5.01 21-VALENT PNEUMOCOCCAL CONJUGATE VACCINE
Injection, 0.5 mL
Capvaxive®
MERCK SHARP & DOHME (AUSTRALIA) PTY LTD.

1 Purpose of submission

1.1 The Category 2 submission requested a National Immunisation Program (NIP) listing for 21-valent pneumococcal conjugate vaccine (21vPCV) for the prevention of pneumococcal disease in the current NIP adult populations: non-Indigenous adults aged ≥ 70 years, adults with medically at-risk conditions (MaR) ≥ 18 years, and Aboriginal and Torres Strait Islander adults aged ≥ 50 years. Additionally, the submission requested listing in Aboriginal and Torres Strait Islander adults 25 to 49 years of age (regardless of risk conditions).

1.2 The submission requested a catch-up program for individuals within the requested populations that were vaccinated prior to implementation of 21vPCV on the NIP (see paragraph 3.8). The submission requested that the catch-up program run for three years.

1.3 The submission noted that the Australian Technical Advisory Group on Immunisation (ATAGI) recently recommended lowering the age threshold to 65 years for non-Indigenous adults (see paragraph 3.3) and presented sensitivity analyses in the economic evaluation and financial estimates to reflect this population.

1.4 Listing was requested on the basis of a cost-utility analysis (CUA) versus the currently listed 13-valent pneumococcal conjugate vaccine (13vPCV) and the near market 20-valent pneumococcal conjugate vaccine (20vPCV). For Aboriginal and Torres Strait Islander adults aged 25 to 49 years, a cost-minimisation approach (CMA) was presented versus 20vPCV on the basis that 20vPCV was recommended for listing by the Pharmaceutical Benefits Advisory Committee (PBAC) in this population in November 2022, although 20vPCV is not yet listed in the NIP schedule for adults. In July 2025, the ATAGI recommended removal of 23vPPV from the adult schedule when the use of 13vPCV is replaced by 21vPCV (or 20vPCV). The key components of the listing are summarised in Table 1.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Prevention of pneumococcal disease in: Current NIP populations • Non-Indigenous adults aged ≥ 70 years (regardless of risk conditions) • Adults (≥18 years) with NIP-funded risk conditions[a] for pneumococcal disease • Aboriginal and Torres Strait Islander adults aged ≥ 50 years (regardless of risk conditions) Proposed expanded NIP population (PBAC approved population) • Aboriginal and Torres Strait Islander adults aged 25 to 49 years (regardless of risk conditions)

Component	Description	
Intervention	21vPCV (described as V116 in the submission). 21vPCV single dose in all requested populations 21vPCV (Pneumococcal 21-valent Conjugate Vaccine) is a sterile solution of purified capsular polysaccharides from *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B individually conjugated to a CRM197 carrier protein. CRM197 is a nontoxic mutant of diphtheria toxin (originating from Corynebacterium diphtheriae C7) expressed recombinantly in Pseudomonas fluorescens.	
Comparator	Current NIP populations Non-indigenous adults aged ≥ 70 years	Main comparator: 13vPCV Near market comparator[b]: 15vPCV/20vPCV
	Adults (≥18 years) newly diagnosed with NIP-funded risk conditions for PD	Main comparator:13vPCV followed by 2x23vPPV Near market comparator: 15vPCV/20vPCV
	Aboriginal and Torres Strait Islander adults aged ≥ 50 years	Main comparator: 13vPCV followed by 2x23vPPV Near market comparator: 15vPCV/20vPCV
	ATAGI Recommended Population Aboriginal and Torres Strait Islander adults aged 25-49 years	Near market comparator: 20vPCV
Outcomes	Efficacy: • Serotype specific opsonophagocytic (OPA) responses for the 21 serotypes in 21vPCV at day 30 geometric mean titre (vaccine strain type) • Serotype specific immunoglobulin G (IgG) responses for the 21 serotypes in 21vPCV at day 30 geometric mean concentrations (GMCs) (vaccine strain type) Safety: • Injection site reactions day 1-5 post vaccination • Systemic AEs from Day 1 through to Day 5 post vaccination • Vaccine related serious adverse events (SAEs) from Day 1 through the duration of participation in the study	
Clinical claim	**Efficacy claims based on immunogenicity trials** For non-Indigenous adults aged ≥ 70 years • 21vPCV has superior efficacy against PD compared to 13vPCV for serotype 3 and non-inferior for serotype 7F (non-inferiority was not demonstrated for the remaining two shared serotypes) • 21vPCV has non-inferior efficacy against PD compared to 20vPCV for the 10 common serotypes • 21vPCV has superior efficacy against PD compared to 20vPCV for the 10 of the 11 unique serotypes (non-inferiority was not demonstrated for the remaining shared serotype) For Aboriginal and Torres Strait Islander adults aged ≥ 50 years • 21vPCV has non-inferior efficacy against PD compared to 15vPCV followed by 23vPPV for the 13 common serotypes • 21vPCV has superior efficacy against PD to 15vPCV, for 8 unique serotypes For adults aged ≥ 18 years with NIP listed risk conditions: • 21vPCV has non-inferior efficacy against PD compared to 15vPCV followed by 23vPPV for the 13 common serotypes • 21vPCV has superior efficacy against PD to 15vPCV, for 8 unique serotypes except for 15C. For Aboriginal and Torres Strait Islander adults aged 25-49 years: • 21vPCV has non-inferior efficacy against PD compared to 20vPCV for the 10 common serotypes (non-inferiority was not demonstrated for the shared serotypes) • 21vPCV has superior efficacy against PD compared to 20vPCV for the 11 unique serotypes	

