Superior
Health Council

Vaccination against Pneumococcal Disease in Adults

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ADVISORY REPORT OF THE SUPERIOR HEALTH COUNCIL no. 9842

Vaccination against Pneumococcal Disease in Adults

In this scientific advisory report, which offers guidance to public health policy-makers, the Superior Health Council of Belgium provides **updated recommendations for pneumococcal vaccination in adults**.

This version was validated by the Board on November 5, 2025[1]

At the time of publishing this advisory report, PCV21 is not available on the Belgian market.

I INTRODUCTION

The evolving epidemiology of invasive pneumococcal disease in Belgium and the increasing serotype coverage by vaccines necessitates updated guidelines for adults. Following the 2024 resurgence of pneumococcal infections to 2,120 cases – the highest in a decade – and significant shifts in serotype distribution, the Superior Health Council (SHC) presents revised recommendations that substantially simplify adult pneumococcal vaccination strategies.

Current surveillance data demonstrate that serotypes not covered by previously recommended vaccines now represent a substantial disease burden, with serotype 12F accounting for 18.9% of cases and emerging serotypes like 9N and 24F gaining prominence. The theoretical serotype coverage varies by age group, with the novel PCV21 currently providing 78.5% coverage in adults ≥65 years compared to 67.6% for PCV20, while PCV20 offers superior coverage in younger adults due to serotype 4 prevalence.

The revised guidelines introduce three major paradigm shifts from the 2022 recommendations. First, a single-dose conjugate vaccine approach eliminates the sequential PCV13/15 + PPV23 regimen for most patients, reducing implementation complexity and potentially improving uptake. Second, an age-stratified vaccine selection strategy recommends PCV20 for adults aged 18-49 years with risk conditions, either PCV20 or PCV21 for adults aged 50-64 years with risk conditions, and either PCV20 or PCV21 for all adults aged ≥ 65 years, with a preference for PCV21 once the age of 85 is reached. Although PCV21 is preferred for certain categories, vaccination should not be delayed until it is commercially available. PCV20 is recommended as an acceptable alternative in case of PCV21 unavailability. Third, routine

[1] The Council reserves the right to make minor typographical amendments to this document at any time. On the other hand, amendments that alter its content are automatically included in an erratum. In this case, a new version of the advisory report is issued.

revaccination is no longer recommended, reflecting the superior immunological memory provided by conjugate vaccines.

Target populations have been expanded to include newly identified high-risk groups such as welders and individuals experiencing homelessness, based on recent epidemiological evidence. The simplified approach addresses the persistently low vaccination coverage among at-risk populations while providing broader serotype protection against contemporary pneumococcal strains circulating in Belgium.

II CONCLUSIONS AND RECOMMENDATIONS

1 Target Groups for Pneumococcal Vaccination

1.1 Adults 18-64 Years with Risk Conditions

Category	Indications
Immunocompromising Conditions	• Primary immunodeficiency • HIV infection • Hematopoietic malignancy • Active chemotherapy or radiation therapy • Immunosuppressive medications • Anatomical or functional asplenia • Sickle cell disease • Hemoglobinopathies
Anatomical Risk Factors	• Cochlear implant • Cerebrospinal fluid leak
Chronic Heart Disease	• Congestive heart failure • Coronary artery disease • Cardiomyopathies
Chronic Lung Disease	• COPD • Asthma • Chronic bronchitis • Emphysema • Current smoking • CF/NCFB (including PCD)
Chronic Liver Disease	• Cirrhosis • Chronic hepatitis • Alcoholism
Chronic Kidney Disease	• Stage 3-5 CKD • End-stage renal disease • Nephrotic syndrome
Neurological Conditions	• Chronic neurological disorders with aspiration risk • Neuromuscular disorders • Seizure disorders
Metabolic Disorders	• Diabetes mellitus
Environmental/Occupational	• Homelessness • Welder

1.2 Adults ≥65 Years

All adults ≥65 years regardless of other risk factors, no upper age limit.

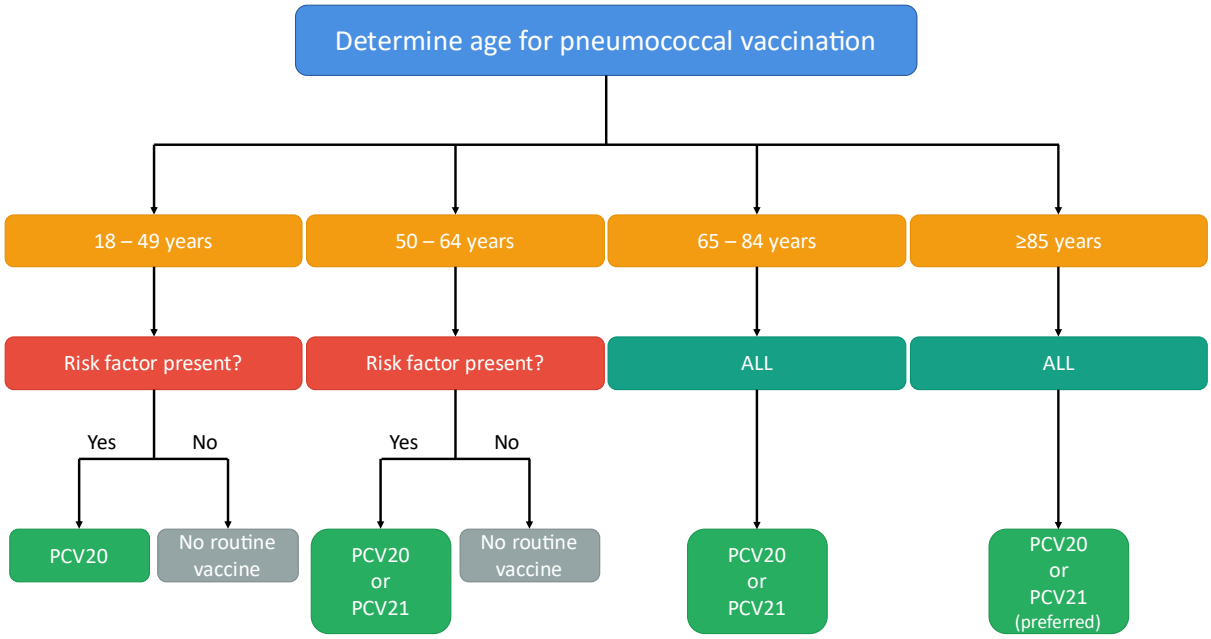
2 Vaccination Strategy

- Single-Dose Conjugate Vaccine Approach
- Eliminates PPV23 from routine vaccination protocols
- No revaccination required after the conjugate vaccines PCV20/PCV21

2.1 Age-Stratified Vaccine Selection

Age Group	Population	Vaccine Choice
18-49 years	With risk conditions	**PCV20**

50-64 years	With risk conditions	**PCV20 or PCV21**
≥65 years	ALL	**PCV20 or PCV21** **PVC21 is preferred for ≥85 years** Although PCV21 is preferred for ≥85 years, PCV20 is recommended as an acceptable alternative in case of unavailability.



2.2 Revaccination Schedule for Previously Vaccinated Adults

Previous Vaccination	**Next Vaccine**	**When to Give**
PPV23 only (any number of doses)	PCV20 or PCV21	≥1 year after last PPV23
PCV13 or PCV15 only	PCV20 or PCV21	≥1 year after PCV13 or PCV15
PCV13 or PCV15 → PPV23	Consider PCV20 or PCV21	≥5 years after PPV23
PCV20 or PCV21	None needed	---

2.3 Key Implementation Remarks

- Co-administration with other age-appropriate vaccines is acceptable
- Regular assessment during routine clinical encounters (e.g., annual influenza vaccination)
- Unknown vaccination history: Administer PCV20 or PCV21 as if vaccine-naïve
- Immunocompromised patients: Individual assessment for earlier revaccination if severely compromised

Keywords

Keywords	**Sleutelwoorden**	**Mots clés**	**Schlüsselwörter**
Pneumococcal disease	Pneumokokkenziekte	Maladie pneumococcique	Pneumokokken-Erkrankung
Invasive pneumococcal disease	Invasieve pneumokokkenziekte	Infection pneumococcique invasive	Invasive Pneumokokken-Erkrankung
PCV20	PCV20	PCV20	PCV20
PCV21	PCV21	PCV21	PCV21
PPV23	PPV23	PPV23	PPV23
Adult vaccination	Vaccinatie van volwassenen	Vaccination adulte	Erwachsenenimpfung
Serotype coverage	Serotype dekking	Couverture sérotypique	Serotyp-Abdeckung
Immunocompromised	Immunogecompromitteerd	Immunodéprimé	Immungeschwächt
Conjugate vaccine	Geconjugeerd vaccin	Vaccin conjugué	Konjugat-Impfstoff
Streptococcus pneumoniae	Streptococcus pneumoniae	Streptococcus pneumoniae	Streptococcus pneumoniae

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IV METHODOLOGY

After analysing the request, the Board and, when appropriate, the Chair of the area Vaccination (NITAG) identified the necessary fields of expertise. An *ad hoc* working group was then set up which included experts in Internal Medicine, Infectious Diseases & Infectiology, Vaccinology, Epidemiology, Clinical & Medical Microbiology, Occupational and Environmental Medicine and Geriatrics. The experts of this working group provided a general and an *ad hoc* declaration of interests and the Committee on Deontology assessed the potential risk of conflicts of interest.

This advisory report is based on a review of the scientific literature published in both scientific journals and reports from national and international organisations competent in this field (peer-reviewed), as well as on the opinion of the experts. No pharmaco-economic analysis was performed.

Once the advisory report was endorsed by the working group and NITAG, it was ultimately validated by the Board.

