical risk groups) to 31% (95%CI 10–47), and the VE against vaccine-type pneumonia was estimated between 38% and 71% (14, 53). In the RCT CAPiTA, a VE of 31% (95%CI 10-47) against pneumococcal pneumonia and of 46% (95%CI 22–63) against vaccine-type pneumonia was found (62). The abovementioned Korean study (58) was not yet included in the systematic review. Based on 167 pneumococcal CAP patients and 1358 non-pneumococcal CAP patients, they estimated a VE of 39% (95%CI, −13%−67%) for PCV13, which is quite similar to CAPiTA (31% (95%CI 10–47)).

Overall, SAGE concludes that both PPV23 and PCV13 show effectiveness against pneumococcal pneumonia. The evidence of PCV13 against non-bacteraemia pneumonia was clear, while for PPV23, this was suggestive to be in the similar range (Table 5).

Table 5 Ranges of vaccine effectiveness point estimates for older adults (including 50+ years in some studies) as discussed above. Negative VEs are here presented as zero effect (0%). The estimates are derived from different studies.

Vaccine effectiveness against:	**PPV23**	**PCV13**
All serotype IPD	43% to 72%	47% to 59%
Vaccine-type IPD	32% to 59%	47% to 75%
All cause pneumonia	8%	6% to 11%
Pneumococcal pneumonia	0% to 64%	0% to 39%
Vaccine-type pneumonia	0% to 36%	38% to 71%

3.3.8 *Effect of age at time of vaccination on the immunogenicity and vaccine effectiveness*

The age of a person when being vaccinated affects the immune response and subsequently the VE (14). In the structured literature review of SAGE on the immunogenicity of PPV23 and PCV13, 44 studies were included for adults aged 50 years or older. Overall, OPA GMTs were higher with younger age of vaccination, but with much variation between studies. Especially in individuals aged 75 years and older, the OPA GMTs were lower than at younger age. Such decreases with age of vaccination was not observed for IgG responses.

The systematic review of Berild *et al*. looked at the effect of age of vaccination on the VE. They included five studies on PPV23 (pneumonia and IPD) and two studies on PCV13 (both pneumonia). Because of inconsistent use of age-groups between the studies, it was difficult to make a clear comparison of the VE by age. However, for PPV23, the VE against IPD seemed to decrease with increasing age and only one study found a significant protective effect at the age of ≥85 years (for VT-IPD) (68). Note that in this latter study, time since vaccination was short, and estimates reflect therefore VEs without significant waning. For the age-group 65-74 years, the pooled VE estimate of PPV23 against IPD was 33% (95%CI 21–43), for the 75-84 year olds, the VE was 25% (95%CI 9–38) and for the ≥85 years, the VE was 28% (95%CI 15–39) based on four indirect cohort studies (14). No effect was found for individuals above 75 years old in case-control studies. For PCV13, SAGE refers to a

post-hoc modelling analysis that estimated a VE against IPD of 65% at 65 years old, 40% at 75 years old and 0% at 85 years old (14).

For pneumococcal pneumonia, a VE of around 35% was found for PPV23 in those aged 65-74 years. Non-significant or negative VE estimates against pneumococcal pneumonia were found for PPV23 among those aged 75 years and older; residual confounding of medical risk conditions may be an explanation for the negative VE. For PCV13, no age-specific VE estimates for pneumonia were included in the Yellow book. Berild *et al*. reported that one study found a decreasing VE against pneumonia with age while another did not find any difference. The recent Korean study found a (substantially) higher VE against pneumococcal pneumonia of PCV13 at 65–74 years (VE 66%, 95%CI 1–87) compared to at age ≥75 years (14%, 95%CI -83–60) (58). A substantially higher VE for the younger age group was especially found for sequential use of PCV13+PPV23. This combination had a VE against pneumococcal non-bacteraemic CAP of 80% (95%CI 14-95) in 65-74 year olds but of -18% (95%CI -160–46) in 75+ year olds (58). Note however that the difference was smaller for VT-CAP (combination of bacteraemic, i.e., IPD, and non-bacteraemic disease): 64% (95%CI -186–95) in 65–74 years and 25% (95%CI -233–83) in 75+, but 95%Cis are large and include 0.

Based on the available data, overlapping VE estimates are observed for PPV23 and PCV13 for IPD and pneumonia, and VE estimates decrease by increasing age of vaccination. It is uncertain whether PPV23 induces an effective response above 80 years despite some studies showing some effectiveness above that age. For PCV13, data on the immune responses and effectiveness of the vaccine are yet still lacking for those above 80 years old.