Component	Description
	Summary efficacy claims (relying on assumption that immunogenicity outcomes will translate to reduction in IPD and CAP): 21vPCV has superior effectiveness against pneumococcal disease compared to 13vPCV with or without 23vPPV and to 20vPCV in the following adult populations • Non-indigenous adults aged ≥ 70 years • Adults (≥18 years) newly diagnosed with NIP-funded risk conditions for pneumococcal disease • Aboriginal and Torres Strait Islander adults aged ≥50 years 21vPCV has non-inferior effectiveness against pneumococcal disease and compared to 20vPCV in the following adult populations • Aboriginal and Torres Strait Islander adults aged 25-49 year **Safety claims** For non-Indigenous adults aged ≥ 70 years, Aboriginal and Torres Strait Islander adults aged ≥ 50 years and adults aged ≥ 18 years with NIP listed risk conditions: • 21vPCV has equivalent safety to 13vPCV, 15vPCV and 20vPCV For Aboriginal and Torres Strait Islander adults aged 25-49: • 21vPCV has non-inferior safety compared to 20vPCV

Source: Table 1.1-3, p6 of the submission and Section 2.8 of the submission.

13vPCV = 13-valent pneumococcal conjugate vaccine; 15vPCV = 15-valent pneumococcal conjugate vaccine; 20vPCV = 20-valent pneumococcal conjugate vaccine; 23vPPV = 23-valent pneumococcal polysaccharide vaccine; AE = adverse event; ATAGI = Australian Technical Advisory Group on Immunisation; GMC = geometric mean concentrations; IgG = immunoglobulin G; NIP = National Immunisation Program; OPA = opsonophagocytic; PBAC = Pharmaceutical Benefits Advisory Committee; PD = pneumococcal disease; SAE = serious adverse events; 21vPCV = 21-valent pneumococcal conjugate vaccine.

a. Medical risk conditions as follows:

A. functional or anatomical asplenia including sickle cell disease, other haemoglobinopathies, congenital or acquired asplenia (e.g. splenectomy) or hyposplenia;

B. immunocompromising conditions including congenital or acquired immune deficiency including symptomatic IgG subclass or isolated IgA deficiency, haematological malignancies, solid organ transplant haematopoietic stem cell transplant (HSCT) or HIV infection;

C. chronic respiratory disease including suppurative lung disease, bronchiectasis and cystic fibrosis or chronic lung disease of prematurity;

D. chronic renal disease including: end stage renal disease – eGFR <15mL/min or relapsing or persistent nephrotic syndrome;

E. proven or presumptive cerebrospinal fluid (CSF) leak;

F. cochlear implants;

G. intracranial shunts;

H. previous episode of invasive pneumococcal disease (IPD).

b. 15vPCV was also identified as a near market comparator, however a clinical comparison in the requested ≥ 70 years population was not presented by the submission. The submission presented comparisons of 21vPCV in Section 3 of submission versus 13vPCV or 20vPCV, and not 15vPCV, stating that these comparisons represented the two extremes of serotype coverage with PBAC recommended PCVs.