V ELABORATION AND ARGUMENTATION

List of abbreviations used

Abbreviation	Full Form
ACIP	Advisory Committee on Immunization Practices
aVE	Adjusted vaccine effectiveness
CAP	Community-acquired pneumonia
CDC	Centers for Disease Control and Prevention
CF/NCFB	Cystic fibrosis / Non-Cystic Fibrosis Bronchiectasis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease of 2019
CSF	Cerebrospinal fluid
EUCAST	European Committee on Antimicrobial Susceptibility Testing
ESRD	End-stage renal disease
GMT	Geometric mean titre
HIS	Health Interview Survey
HIV	Human immunodeficiency virus
IPD	Invasive pneumococcal disease
LRTI	Lower respiratory tract infections
MIC	Minimum inhibitory concentration
NIPD	Non-invasive pneumococcal disease
NRC	National Reference Centre
OPA	Opsonophagocytic activity
OR	Odds Ratio
PCD	Primary Ciliary Dyskinesia
PCV10	10-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PCV15	15-valent pneumococcal conjugate vaccine

PCV20	20-valent pneumococcal conjugate vaccine
PCV21	21-valent pneumococcal conjugate vaccine
PPV23	23-valent pneumococcal polysaccharide vaccine
QIV	Quadrivalent influenza vaccine
RCT	Randomized controlled trial
RR	Relative Risk
SHC	Superior Health Council
SMR	Standardized Mortality Ratio
SOT	Solid organ transplant
TND	Test-negative design
VE	Vaccine effectiveness

1 Pneumococcal Disease

Pneumococcal infections are caused by *Streptococcus pneumoniae* (pneumococcus), a gram-positive, facultative anaerobic bacterium. Pneumococcus can colonize the upper respiratory tract, most commonly in young children, and is transmitted to others through contact with respiratory droplets from a person with pneumococcal colonization in the upper respiratory tract (Weiser et al., 2018).

Certain persons with pneumococcal colonization might develop invasive pneumococcal disease (IPD) or non-invasive pneumococcal disease (NIPD) (Bogaert et al., 2004). IPD is infection of normally sterile sites, including pneumonia with bacteraemia, meningitis, osteomyelitis, septic arthritis, and bacteraemia without a focus of infection; examples of noninvasive disease include pneumonia without bacteraemia, sinusitis, or otitis media (Kobayashi et al., 2023). In adults, pneumococcal pneumonia is the most common type of pneumococcal disease, and pneumococcus is the most common bacterial cause of pneumonia that results in hospitalization (Bonten et al., 2015).

Pneumococci are classified into serotypes depending on their capsular polysaccharide, which is a main virulence factor for pneumococcus. Based on capsular typing, at least 100 serotypes are distinguished (Ganaie et al., 2021; Ganaie et al., 2020; Gingerich & Mousa, 2022).

The pathogenesis of *Streptococcus pneumoniae* begins with the colonization of the human nasopharynx, an essential step preceding invasive disease. Pneumococcal adherence to epithelial cells of the nasopharynx is facilitated by specific virulence factors, notably pneumococcal pilus 1 and surface proteins such as PspC and PspA. The neuraminidase NanA also enhances colonization by removing terminal sialic acids from host mucins, thereby exposing epithelial surfaces for bacterial attachment. Once attached, pneumococci form microcolonies or biofilms, triggering local inflammatory responses that either clear the bacteria or contribute to disease progression through tissue damage and increased transmission potential (Narciso et al., 2024).

If pneumococci escape local immune defences, they can invade deeper tissues, leading to IPDs such as pneumonia with bacteraemia, bacteraemia and meningitis. A critical factor in invasive disease is the pneumococcal capsule, a polysaccharide layer that helps evade host immune responses, particularly by inhibiting phagocytosis. Capsular polysaccharides vary greatly between pneumococcal serotypes, significantly affecting their virulence and invasiveness. Certain serotypes, e.g., 1 and 7F, act predominantly as primary pathogens, capable of causing severe invasive disease in previously healthy individuals, while other serotypes primarily colonize and are associated with opportunistic infections in immunocompromised hosts, e.g., serotype 11A (Narciso et al., 2024).

2 Epidemiology

2.1 Invasive pneumococcal disease

2.1.1 IPD incidence

In Belgium, the epidemiology of IPD has recently demonstrated significant shifts. After a notable decline during the Coronavirus Disease of 2019 (COVID-19) pandemic years (2020-2021), there has been a marked resurgence, with 2120 reported cases in 2024, exceeding pre-pandemic levels (mean of 1560 cases/year (period 2017-2019)) and representing the highest number recorded in the past decade. The increase is particularly evident among elderly individuals aged 65 years and older, primarily driven by serotypes included in the 20-valent pneumococcal conjugate vaccine (PCV20) (Desmet & Cuypers, 2025). Importantly, also the number of pneumococcal meningitis cases increased from 106 cases in 2023 to 130 cases in 2024 (Desmet & Cuypers, 2025). Surveillance data demonstrate a continued increase in IPD during 2025, with 1,631 isolates identified in the first six months compared to the typical annual burden of approximately 1,560 cases (pre-COVID-19), representing a 38% increase versus the corresponding period in 2024. Serotype distribution analysis shows serotype 12F remains predominant at 18.9%, with persistently elevated levels of serotypes 4 (6.8%) and 14 (5.0%).

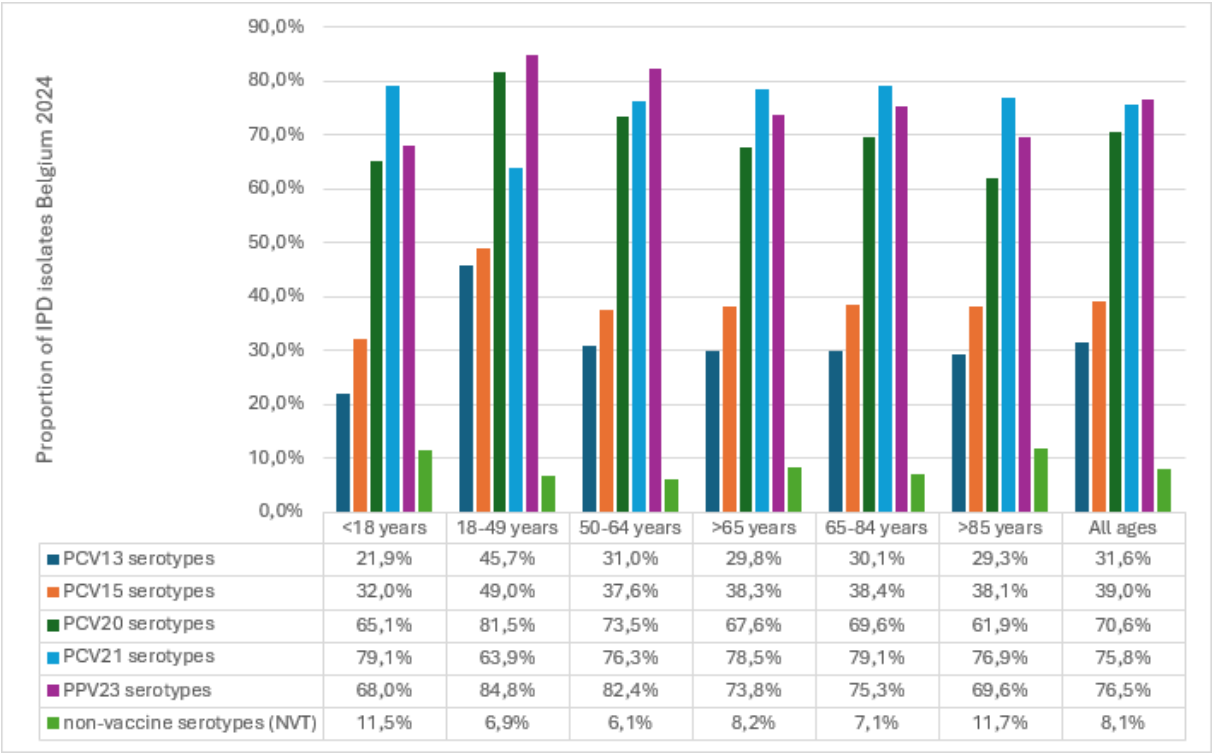
The disease predominantly manifests as pneumonia (64%) and bacteraemia (29%) in older age groups, whereas in children under 2 years, the most common presentations are bacteraemia (48%), pneumonia (36%), and meningitis (12%). In 2023 there were at least 12 deaths due to pneumococcal meningitis, 110 due to pneumococcal sepsis and 82 due to pneumococcal pneumonia (both invasive and non-invasive pneumonia), corresponding to an in-hospital mortality rate of 13%, 15% and 5% respectively (Dambre, 2024). Of note, a large proportion, up to seventy percent, of all pneumococcal bacteraemia cases occur in individuals over 50 years of age (Desmet et al., 2021). The mortality rate of pneumococcal bacteraemia is 12% in 65-year-olds and twice as high in people over 85 years of age (Ruiz et al., 2014).

2.1.2 IPD Serotype distribution

The serotype distribution among adults in 2024 shows evolving patterns and is influenced by the vaccine used in the childhood immunization program. This was illustrated in Belgian IPD data by an increase in IPD cases caused by PCV13 non-PCV10 serotypes (mainly serotype 19A) after the switch from PCV13 to 10-valent pneumococcal conjugate vaccine (PCV10) in the childhood immunization program (Cuypers et al., 2024).

Since the switch back from PCV10 to PCV13 in 2019 in the childhood immunisation programmes and following the COVID-19 pandemic, changes in serotype-specific IPD were observed. The top 6 serotypes causing IPD in the winter season 2024–2025 were all vaccine serotypes: PCV20 non-PCV15 serotypes 12F and 8, PCV13 non-PCV10 serotypes 3 and 19 A and PCV7 serotypes 4 and 14. They represent 16.4 %, 14.1 %, 10.8 %, 6.9 %, 5.8 % and 5.3 % of overall IPD cases in 2024–2025, respectively. All these serotypes were heavily reduced between 2018-2019 and 2020–2021 (ranging between −61.1 % and − 78.8 %), except for serotype 4 that started to increase. The largest increase in serotype 4 (nearly 8-fold) was observed between winter seasons 2020–2021 and 2022–2023, with most cases diagnosed in adults (18–64 years). Case numbers of IPD caused by serotypes 12F, 14 and 4 were respectively three, nearly five and more than ten times higher in winter season 2024–2025 compared to pre-COVID winter season 2019–2020. Except for serotype 19A for which lower absolute case numbers were observed post-COVID compared to pre-COVID, for all other serotypes part of the top six serotypes causing IPD in 2024–2025, the number of IPD infections has increased remarkably (Cuypers et al., 2025a).