3.3.9 *Effect of time since vaccination*

In the Yellow Book, the comparison of immunogenicity data reporting on waning of antibody responses reports heterogenous results, and clinical significance is unclear. Overall, OPA antibody levels were lower at 12 and 24 months compared to 1 month post-vaccination, but they did not find an effect of age on the reduction in antibody at 12 or 24 months (14). For the higher-valent vaccines, waning with time since vaccination was observed for PCV15, but the levels of all PCV15-serotypes remained above baseline level up to follow-up at 12 months (43). Waning as measured by OPA GMTs and IgG GMCs was generally comparable between PCV13 and PCV15 at month 12 for the 13 shared serotypes. For PCV20, no data on the persistence of the immune response was available.

Follow-up data for the VE of PPV23 is available up to ≥10 years for older adults, as reported in the Yellow Book. Generally, the different studies showed a decrease in VE already in the first few years. Between age-groups, no difference in decline was observed. Because of the decline in VE, the revaccination interval is set at 5 years in the Netherlands as well as in several other countries.

For PCV13, few VE estimates are available, except for the CAPiTA study where the mean duration of follow-up was 4 years. Note that the CAPiTA

study excluded (most) immunocompromised individuals. Within the time of follow-up up to 5 years, no decline in protection was observed against vaccine-type pneumococcal pneumonia, pneumococcal pneumonia, or vaccine-type IPD.

3.3.10 *Effect of revaccination*

Because of waning (see above), revaccination with PPV23 is advised for older adults. As hypo-responsiveness can occur when two PPV23 are given at a short interval (69), revaccination with PPV23 should not within one year. When revaccinating ≥5 year after primary PPV23 vaccination, no hypo-responsiveness is seen based on immunogenicity data (70, 71). The Dutch recommendation based on VE and immunogenicity is therefore to re-vaccinate every 5 years to prevent hypo-responsiveness and increase VE. Revaccination with PPV23 does not provide a booster-response, as PPV23 induces a mainly T-cell independent response resulting in weak B cell memory. The response after revaccination may be lower than the initial response, but this seems mainly to be because of the higher age at vaccination and not due to hypo-responsiveness (70-72).

Currently, little knowledge of revaccination with PCV is available. However, because of slower waning of immune responses, revaccination after PCVs may only be needed after 10-15 years. Revaccination with PCV is expected to provide a booster response, at least for several serotypes (73, 74). As individuals will be older at time of revaccination, the fact that PCV induces a booster response unlike PPV23, may be more relevant; it can be hypothesized that the immune response after revaccination with PCV will be increasingly better than PPV23 at increasing age.

3.4 Vaccine responses in medical risk groups

In medical risk groups that are immunosuppressed, vaccine responses can be diminished compared to immunocompetent individuals (75-77). For e.g. people living with HIV, that use immunosuppressive medication or individuals that have undergone allogenic stem cell transplantation, PPV23 only provides limited protection but with a PCV given alone or in combination with PPV23, higher antibody titres can be achieved (76, 78-80). Note furthermore, that waning occurs (76). Also in other risk groups, PCVs are more immunogenic then PPV23 (81, 82).

Immunogenicity results of PCV15 in individuals with immunosuppressive disease (RCT among 300 individuals living with HIV (83)) or immunocompetent adults with medical risk conditions (84) have shown promising results, with antibody responses to all 15 vaccine-serotypes. For PCV20, no studies are yet available for individuals with immunosuppressive conditions, but studies have been performed in immunocompetent individuals with stable underlying conditions (chronic cardiovascular disease, chronic pulmonary disease, renal disorders, diabetes mellitus, chronic liver disease). Substantial increases in OPA GMTs were observed in this group at 1 month post-PCV20 (85), but generally, OPA GMTs were slightly lower after PCV20 than after PCV13 in individuals with medical risk conditions (56). Clinical relevance of these lower values is not yet known.

We did not find comparative vaccine effectiveness data of PPV23 versus a PCV in medical risk groups. Based on the immunogenicity data of lower-valent vaccines, it may be expected that the (higher-valent) PCVs provide better protection in (immunosuppressed) medical risk groups than PPV23.

3.5 Potential effects on pneumococcal carriage in adults

The use of PCVs in infants has been shown to affect pneumococcal carriage (25, 86). The decrease in vaccine-type carriage indirectly protects other age groups from IPD (12). The current PCVs show little effect against serotype 3 carriage and thus induce no indirect protection against this serotype. It is assumed that PPV23 vaccination does not affect carriage (for a longer time) and therefore offers no indirect protection of PPV23 among older adults have been described.