Overall, in 2024 serotype 12F was the most prevalent, responsible for 14.6% of IPD cases. Other frequent serotypes included serotype 8 (11.5%), serotype 3 (9.4%), serotype 4 (7.7%), and serotype 19A (6.8%). Importantly, serotype distribution varied by age group. In the youngest age group (children < 2 years old) next to these serotype 12F (13.4%), 3 (6.0%) and 19A (6.0%), also serotype 24F (16.4%) and 33F (12.7%) were in the top 5 of serotypes causing IPD in 2024. Focussing on adult age groups, serotype 4 was particularly prevalent among younger adults aged 18-49 years, accounting for 21.2% of cases in this age group, while its prevalence was lower in older age groups – 11.0% among 50-64-year-olds, 4.7% in the 65-84 age group, and only 1.8% in adults over 85 years old (Desmet & Cuypers, 2025). Based on 2024 IPD data, these variations in serotype distribution by age also result in variations in theoretical serotype coverage of the different available vaccines by age group (Figure 1). In adults aged >65 years old, the highest theoretical serotype coverage was observed for PCV21 (78.5%), 23-valent pneumococcal polysaccharide vaccine (PPV23) (73.8%) and PCV20 (67.6%). In the younger adults (18-49 years old) more than 80% of IPD cases were caused by serotypes included in PPV23 and PCV20, while a lower proportion of IPD cases in this age group were caused by PCV21 serotypes (63.9%). For more detailed description of the serotype distribution, we refer to the report of the National Reference Centre (NRC) (Desmet & Cuypers, 2025).



	<18 years	18-49 years	50-64 years	>65 years	65-84 years	>85 years	All ages
PCV13 serotypes	21,9%	45,7%	31,0%	29,8%	30,1%	29,3%	31,6%
PCV15 serotypes	32,0%	49,0%	37,6%	38,3%	38,4%	38,1%	39,0%
PCV20 serotypes	65,1%	81,5%	73,5%	67,6%	69,6%	61,9%	70,6%
PCV21 serotypes	79,1%	63,9%	76,3%	78,5%	79,1%	76,9%	75,8%
PPV23 serotypes	68,0%	84,8%	82,4%	73,8%	75,3%	69,6%	76,5%
non-vaccine serotypes (NVT)	11,5%	6,9%	6,1%	8,2%	7,1%	11,7%	8,1%

Figure 1: Serotype coverage of different current authorized pneumococcal vaccines per age group based on IPD isolates received at the NRC 2024. NVT: non vaccine serotypes.

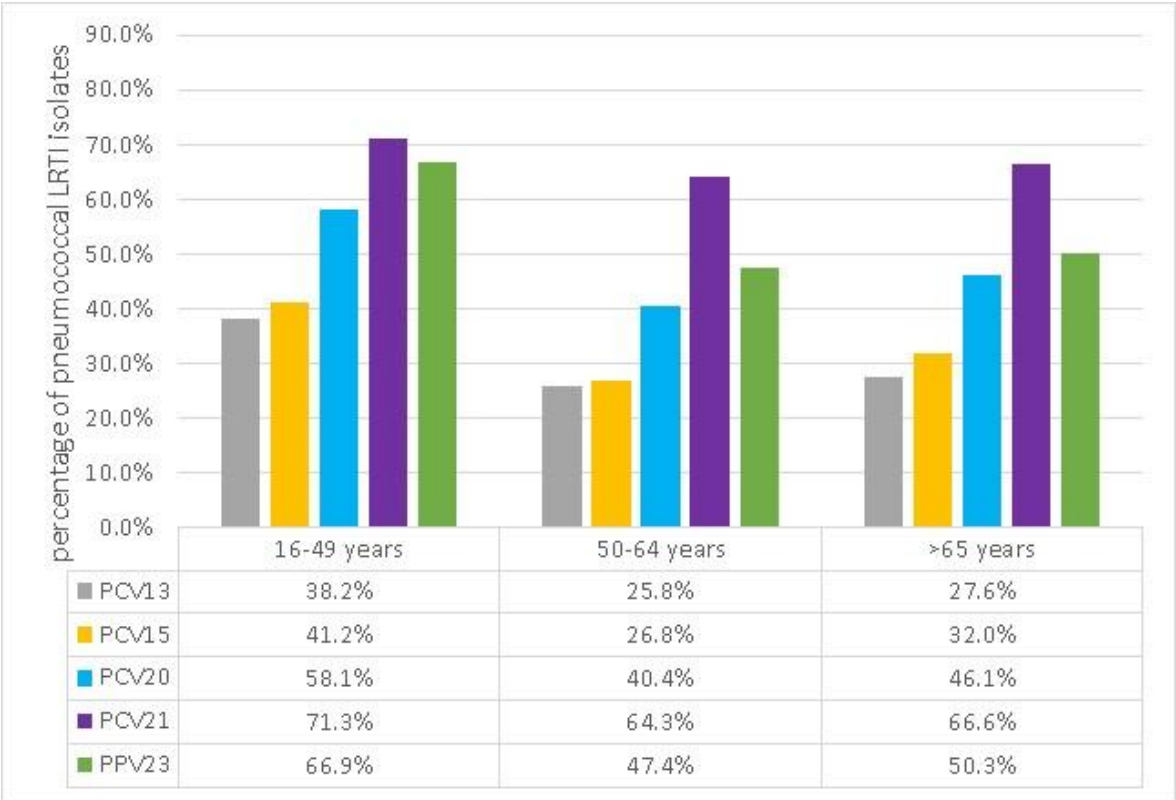
2.1.3 Antibiotic resistance

In 2024 reduced susceptibility to penicillin (Minimum inhibitory concentration (MIC) >0.06 mg/L) was observed in 318 (15.0%) of 2120 IPD strains, a slight increase from the previous year. Among these, 54 strains exhibited a penicillin MIC above 2 mg/L, corresponding to the non-meningitis resistance breakpoint. Resistance rates to cefotaxime remained stable compared to last year, with 75 strains (3.5%) showing MICs above 0.5 mg/L (European Committee on Antimicrobial Susceptibility Testing (EUCAST) meningitis resistance breakpoint). Only four strains had a cefotaxime MIC exceeding 2 mg/L, classifying them as resistant according to the EUCAST non-meningitis breakpoint. Notably, six serotypes – 24F,

23B, 11A, 6C, 19A, and 14 – accounted for 10% or more of isolates with reduced susceptibility to penicillin (Desmet & Cuypers, 2025).
For strains isolated from meningitis patients specifically (n=130), 23 (17.7%) were penicillin-resistant, 3 (2.3%) were resistant to amoxicillin, and 2 (1.5%) exhibited resistance to cefotaxime according to meningitis clinical breakpoints. Both cefotaxime-resistant isolates had MIC values close to the breakpoint (1 mg/L) and belonged to serotypes 11A and 15A. Erythromycin resistance in 2024 increased slightly to 16.7% from the previous year, while tetracycline resistance remained stable at 18.4%. Levofloxacin resistance continues to be rare, with no resistant isolates reported in 2024 (Desmet & Cuypers, 2025). Based on data from IPD cases between 2018-2023, PVC13 and PCV20-non-PCV15 serotypes are more often associated with resistance to amoxicillin and cefotaxime compared to non-PCV20 serotypes (Vermeulen et al., 2025).

2.2 Non-invasive pneumococcal disease

Although IPD is associated with more severe outcomes, NIPD is more common, and mortality rates of community-acquired pneumonia (CAP) can range from 6.4% to >40%, depending on the medical care setting (Blasi et al., 2012). Despite the disease burden of NIPD, the serotype distributions of pneumococci causing NIPD are less studied than those causing IPD due to the greater difficulty in setting up surveillance systems. In 2020 a Belgian study coordinated by Sciensano was initiated to study both serotype distribution and antimicrobial resistance of pneumococci associated with lower respiratory tract infections (LRTI's). During the period 2020-2023 serotypes 3, 6C, 1, 23B and 19A were the top 5 pneumococcal serotypes associated with LRTI's. The difference in serotype distribution between NIPD and IPD, resulted also in a lower theoretical serotype coverage for the different higher-valency pneumococcal vaccines (Figure 2) (Passaris et al., 2025).



	16-49 years	50-64 years	>65 years
PCV13	38.2%	25.8%	27.6%
PCV15	41.2%	26.8%	32.0%
PCV20	58.1%	40.4%	46.1%
PCV21	71.3%	64.3%	66.6%
PPV23	66.9%	47.4%	50.3%

Figure 2: serotype coverage of different current authorized pneumococcal vaccines per adult age group based on pneumococcal isolates associated with lower respiratory tract infections (LRTI) in Belgium (2020-2023) (Passaris et al., 2025).

3 Vaccination uptake in adults in Belgium

Pneumococcal vaccination uptake among European adults varies significantly across countries and age groups. A 2021 report highlighted that coverage rates for individuals aged 65 years and older range from 1% to 70%, with an average of 17.95% across 13 European countries (Ozisik, 2025).
Several factors appear to influence the uptake of pneumococcal vaccination, particularly socioeconomic status. Individuals from lower socioeconomic backgrounds have consistently lower odds of initiating and completing vaccination schedules as recommended (Janssens et al., 2023).

The Belgian Health Interview Survey (HIS), conducted every 4-5 years since 1997, provides comprehensive self-reported data on population health status, healthcare utilization, and preventive services uptake., including vaccination coverage. The most recent survey (2023-2024) revealed alarmingly low pneumococcal vaccination coverage among high-risk populations in Belgium. Only 13.6% of at-risk individuals (adults ≥65 years or ≥45 years with chronic conditions) received pneumococcal vaccination in the past five years, with coverage reaching just 16.0% when considering only those aged 65 and older.
While vaccination rates showed improvement from 8.6% in 2018 to 13.6% in 2023, uptake remains far below optimal levels for protecting vulnerable populations (Health Interview Survey | sciensano.be).

4 Vaccine composition of available vaccines in Belgium

Vaccine (Brand name)	Serotypes	Antigen content (per dose)	Contains adjuvant
Prevenar 13 (PCV13)	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F	2.2 µg per serotype except 6B = 4.4 µg; CRM197 carrier protein ~34 µg	Aluminium phosphate (0.125 mg Al)
Vaxneuvance (PCV15)	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F	2 µg per serotype except 6B = 4 µg; CRM197 carrier protein ~30–40 µg	Aluminium phosphate (0.125 mg Al)
Prevenar 20 (PCV20)	1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F	2.2 µg per serotype except 6B = 4 µg; CRM197 carrier protein ~51 µg	Aluminium phosphate (0.125 mg Al)
Capvaxive (PCV21 / V116)	3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, 35B	4 µg polysaccharide per serotype (conjugated to CRM197 carrier protein ~65 µg)	No adjuvant
Pneumovax 23 (PPV23)	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20A, 22F, 23F, 33F	25 µg purified polysaccharide per serotype	No adjuvant

5 23-valent polysacharidevaccine (PPV23)

5.1 Vaccine

The PPV23 is a mixture of capsular polysaccharides from 23 serotypes in invasive pneumococcal infections, each at a dose of 25 µg. PPV23 is a vaccine for deep subcutaneous or intramuscular injection.
Serotypes included in PPV23: 1, 2, 3, 4, 5, 6B, 7F,8, 9V, 9N, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20A, 22F, 23F, 33F.
The vaccine contains no adjuvant.

5.2 Registration

The PPV23 is registered for active immunization against diseases caused by pneumococcal disease in children from 2 years of age, adolescents and adults.

5.3 Immunogenicity

Although not all components of PPV23 are equally immunogenic, (functional) antibody concentrations are achieved in healthy adults and the elderly that remain higher than before vaccination 5 to 10 years after administration (Grabenstein & Manoff, 2012). In frail elderly and very elderly people (> 80 years) and in patients with an immune disorder, the antibody response after vaccination with PPV23 is lower (Hamza et al., 2012). In people between 60 and 65 years of age who have never been vaccinated with PPV23, a reduced immune response was observed when revaccinated after 4 years with PPV23 (Jackson et al., 2013). When revaccinated after five years, the functional immune response is again comparable to the primary immune response (Remschmidt et al., 2016).

5.4 Protection against invasive pneumococcal disease

A systematic review and meta-analysis by Sikjær et al., 2023, including studies from various populations and regions (Andrews et al., 2012; Djennad et al., 2019; Gutiérrez Rodríguez et al., 2014; Kim et al., 2019; Leventer-Roberts et al., 2015; Shimbashi et al., 2020; Tsai et al., 2015), reported that the PPV23 vaccine significantly reduced the odds of all-type IPD compared with unvaccinated controls (Odds Ratio [OR]: 0.69; 95% confidence interval [CI]: 0.54–0.88). The same meta-analysis also showed a reduced odds ratio for vaccine-type IPD compared to non-vaccine type IPD (OR: 0.69; 95% CI: 0.63–0.76).
Vaccine effectiveness (VE) against vaccine-type IPD, as presented in the meta-analysis by Sikjær et al., 2023, varied notably by age, with effectiveness ranging from 28% to 54.1% in individuals aged 65–79 years and from 7.5% to 34% for those aged ≥80–85 years. These findings are supported by consistent evidence from additional large retrospective case-control or cohort studies, confirming that PPV23 provides approximately 50% protection against invasive pneumococcal infections in healthy older adults between 65 and 80 years (Kraicer-Melamed et al., 2016). Other meta-analyses reinforce this observation, reporting protection ranging from 45% to 74% against IPD in healthy adults, though this protective effect is less consistent among vulnerable elderly individuals and populations with increased risk (Falkenhorst et al., 2017; Kraicer-Melamed et al., 2016; Moberley et al., 2013).
The overall vaccine effectiveness, according to Sikjær et al., 2023, was generally lower in individuals with comorbidities and immunocompromised populations compared to healthier populations. Furthermore, published studies with randomized or quasi-randomized controlled designs demonstrate conflicting results and typically involve too few patients to draw definitive conclusions.

5.5 Protection against non-invasive pneumococcal pneumonia

Data from a cohort of 2,357 hospitalized adults indicate moderate effectiveness of PPV23 in preventing pneumococcal pneumonia hospitalizations caused by vaccine-covered serotypes. Specifically, the adjusted vaccine effectiveness (aVE) against PPV23 serotype-specific pneumococcal pneumonia was estimated at 24% (95% CI: 5%–40%, p=0.02) (Lawrence et al., 2020).
In vaccine-eligible patients (n=1,768), a similar aVE of 23% (95% CI: 1%–40%) was observed, whereas effectiveness appeared reduced in older subsets: 20% (95% CI: −5%–+40%) in patients aged ≥65 years (n=1,407) and significantly lower at 5% (95% CI: −37%–+35%) in patients aged ≥75 years (n=905), highlighting potential waning immunity over time (Lawrence et al., 2020).

5.6 Pneumococcal Vaccination and Protection against Cardiovascular Events

A systematic review evaluating the impact of pneumococcal vaccines reported that PPV23 significantly reduced the risk of cardiovascular events in individuals aged 65 years and older, with a relative risk (RR) of 0.94 (95% CI: 0.89–0.99) (Addario et al., 2023).
During influenza seasons, PPV23 demonstrated effectiveness against acute exacerbations of cardiopulmonary disease, particularly during seasons characterized by poor influenza vaccine effectiveness. This protective effect was less evident during seasons with high influenza vaccine effectiveness (Song et al., 2018). Dual vaccination strategies with influenza and pneumococcal vaccines, including PPV23, were associated with reduced incidences of specific cardiovascular events such as stroke, congestive heart failure, ischemic heart disease, and myocardial infarction (Addario et al., 2023).

6 20-valent conjugate vaccine (PCV20, Prevenar 20)

6.1 Vaccine

The PCV20 is a mixture of capsular polysaccharides of 20 frequently occurring serotypes, each at a dose of 2.2 µg (4.4 µg for capsular type 6B), coupled with a carrier protein that produces a T-cell-dependent immune response. The PCV20 is a vaccine for intramuscular administration.
Serotypes included in PCV20: 1, 3, 4, 5, 6A, 6B, 7F,8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F.
The vaccine contains aluminium phosphate as adjuvant.

6.2 Registration

Active immunization for the prevention of invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* in infants, children and adolescents aged 6 weeks to 18 years. Active immunization for the prevention of invasive disease and pneumonia caused by Streptococcus pneumoniae in individuals 18 years of age and older.

6.3 Immunogenicity of 20-Valent Pneumococcal Conjugate Vaccine (PCV20) vs PCV13 and PPV23 (2023–2025 Evidence)

The cumulative evidence underscores that PCV20 offers broad serotype coverage with immunogenicity non-inferior to PCV13/PPV23, even in older adults and those with comorbidities.

6.4 Immunogenicity in Healthy Adult Populations

Multiple recent trials have compared PCV20 to the established PCV13 and the PPV23 in adults. These studies consistently show that PCV20 elicits immune responses that are non-inferior to PCV13 for all shared serotypes, and similarly robust responses to the additional serotypes when compared to PPV23 (Essink et al., 2022; Haranaka et al., 2024). In a Phase 3 trial, one month after vaccination, OPA (opsonophagocytic activity) geometric mean titres (GMTs) induced by PCV20 were non-inferior to those induced by PCV13 for the 13 overlapping serotypes; for the 7 extra serotypes (not in PCV13), PCV20's responses were non-inferior to PPV23 for 6 of 7 serotypes (failing only for serotype 8) (Essink et al., 2022). Similarly, a 2024 trial in East Asia confirmed PCV20 met immunogenicity non-inferiority criteria for all 13 PCV13-types and 6 of 7 unique types, again with serotype 8 narrowly missing the statistical threshold (Haranaka et al., 2024). Importantly, functional antibody responses (*i.e.* OPA titres) against all 20 vaccine serotypes were robust after a single PCV20 dose (Essink et al., 2022). Minor numerical differences have been observed – for example, PCV20 tended to yield slightly lower antibody titres than PCV13 for some shared serotypes, though still well within non-inferiority bounds (ACIP/CDC, 2025; Feemster et al., 2024). Conversely, for serotypes exclusively in PCV20, antibody responses were on par with or higher than those generated by PPV23 (ACIP/CDC, 2025). Overall, these trials establish that PCV20's broader antigen range does not come at the cost of meaningful immunogenicity loss for the original serotypes (ACIP/CDC, 2025; Feemster et al., 2024). The clinical significance of the modest titre differences is uncertain (ACIP/CDC, 2025; Feemster et al., 2024) and all evidence points to PCV20 providing expanded protection without compromising immune response quality.