In the RCT CAPiTA, carriage among older adults after PCV13 was only temporarily decreased at 6 months post-PCV13 but returned to values as observed in controls by 12 and 24 months post-PCV13(87). Contradictory, an effect of PCV13 vaccination on carriage in older adults was suggested in a study performed in the US, where PCV13 vaccinated older adults had lower carriage rates than non-PCV13 vaccinated age-matched individuals (88). Whether potential vaccine-induced effects on carriage will affect transmission between older adults needs to be investigated. Currently, indirect protection of non-vaccinated older adults are expected to be limited.

3.6 Safety / reactogenicity

PCV15, PCV20 and PCV21 have an acceptable safety profile that is quite similar to PCV13. Safety of PCV15 has been assessed in clinical trials including 7,136 adults of which 2,478 individuals aged 65 years of age and older (43). The most commonly reported side-effects were: injection-site pain (65%), fatigue (23%), myalgia (21%), headache (17%), injection-site swelling (16%), injection-site erythema (11%) and arthralgia (8%). Older adults reported fewer adverse reactions than younger adults.

Reactogenicity of PCV20 has been investigated in 2131 individuals aged 60 years and older in a phase-III RCT (56). The most common adverse events were pain at injection site (55%), myalgia (39%), fatigue (30%), headache (22%), and arthralgia (13%). No safety signals were identified andno new adverse reactions compared to PCV13. In those aged 65+ years who had received prior PCV13 (+ PPV23) vaccination, pain at injection site was reported by 61% and arthralgia was reported by 17% in those previously vaccinated with PCV13 followed by PPV23.

Safety of PCV21 in older adults was assessed among 520 individuals aged 50 years and older (59). No vaccine-related serious adverse events or vaccine-related deaths were observed and the most frequently reported systemic adverse event was fatigue (19%) followed by head ache (17%). Similarly, the 24-valent vaccine was well-tolerated in the approximately 300 previously vaccine-naïve individuals (47).

Repeated vaccinations can lead to more side-effects. PPV23 revaccination was associated with more local and systemic adverse events than at primary vaccination, but these were usually mild and self-limiting (joint pain, fatigue, headache, swelling) (71, 72). For PPV23, fewer side effects where found when revaccinating more than 5-years post-primary vaccination compared to at shorter intervals (71). Whether repeated vaccination with PCV after e.g. 10 years will show the same in older adults, is yet unknown.

4 Connection between childhood vaccination and the preventive potential of adult vaccination

The impact that the different pneumococcal vaccines can have in the adult population are highly dependent on the epidemiology in children and therefore, the choice of the vaccine in the NIP. This dependency results from herd immunity of vaccine-serotypes and serotype replacement ((9, 12), see below). Currently, PCV10 is used in the Dutch NIP. PCV13 has available for children since 2010 and since recently, PCV15 has been licenced for children in the EU (5, 43). PCV20 may be licenced for use in children in 2023. Pfizer, the manufacturer of PCV13 and PCV20, already announced that PCV13 will be replaced with PCV20 and PCV13 will therefore no longer be available in the near future after licensure PCV20 for children.

The European PSERENADE project, to which the Netherlands has contributed, has shown substantial indirect effects on IPD in elderly of the different PCVs used in NIPs in several countries (9). IPD in adults caused by serotypes included in the PCVs used in infants was largely prevented by the vaccines, but due to serotype replacement, there was only some to no decrease in all-type IPD in adults, though data varied to some extent by country. If a higher-valent PCV will replace PCV10 in the NIP for infants, it is expected that indirect protection will reduce the VT-IPD incidence in the whole population again. However, similar to currently applied lower-valent vaccines such as PCV10 and PCV13, colonization by non-vaccine serotypes is expected to increase if higher-valent vaccines are used in the NIP (86). Indirect protection takes approximately 2-3 years longer than for children, and the serotype distribution/serotype replacement had become stable after about seven years post-implementation (9, 89). Whether or not the overall impact, resulting from direct and indirect protection and serotype replacement, will ultimately result in less disease depends on the invasive capacity of the serotypes (90), which differs between age groups and risk groups (27, 31). The resulting serotype coverage of the different vaccines in older adults will therefore depend on the size of the indirect effects and the (invasive capacity of the) replacing serotypes. In case that a higher-valent PCV will be implemented in the NIP, the proportion of IPD cases among older adults that are caused by that vaccine or lower-valent PCVs may become so low that vaccination of older adults with these same vaccines may become redundant in the future.

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