6.5 Age Group Considerations

PCV20 has been evaluated across adult age cohorts, including younger adults (18–49 years), middle-aged adults, and seniors ≥60–65 years (Essink et al., 2022). Immune responses were strong in all groups and generally age-independent, aside from the expected lower absolute titres in the oldest adults. Immune responses in younger adults were "bridged" to older adults, confirming that those 18–49 years old mount responses that are at least as high as in 60–64-year-olds (Essink et al., 2022). Thus, PCV20 is immunogenic throughout adulthood, from young adults to the elderly, supporting its use in all adult age strata. In older adults (≥65), who can have blunted vaccine responses, PCV20 still induced high OPA GMTs for all 20 serotypes (Cannon et al., 2021). Notably, serotype 8 was the one serotype where PCV20's response fell just below the non-inferiority margin relative to PPV23 in older populations (Essink et al., 2022). Despite this, secondary analyses showed that serotype 8 responses to PCV20 were robust in absolute terms (Haranaka et al., 2024). The non-inferiority criterion (defined as a lower bound of the 95% CI for the GMT ratio >0.5) was essentially met for serotype 8 in some analyses, but just missed in others (Haranaka et al., 2024; Sabharwal et al., 2022). Apart from this single serotype, PCV20 provided uniformly strong responses in seniors, and its overall immunogenicity profile in ≥65-year-olds is comparable to that in younger adults (Cannon et al., 2021). In fact, PCV20 has been shown to elicit robust immune responses regardless of prior pneumococcal vaccination in older adults (Cannon et al., 2021). This includes individuals who previously received PCV13 or PPV23: giving PCV20 to such patients yielded high OPA titres to all 20 serotypes, indicating that prior exposure did not dampen the conjugate vaccine's immunogenicity (Cannon et al., 2021).

6.6 Immunogenicity in Special Populations (High-Risk and Immunocompromised)

<u>Chronic Medical Conditions</u>

A 2023 post hoc study pooled >1,300 adults (18–64 years) with at least one risk factor from the PCV20 clinical trials (Sabharwal et al., 2022). The findings showed substantial increases in OPA GMTs across the 20 vaccine serotypes after PCV20, with robust immune responses to all 20 serotypes in participants with chronic conditions (Sabharwal et al., 2022). PCV20 was

highly immunogenic even in those with diabetes, chronic lung disease, smokers, etc. Importantly, the relative efficacy of PCV20 vs. PCV13 was preserved in this at-risk cohort: for the 13 shared serotypes, PCV20's antibody responses remained non-inferior (Sabharwal et al., 2022). The same serotype 8 pattern was noted (slightly lower PCV20 response) in this subset (Sabharwal et al., 2022), mirroring the overall trial population. These data suggest that common medical co-morbidities do not impair the immunogenicity of PCV20 – it meets immunogenicity criteria in high-risk adults just as in healthy adults (See, 2023).

Immunocompromised Hosts (e.g. HIV, Transplant)

Data specifically in severely immunocompromised adults are still emerging. Direct studies of PCV20 in people with Human immunodeficiency virus (HIV) or transplant recipients have not yet been published as of 2025, but extrapolation from similar vaccines and early clinical experience guides expectations. It remains prudent to vaccinate immunocompromised individuals at a point of minimal immunosuppression (e.g. pre-transplant or when HIV is controlled) to maximize responses. In solid organ transplant (SOT) recipients, official recommendations now prioritize PCV20 for pneumococcal prevention (Viganò et al., 2023), though specific immunogenicity studies are pending. Given that SOT patients historically responded better to conjugate vaccines than to PPV23, PCV20 is anticipated to confer at least non-inferior, if not superior, antibody responses relative to previous PCV13+PPV23 regimens in this group. Further clinical trials are underway or needed to quantify immunogenicity in these high-risk groups.

Selected Comparative Immunogenicity Studies (PCV20 vs. PCV13 and PPV23, 2023–2025)

Study (Author, Year)	Population (Age / Risk Group)	Study Type	Vaccines Compared	Key Immunogenicity Outcomes	Special Notes
Essink et al., 2022	~3,000 healthy adults (18–49, 50–59, ≥60 years); PCV-naïve	Phase 3 RCT (pivotal trial)	PCV20 vs. PCV13; ≥60 cohort: PCV20 vs. PCV13+PPV23	PCV20 responses non-inferior to PCV13 (shared serotypes); non-inferior to PPV23 (6/7 additional serotypes; exception: serotype 8). Robust functional antibodies for all 20 serotypes.	Age-stratified responses consistent; minor numeric reductions noted for serotype 8.
Cannon et al., 2021	~1,500 adults ≥65 yrs; prior vaccination with PCV13, PPV23, or both	Phase 3 open-label RCT	PCV20 vs. PCV13 (prior PPV23-only); PCV20 vs. PPV23 (prior PCV13-only); single-arm PCV20 (prior PCV13+PPV23)	Robust immune responses (OPA) to all 20 serotypes regardless of prior pneumococcal vaccination.	Prior vaccination history did not impair PCV20 responses; suitable as a catch-up vaccine.
Haranaka et al., 2024	1,421 adults ≥60 yrs, PCV-naïve, East Asia	Phase 3 RCT (multicentre)	PCV20 vs. PCV13+PPV23 (1 mo. interval)	PCV20 non-inferior for all 13 PCV13 serotypes, 6/7 additional serotypes (exception: serotype 8 narrowly missed NI criteria).	First immunogenicity trial in East Asian populations; consistent global findings.
Sabharwal et al., 2022	1,329 adults (18–64 yrs) with ≥1 risk factor (chronic illness/smoking); subset of larger trials	Post hoc pooled analysis (RCT subset)	PCV20 vs. PCV13	Significant antibody increases post-PCV20; responses comparable to healthy cohorts. No loss of relative immunogenicity due to chronic conditions.	Highlights PCV20 effectiveness in at-risk populations; excludes severely immunocompromised individuals (HIV/transplant).
MSD V116-010 (ongoing, expected 2025–2026)	~2,000 adults ≥50 yrs, PCV-naïve; US/EU multicentre	Phase 3 RCT & immunogenicity sub-study	PCV21 (V116) vs. PPV23	Preliminary: PCV21 induces robust OPA responses across 21 serotypes, including unique serotypes (15A, 15C, 16F, 23A, 23B, 24F, 31, 35B). Durability under study.	Durability substudy (24 months) ongoing; results expected Dec 2025–Jan 2026.

Abbreviations: RCT – randomized controlled trial; OPA – opsonophagocytic activity; NI – non-inferiority; PCV – pneumococcal conjugate vaccine; PPV23 – 23-valent pneumococcal polysaccharide vaccine

6.7 Effectiveness

Recent real-world effectiveness data from a large U.S. Medicare claims study (16.5 million adults ≥65 years, July 2022-June 2024, CDC) demonstrated PCV20 effectiveness of 25.6% (95% CI: 19.5-31.3%) against all IPD (*i.e.* vaccine-type and non-vaccine-type) and 15.2% (95% CI: 14.6-15.8%) against all-cause pneumonia. Effectiveness was consistent across risk groups: for IPD, effectiveness was 25.0% in immunocompromised patients, 22.6% in those with chronic medical conditions, and 33.8% in low-risk individuals. For all-cause pneumonia, effectiveness was 16.5%, 14.6%, and 17.3% respectively across these same risk groups (Miles, 2025). A multinational post-marketing study in Europe and Israel is planned to evaluate PCV20's effectiveness against vaccine-type IPD in adults ≥65 (HMA-EMA, 2025). One notable finding from early U.S. uptake is an improvement in vaccine strategy simplicity and potentially uptake. Advisory Committee on Immunization Practices (ACIP) noted that replacing the prior complex regimen (PCV13+PPV23 in series for some groups) with a single PCV20 dose might improve adult vaccination uptake (ACIP/CDC, 2024). Several countries in Europe have moved to simplify adult pneumococcal immunization using PCV20. For example, Germany updated its recommendation in late 2023 to use a single PCV20 dose for all adults ≥60, as well as for younger adults (18–59) with risk factors, replacing the old PPV23-based schedule (Ta et al., 2024). France has similarly recommended PCV20 (replacing PCV13+PPV23) for adults at risk as of August 2023 (ECDC, 2025).

6.8 Co-administration with the influenza vaccine

Co-administering the PCV20 with seasonal influenza vaccine is a convenient strategy to protect adults – especially older adults – against two major respiratory infections in a single visit. A large double-blind trial in 1,796 older adults (≥65) tested PCV20 co-administered with an MF59-adjuvanted quadrivalent influenza vaccine (Fluad®) versus giving the two vaccines one-month apart. Co-administration met the noninferiority criteria for immunogenicity: antibody responses to all 20 pneumococcal serotypes (OPA titres) and all 4 influenza strains (HAI titres) were statistically non-inferior when given together compared to separate injections (Cannon et al., 2023).
Local and systemic reactions were mostly mild to moderate; injection-site pain was the most common local reaction, and fatigue was the most common systemic symptom (Cannon et al., 2023). Mild fatigue was reported more often with coadministration (about 20% of recipients) than when the shots were given separately (~11%), and moderate fatigue in ~12% vs ~9%, but this slight increase was not deemed clinically significant. Overall adverse event rates were similar between groups, and no serious adverse events were attributed to the vaccines (Cannon et al., 2023).

7 21-valent conjugate vaccine (PCV21, Capvaxive)

7.1 Vaccine

A 0.5 mL 21-valent pneumococcal conjugate vaccine (PCV21) dose contains a total of 84 µg of pneumococcal polysaccharide antigen (4 µg each of polysaccharide serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C (deOAc 15B), 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B) conjugated to approximately 65 µg of CRM197 carrier protein, 1.55 mg L-histidine, 0.50 mg of polysorbate 20, 4.49 mg sodium chloride, and water for injection. The vaccine does not contain an adjuvant (CDC, 2024).

PCV21 contains eight serotypes that are not included in other licensed pneumococcal vaccines (15A, 15C, 16F, 23A, 23B, 24F, 31, 35B), In contrast PCV21 does not include serotypes present in PCV13/PCV15/PCV20 (serotype 1, 4, 5, 6B, 9V, 14, 18C).

7.2 Registration

On 30 January 2025, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for PCV21 (CAPVAXIVE; Merck Sharp & Dohme, B.V.) for adults aged ≥18 years (CHMP, 2025). CAPVAXIVE is indicated for active immunization for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in individuals 18 years of age and older.

At the time of publishing this advisory report, PCV21 is not yet available on the Belgian market.

7.3 Immunogenicity

7.3.1 Immunocompetent

Findings from one phase II (Platt et al., 2023) and three phase III (ClinicalTrials.gov, 2025; Platt et al., 2024; Scott et al., 2024) randomized controlled trials (RCTs) compared the immunogenicity of PCV21 (as measured by opsonophagocytic activity GMTs and percentage of seroresponders to that of comparator vaccines (PCV15, PCV20, or PPV23).

One study assessed the safety and immunogenicity of PCV21 with concomitant or sequential administration of the quadrivalent influenza vaccine (QIV) (Platt et al., 2024). Among immunocompetent, pneumococcal vaccine–naive adults aged ≥50 years, PCV21 met noninferiority criteria for serotypes shared with comparator vaccines (PPV23 and PCV20) (Platt et al., 2023; Platt et al., 2024).

PCV21 elicited statistically significantly higher immune responses for most serotypes unique to PCV21, except for serotype 15C, although the immune response was numerically higher when compared with PCV20 (Platt et al., 2024). Among immunocompetent adults aged ≥50 years who had previously received a pneumococcal vaccine (PCV13 or PPV23) ≥1 year before enrolment, PCV21 demonstrated comparable immunogenicity for shared serotypes and was immunogenic for unique serotypes compared with PPV23 or PCV15; among adults who had previously received PPV23 followed by or preceded by PCV13, PPV23 preceded by PCV15, or PCV15 alone, PCV21 was immunogenic for all serotypes (Scott et al., 2024).

PCV21 demonstrated non-inferiority to PPV23 for all 12 common serotypes based on opsonophagocytic activity GMTs at 30 days post-vaccination. Additionally, PCV21 showed superiority to PPV23 for all nine unique serotypes based on GMT ratios, and superiority for eight of nine unique serotypes (except serotype 15C) based on the proportion of participants achieving ≥4-fold rises in functional antibody responses from baseline to 30 days post-vaccination (Jotterand et al., 2025).

The safety profiles of both vaccines were comparable, with 61.0% of PCV21 recipients and 56.8% of PPV23 recipients experiencing at least one adverse event. Solicited adverse events occurred in 49.9% of PCV21 participants versus 48.4% of PPV23 participants, with most events being mild-to-moderate in intensity and lasting ≤3 days. No vaccine-related serious adverse events were reported in either group, and there were no deaths attributed to vaccination in the study (Jotterand et al., 2025).

7.3.2 Immunocompromised

Among adults aged ≥18 years living with HIV, comparison of recipients of PCV15 followed by PPV23 8 weeks later with recipients of PCV21 followed by placebo 8 weeks later showed comparable immunogenicity for shared serotypes and was immunogenic for unique serotypes (ClinicalTrials.gov, 2025).

7.4 Vaccine effectiveness

Data regarding the real-world impact of PCV21 on reducing vaccine-type IPD are not yet available at the time of issuing this advice. Given that vaccine effectiveness in the general population is influenced by numerous factors – including host characteristics, environmental conditions, and health system factors – it is not possible to predict the true effectiveness of PCV21 in routine clinical practice.
To assess overall real-world performance, MSD is planning a large test-negative design (TND) case-control study to evaluate vaccine effectiveness against pneumococcal pneumonia, including both invasive and non-invasive CAP caused by PCV21 serotypes and selected cross-reactive serotypes (6C, 15B). While this study may incidentally generate information on breakthrough infections, including those associated with serotype 8 – a strain for which vaccine failures have been documented with PCV20 – such analysis is not a stated primary endpoint. Instead, MSD's approach to monitoring these unique serotypes (15A, 15C, 16F, 23A, 23B, 24F, 31, 35B) will rely primarily on the combination of spontaneous reporting systems and broader observational vaccine effectiveness studies conducted after market introduction and adequate uptake (see https://catalogues.ema.europa.eu/node/4543/administrative-details).
There is yet no information regarding long-term persistence of the immune response to PCV21. However, a study (V116-010) is ongoing and does include an immunogenicity sub-study, which will investigate immunogenicity up to 24 months after vaccination with PCV21. This is especially relevant as it is not ensured that the kinetics of the response generated with PCV21 (which does not include an adjuvant, but higher dose of antigen) are comparable to other conjugated vaccines which included aluminium as an adjuvant.

7.5 Co-administration with Influenza

Among immunocompetent adults aged ≥50 years who received PCV21 and QIV concomitantly or sequentially (Omole et al., 2025), co-administration of PCV21 and QIV resulted in numerically lower pneumococcal and influenza antibody titres compared with sequential administration. Coadministration of PCV21 and QIV met noninferiority criteria for immunogenicity for all except pneumococcal serotype 23B and influenza strain A/H3N2. This trend toward lower immune responses in concomitant administration is consistent with other PCV-influenza co-administration studies and recent influenza-RSV vaccine studies, suggesting this is a recognized phenomenon rather than a unique PCV21 limitation. Despite these technical non-inferiority failures, the totality of immunogenicity data supports concomitant administration as both vaccines still produce robust immune responses, and concomitant vaccination offers important public health benefits by encouraging compliance, increasing vaccination rates, and preventing pneumococcal and influenza diseases, as demonstrated by effectiveness studies showing reduced pneumonia, death, and hospitalizations during influenza season.

8 Target groups for pneumococcal vaccination in adults

8.1 General remark: Vaccination Assessment and Administration Guidelines

Regular assessment of patient vaccination status is recommended during routine clinical encounters, such as annual influenza vaccination visits, with consideration of pneumococcal vaccination indications. Verification of vaccination status may be particularly important for patients admitted to or residing in care facilities. Once pneumococcal vaccination indication is established, vaccination should be administered according to the recommendations outlined below.

Consistent with ACIP Best Practice Guidelines for Immunization (Kroger et al.), pneumococcal vaccine may be co-administered with other age-appropriate vaccines during the same clinical visit for adults without specific contraindications.

8.2 Adults aged 18 to 64 years with an increased risk of pneumococcal infection (Van Aalst et al., 2018)

- **Adults with primary (congenital) immunodeficiency or secondary (acquired) immunodeficiency**
  - Adults with primary (congenital) immunodeficiency (i.e., conditions that cause B- or T-cell deficiency, complement deficiency, or phagocytic disorders) or secondary (acquired) immunodeficiency (e.g., HIV infection, hematopoietic malignancy, and treatment with radiation or immunosuppressive medications) are at increased risk for infection or severe manifestations from vaccine-preventable diseases including pneumococcal disease (Ahmed et al., 2020; Baxter et al., 2016; Kobayashi et al., 2024; Kobayashi et al., 2025; Kobayashi et al., 2023; Shea et al., 2014; Shigayeva et al., 2016; Van Aalst et al., 2018).
- **Adults with anatomical and/or functional asplenia, sickle-cell disease or a hemoglobinopathy**
  - Persons with anatomical or functional asplenia, sickle cell disease, or hemoglobinopathies have a 50-600 times higher risk of IPD compared to the general population. (Sabatino et al., 2011).
- **Adults with cerebrospinal fluid leak or a cochlear implant**.
  - Persons with cochlear implants or cerebrospinal fluid (CSF) leaks face significantly increased risk of pneumococcal disease. After findings in 2002 linked cochlear implants to higher rates of bacterial meningitis (particularly pneumococcal), the Centers for Disease Control and Prevention (CDC) updated recommendations to include these individuals among high-risk groups. Adults aged ≥65 years with cochlear implants have 10.5 times the risk for IPD compared to those without underlying conditions (Biernath et al., 2006; CDC, 2002; Kobayashi et al., 2023; Reefhuis et al., 2003; Shea et al., 2014).
  - Individuals with CSF leaks from congenital lesions, skull fractures, or neurosurgical procedures demonstrate a 6.4 times higher risk for IPD, with 59% of adults with CSF leaks experiencing recurrent episodes of bacterial meningitis (Baxter et al., 2016; Kobayashi et al., 2023; ter Horst et al., 2020; ter Horst et al., 2021).
- **Occupational or Environmental Exposures**
  - Workers exposed to welding fumes are at significantly increased risk of IPD, with meta-analyses showing more than a twofold higher likelihood of both developing and dying from IPD compared to non-exposed populations (OR: 2.59; Standardized Mortality Ratio [SMR]: 2.42). Outbreak reports in European shipyards and construction sites have documented high attack rates, hospitalizations, and clusters of cases predominantly caused by serotypes covered by PPV23 and PCV20. These findings underpin recommendations already implemented in other European countries to vaccinate welders with pneumococcal vaccine. Given the consistent evidence of increased susceptibility and occupational clustering, welders should be explicitly included as a priority target group for pneumococcal vaccination strategies (Riccò et al., 2023).
  - Recent Belgian research on serotype 4 IPD (Cuypers et al., 2025b) has identified this additional high-risk population that has significantly increased

IPD risk among tobacco-smoking adult males experiencing homelessness in urban settings who use hard drugs and/or consume heavy alcohol and is consistent with ACIP's framework to include this group to targeted vaccination groups (Donoghue & Wesdock, 2019; Kobayashi et al., 2023; Palmer & Cosgrove, 2012; Wong et al., 2010).

8.3 Adults 18 to 64 years of age with comorbidities

- **Chronic heart disease**
  - Persons with chronic heart disease have up to 3.3 times higher odds for CAP and 9.9 times higher odds for IPD compared to those without, with risk being particularly elevated in severe congestive heart failure. Pneumococcal vaccination has been associated with a 22% reduction in all-cause mortality among adults with cardiovascular disease or very high cardiovascular risk (Marques Antunes et al., 2021; Torres et al., 2015).
- **Chronic lung disease, COPD, asthma or smokers**
  - Persons with chronic lung diseases have higher risk for pneumococcal infections, with chronic obstructive pulmonary disease (COPD) patients demonstrating 18 times higher risk for CAP compared to those without COPD. The increased risk among persons with COPD might be because of increased inhaled corticosteroid use, reduced airway defence mechanisms, and an association with smoking. Asthma is added to pneumococcal vaccination indications based on data showing a 2.4-fold increased risk for IPD even after adjusting for other underlying conditions (Ahmed et al., 2020; Bordon et al., 2020; Inghammar et al., 2013; Ramirez et al., 2017; Talbot et al., 2005; Torén et al., 2020; Torres et al., 2015). There is little data demonstrating IPD in CF, meaning that the clinical relevance of vaccination remains unclear (Lommatzsch, 2020). Nevertheless, patients are at higher risk of both pulmonary disease and IPD after lung transplantation. Therefore, pre-transplant vaccination is important, as immunosuppression reduces immune responsiveness.
- **Chronic liver disease or alcoholism**
  - Persons with excessive alcohol use have 8.2 times higher risk of CAP and 2.3-7.7 times higher risk of IPD compared to those without such conditions due to impaired host immune response. Persons with chronic liver disease, especially those with cirrhosis, have 4.1-5.6 times higher risk of all-cause pneumonia, 4.3-6.4 times higher risk of pneumococcal pneumonia, and 3.8-15.4 times higher risk of IPD compared to adults without underlying health conditions (Ekpanyapong & Reddy, 2019; Mehta & Guidot, 2012; Piano et al., 2018; Raasch et al., 2010; Samokhvalov et al., 2010; Torres et al., 2013).
- **Chronic kidney disease**
  - Persons with chronic kidney disease (CKD), particularly those with nephrotic syndrome and end-stage renal disease (ESRD), have an altered immune system and increased risk for pneumococcal disease, with adults having stage 3-4 CKD showing 1.7 times higher risk and those with ESRD showing 3.7 times higher risk for IPD. Studies demonstrate that CKD patients have significantly lower immune responses to PPV23 and experience rapid decline of antibody levels after vaccination. Guidelines recommend pneumococcal vaccination for

adults with stages 4 and 5 CKD, despite challenges with antibody maintenance in dialysis patients due to impaired immunity and removal of antibodies during treatment (Baxter et al., 2016; Goonewardene et al., 2019; Kato et al., 2008; KDIGO, 2013; Krueger et al., 2019; Mahmoodi et al., 2009; Mitra et al., 2016).

- **Chronic neurological or neuromuscular disorders with aspiration risk**
  - Patients with chronic neurological or neuromuscular disorders with aspiration risk demonstrate significantly elevated susceptibility to pneumococcal disease. Epidemiological data reveal that among 307,529 individuals with neuromuscular/seizure disorders, the rates of all-cause pneumonia are substantially higher than the general population. Specifically, these patients exhibit approximately 4-5 times higher risk of pneumococcal pneumonia and IPD compared to healthy adults (Shea et al., 2014).
- **Diabetes mellitus**
  - Adults under 40 years with diabetes have a 3.2-fold increased risk for pneumonia-related hospitalization compared to those without diabetes, with this risk decreasing to 1.1-fold in adults aged 80 years or older. Persistent hyperglycaemia in diabetes impairs immune function, contributing to infection risk beyond the comorbidities associated with the disease (Ahmed et al., 2020; Dowey et al., 2021; Kornum et al., 2008; Peleg et al., 2007; Torres et al., 2015).

8.4 Age-based recommendations

8.4.1 Adults aged 50 to 64 years

Belgian NRC data show IPD cases reached 2,120 in 2024, with up to 70% of pneumococcal bacteraemia cases occurring in individuals over 50 years. It could therefore be considered to lower the age for universal PCV vaccination to 50 years. However, healthy adults aged 50-64 have lower absolute risk compared to those ≥65 years, with most IPD cases occurring in individuals with underlying conditions (Altawalbeh et al., 2024a; Altawalbeh et al., 2024b; Yi et al., 2025).

There remains a gap in the contemporary European literature regarding the impact and value of pneumococcal vaccination specifically in healthy adults aged 50–64 years.

The immediate priority should be to implement systematic and proactive approaches to reach the 84–86% of high-risk individuals in this age group who remain unvaccinated despite clear medical indications. Efforts should be concentrated on improving uptake in these well-defined risk groups before considering any expansion of age-based vaccination criteria. In the long term, a coherent adult vaccination program with appropriate structural financing would be more effective than managing reimbursement criteria on a per-vaccine basis. Such a program would enable a more equitable, transparent, and sustainable approach to adult immunization.

8.4.2 Adults aged 65+ years old

Adults aged 65 years and older face a disproportionately high burden of pneumococcal disease. The epidemiological data demonstrate that approximately 70% of pneumococcal bacteraemia cases occur in individuals over 50 years of age, with the highest mortality rates observed among adults over 65. The mortality rate from pneumococcal bacteraemia reaches 12% in 65-year-olds and doubles in those over 85 years of age.

8.4.3 Adults aged 85+ years old

The high disease burden in the very elderly, provides strong rationale for vaccination in the 85+ age group. While acknowledging the limited specific data in this population, the established safety profile and potential for significant benefit support vaccination.
Healthcare systems increasingly recognize the importance of healthy aging, and the 85+ age group constitutes a heterogeneous population in comorbidities (multimorbidity) and frailty profile (with or without immunosenescence) and immune response is difficult to predict. High incidence and complications (hospitalization, institutionalization, mortality, functional loss) of vaccine-preventable pneumococcal vaccination represents a key preventive intervention. Lack of evidence of vaccine efficacy should not exclude older adults, as effectiveness data (for other vaccines, such as COVID-19) do show reduced VPD burden in the oldest old persons.

9 Recommendations

9.1 Adults 18-64 Years

Category	Indications
Immunocompromising Conditions	• Primary immunodeficiency • HIV infection • Hematopoietic malignancy • Active chemotherapy or radiation therapy • Immunosuppressive medications • Anatomical or functional asplenia • Sickle cell disease • Hemoglobinopathies
Anatomical Risk Factors	• Cochlear implant • Cerebrospinal fluid leak
Chronic Heart Disease	• Congestive heart failure • Coronary artery disease • Cardiomyopathies
Chronic Lung Disease	• COPD • Asthma • Chronic bronchitis • Emphysema • Current smoking • CF/NCFB (including PCD)
Chronic Liver Disease	• Cirrhosis • Chronic hepatitis • Alcoholism
Chronic Kidney Disease	• Stage 3-5 CKD • End-stage renal disease • Nephrotic syndrome
Neurological Conditions	• Chronic neurological disorders with aspiration risk • Neuromuscular disorders • Seizure disorders
Metabolic Disorders	• Diabetes mellitus
Environmental Exposure or living condition	• Homelessness • Welder

9.2 Adults ≥65 Years

Category	Indications
Age-based	• All adults ≥65 years regardless of other risk factors

10 Vaccine schedule

10.1 Single-Dose Conjugate Vaccine Approach: Eliminating the need for PPV23

Vaccination of medical risk groups with the highest-valent conjugate vaccine available (PCV20 or PCV21) is preferred over the sequential PCV13/15/20 + PPV23 schedule. When PCV20 or PCV21 is administered as a single dose to individuals, subsequent vaccination with PPV23 is no longer necessary.

This approach is supported by:

- Limited additional serotype coverage provided by PPV23 compared to PCV20 and PCV21
- Superior duration of protection offered by conjugate vaccines
- International guidance supporting this simplified approach

The conjugate vaccines PCV20 and PCV21 offer several advantages that make PPV23 redundant in most clinical scenarios. Conjugate vaccines provide T-cell dependent immune responses resulting in immunological memory, longer duration of protection, and reduced nasopharyngeal carriage. In contrast, PPV23 elicits T-cell independent responses with no memory formation, waning effectiveness over time, and the phenomenon of hyporesponsiveness with repeated doses. Importantly, PPV23 adds minimal incremental serotype coverage beyond PCV20 or PCV21 – the additional serotypes represent less than 5% of current IPD in most populations.

Eliminating PPV23 from adult vaccination protocols simplifies implementation and potentially improves uptake rates. The current sequential approach requiring PCV13/15 followed by PPV23 creates confusion among providers and patients, requires tracking multiple doses with specific timing intervals, and results in many patients receiving incomplete series. A single-dose strategy with PCV20 or PCV21 reduces complexity, eliminates the need for revaccination every 5 years as previously recommended for high-risk groups, and aligns with international trends toward conjugate-only strategies.

10.2 PCV20 versus PCV 21

The choice between PCV20 and PCV21 depends primarily on local serotype epidemiology, with PCV21 offering better overall coverage but PCV20 remaining essential in regions and age groups with significant serotype 4 circulation.

Based on the epidemiological data of 2024 and vaccine characteristics, an age-stratified approach has merit but requires nuanced consideration. The key factor is that serotype 4 prevalence is highest in younger adults (21.2% in 18-49 years in Belgium) and decreases significantly with age (11.0% in 50-64 years, 4.7% in 65-84 years, and only 1.8% in adults over 85 years), while PCV21's broader coverage becomes increasingly valuable in older populations where serotype 4 represents a minimal disease burden.

10.2.1 Adults 18-49 Years with Risk Conditions: PCV20 Recommended

For adults aged 18-64 years with underlying risk conditions, PCV20 is the recommended vaccine. This recommendation is based on PCV20's substantial 17% coverage advantage over PCV21 in this age group, maintained consistently in both 2023 and 2024 surveillance

data. Additionally, the critical importance of serotype 4 protection in younger adults supports PCV20 selection.

10.2.2 Adults ≥50 Years: Both PCV20 and PCV21 Acceptable Options, with a Preference for PCV21 for ≥ 85 Years

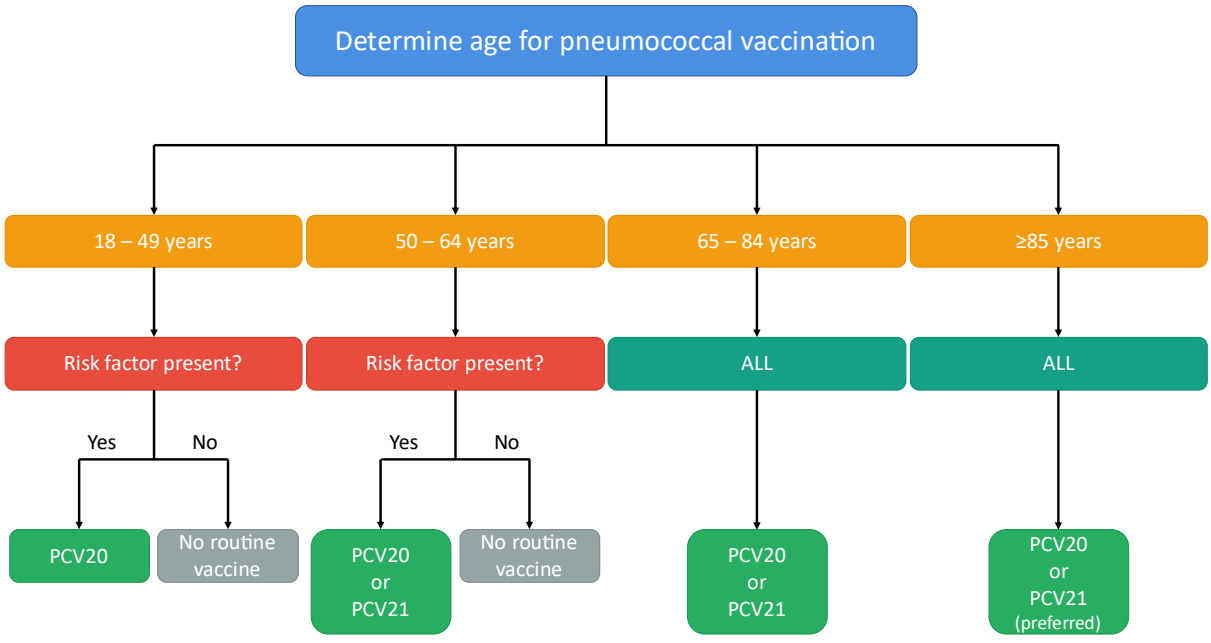
For adults aged 50-64 years, serotype coverage data shows no meaningful difference between PCV20 and PCV21, with minimal year-to-year variations (2022: -2.8% favouring PCV20; 2023: 0.8% favouring PCV21; 2024: -2.8% favouring PCV20).

For adults aged 65-84 years, both PCV20 and PCV21 are considered acceptable options without a specific preference. While PCV21 demonstrates a theoretical coverage advantage in 2024 data, this difference has varied over recent years (ranging from 6.3% in 2023 to 14.0% in 2022), indicating temporal variation. The moderate and fluctuating nature of these coverage differences, combined with reimbursement considerations that may impact vaccine uptake for PCV20 in the 65-80 age group, supports maintaining both options across these age ranges.

For adults aged 85 years and older, PCV21 is the preferred vaccine based on its consistently substantial coverage advantage over PCV20, ranging from 11.9% to 22.6% over the past five years with 15% in 2024. This age group represents the most vulnerable population for severe pneumococcal disease outcomes, justifying the pursuit of optimal serotype coverage.
While PCV21 is the preferred vaccine for individuals aged ≥85 years, vaccination should not be delayed until it is commercially available. PCV20 is recommended as an acceptable alternative in case of unavailability.

10.3 Primary Vaccination Schedule

Age Group	Population	Vaccine Choice
18-49 years	With risk conditions	**PCV20**
50-64 years	With risk conditions	**PCV20 or PCV21**
≥65 years	ALL	**PCV20 or PCV21** **PCV21 is preferred for ≥85 years** Although PCV21 is preferred for ≥85 years, PCV20 is recommended as an acceptable alternative in case of unavailability.



10.4 Revaccination Schedules for Previously Vaccinated Adults

Previous Vaccination	Next Vaccine	When to Give
PPV23 only (any number of doses)	PCV20 or PCV21	≥1 year after last PPV23
PCV13 or PCV15 only	PCV20 or PCV21	≥1 year after PCV13 or PCV15
PCV13 or PCV15 → PPV23	Consider PCV20 or PCV21 (see 10.5.1)	≥5 years after PPV23
PCV20 or PCV21	None needed	—

10.5 Special Considerations

10.5.1 Immunocompromised Patients

- **Prior vaccination ≥5 years ago**: Consider PCV20/21 regardless of prior vaccines received
- **Recent vaccination (<5 years)**: Individual assessment based on degree of immunosuppression. For patients at highest risk of pneumococcal disease, including those with severe immunocompromise, functional asplenia, or multiple comorbidities, earlier revaccination may be considered on a case-by-case basis. The decision should balance the theoretical concerns about shortened intervals against the urgent need for protection. Clinical judgment should guide whether to adhere strictly to recommended intervals or to prioritize earlier protection in patients whose underlying conditions place them at exceptional risk for severe pneumococcal disease.
- **Rationale**: Immunocompromised patients may have suboptimal responses to prior vaccines and benefit from conjugate vaccine properties

10.5.2 Unknown Vaccination History

- **Approach**: Administer PCV20 or PCV21 as if vaccine-naïve
- **Rationale**: Conjugate vaccines are safe to repeat; ensuring protection outweighs theoretical concerns

10.5.3 Minimum Intervals Between Vaccinations

The timing between pneumococcal vaccinations depends on the types of vaccines previously received. When transitioning from one conjugate vaccine to another (such as PCV13 to PCV20), a minimum interval of one year is sufficient due to the similar immunological mechanisms of these vaccines. For individuals who received PPV23 transitioning to a conjugate vaccine, while a minimum of one year is acceptable, waiting five years may optimize the immune response by allowing full recovery from potential PPV23-induced hyporesponsiveness. In cases where individuals have received multiple prior vaccines, the longest applicable interval should be used to ensure optimal immunogenicity.

11 Duration of validity of the recommendations

Given the rapidly evolving pneumococcal vaccination landscape, including ongoing clinical trials, emerging vaccine technologies, and anticipated regulatory changes, the recommendations and perspectives presented here reflect the current state of knowledge but should be interpreted with the understanding that guidance will evolve as new evidence emerges from clinical research and technological advances (Ozisik, 2025).

These guidelines will require ongoing adaptation based:

- Epidemiological data from surveillance systems such as the NRC for Invasive Pneumococcal Infections
- Post-application surveillance data (e.g. vaccine coverage by age group, vaccine used and missed vaccination opportunities)
- The availability of new vaccines.

The situation will be re-examined in a few years' time (in 2028-2029).

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VII COMPOSITION OF THE WORKING GROUP

The composition of the Committee and that of the Board as well as the list of experts appointed by Royal Decree are available on the following website: About us.

All experts joined the working group ***in a private capacity***. Their general declarations of interests as well as those of the members of the Committee and the Board can be viewed on the SHC website (site: conflicts of interest).

For this specific document, the following interests were declared in the ad hoc declaration of interests and the general declaration of interests:

- Stefanie DESMET: "*Research Investigator Initiated Grant* for an epidemiological study on invasive pneumococcal infections since 2017" and "*MSD grant* to conduct independent researcher-initiated research at the National Reference Centre for Invasive Pneumococcal Infections"
- Johan FLAMAING: Participation in a webinar for MSD's Pneumovax® vaccine in 2020. Remuneration for consulting and speaking engagements at GSK and MSD symposia. The ad hoc chair is linked to Pfizer's vaccine through expert work for Prevenar 13® in 2020.

The following experts were involved in drawing up and endorsing this advisory report. The working group was chaired by **Steven CALLENS**; the scientific secretaries were Veerle MERTENS and Michael PEETERS.

CALLENS Steven	Internal Medicine, Infectious Disease Medicine, Emerging Communicable Diseases, Travel Medicine, Vaccinology, Tuberculosis, AIDS-HIV, Ebola, COVID-19.	Ugent, UZ Gent
DAMBRE Cato	Epidemiology	Sciensano
DE SCHRYVER Antoon	Occupational and environmental medicine	U Antwerpen
DESMET Stefanie	Clinical microbiology, Epidemiology	UZ Leuven, NRC for Pneumococci
FLAMAING Johan	Geriatrics, Infectiology, Oncology, Epidemiology	UZ Leuven
VAN LAETHEM Yves	Infectiology, Vaccinology, Travel medicine	ex-CHU Saint-Pierre, ULB
VIGNERON Laurence	Coordinator of the Spearhead Domain Vaccines	AFMPS/FAGG

The standing working group NITAG has endorsed the advisory report. Discussions over conclusions and recommendations held on September 18, 2025. The NITAG was chaired by **Steven CALLENS** and **David TUERLINCKX**; the scientific secretaries were Veerle MERTENS, Michael PEETERS and Fabrice PETERS. The following experts explicitly approved the present document by e-mail on October 13, 2025.

BLUMENTAL Sophie	Pediatrics, Infectious Disease Medicine, Vaccinology, Primary Immunodeficiency Diseases,	ULB, CHIREC

	Pneumococcal Infections, Tuberculosis.	
BOIY Tinne	Pediatrics, Rare Diseases, Congenital Hereditary and Neonatal Diseases and Abnormalities, Down Syndrome.	UAntwerpen, UZA
CORNELISSEN Laura	Obstetrics, Gynecology, Epidemiology, Infectious Disease Medicine, Maternal Health, Public Health.	Sciensano
DE SCHEERDER Marie-Angélique	Internal Medicine, Infectious Disease Medicine, Travel Medicine, AIDS-HIV, Anti-Bacterial Agents.	UGent, UZ Gent
SCHELSTRAETE Petra	Pediatrics, pneumology and infectiology	UZ Gent
VANDAMME Pierre	Epidemiology, vaccinology, infectiology, public health	U Antwerpen

The following experts were heard but did not take part in endorsing the advisory report:

DAEMS Joël	Directorate Drugs	RIZIV-INAMI
PERIN Belinda	General medicine, Vaccinology	AVIQ – ONE
THEETEN Heidi	Vaccinology	VAZG

The following firms/associations/etc. were heard on September 4, 2025:

MSD	JAGANNATH Vinita	Principal Scientist – Global Clinical Development Vaccines
	SONNENSCHEIN Agnes	Regional Associate Director Medical Affairs – Pneumococcal Vaccines Europe
Pfizer	MIGNON Annick	Sr. Medical Affairs Scientist Vaccines

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