2 Background

Registration status

2.1 Therapeutic Goods Administration (TGA) approval was received on Jan 30, 2025. The approved TGA indication for 21vPCV is for active immunisation for the prevention of pneumococcal disease caused by *Streptococcus pneumoniae* (*S. pneumoniae*) serotypes (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B) in adults 18 years of age and older. The TGA approved product information (PI) states that 21vPCV "may not prevent disease caused by *S. pneumoniae* serotypes that are not listed in the indications", and that the use of 21vPCV "should be guided by official recommendations".

Previous PBAC consideration

2.1 There have been no previous PBAC considerations of 21vPCV. The sponsor previously submitted an application requesting listing of 21vPCV on the NIP for consideration by the PBAC at its November 2024 meeting. However, the sponsor withdrew the submission prior to the PBAC meeting[1].

2.2 The current application was lodged as a de-novo submission, incorporating some changes in response to comments received previously from the ATAGI and ESC.

2.3 In November 2021[2], the PBAC recommended the listing of 15-valent pneumococcal conjugate vaccine (15vPCV) on the NIP, for the prevention of pneumococcal disease in non-Indigenous adults aged ≥ 70 years, Aboriginal and Torres Strait Islander adults aged ≥ 50 years, and individuals at increased risk of PD aged ≥ 18 years. The PBAC considered that the cost-effectiveness of 15vPCV would be acceptable if it were cost-minimised against the nominated comparator, 13vPCV. At the time of PBAC consideration in November 2025, 15vPCV was not listed on the NIP.

2.4 In November 2022[3], the PBAC recommended the listing of 20vPCV on the NIP, for the prevention of pneumococcal disease in individuals with an at-risk condition aged ≥ 18 years, non-Indigenous adults aged ≥ 70 years and Aboriginal and Torres Strait Islander adults aged ≥ 25 years. There was reduced immunogenicity observed for some serotypes in comparison with lower valency vaccines and uncertain translation of immunogenicity results to clinical outcomes. Overall, the PBAC considered the submission's claim of non-inferior effectiveness for 20vPCV versus 13vPCV (and 15vPCV) for the shared serotypes was not well supported. The PBAC considered that the submission's claim of superior comparative effectiveness for the additional 7 (5) serotypes in 20vPCV versus 13vPCV (15vPCV) to be supported although the magnitude of benefit in terms of disease prevention was uncertain. On the basis of the available evidence, the PBAC considered a claim of non-inferior comparative effectiveness to be appropriate (paragraph 7.7, 20vPCV Public Summary Document [PSD], November 2022 PBAC Meeting). Consistent with the conclusion of non-inferiority, the PBAC considered that the cost-effectiveness of 20vPCV would be acceptable if it was cost-minimised against the nominated comparators, 13vPCV and 15vPCV. The PBAC acknowledged the disproportionately high burden of pneumococcal disease in the proposed expanded NIP population, Aboriginal and Torres Strait Islander adults aged 25-49 years, and recommended listing on the basis that 20vPCV, with or without one or two subsequent doses of 23vPPV, would be cost-effective at the cost per dose

[1] https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/recommendations-made-by-the-pbac-november-2024

[2] https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2021-11/pneumococcal-polysaccharide-conjugate-vaccine-15-valent-ads

[3] https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2022-11/pneumococcal-polysaccharide-conjugate-vaccine-Prevenar-20-PSD-November-2022

proposed in the sponsor's pre-PBAC response. At the time of PBAC consideration in November 2025, 20vPCV was not listed on the NIP for adults.

2.5 In May 2025, the PBAC noted updated advice from ATAGI that recommended a set of changes to the pneumococcal paediatric schedule[4]. The changes to the NIP childhood schedule commenced on 1 September 2025. These changes include[5]:

- 20vPCV replacing 13vPCV as the NIP-funded vaccine for children aged under 18 years;
- Expansion of the 4-dose (3+1) PCV schedule to include all Aboriginal and Torres Strait Islander children in all states and territories;
- Doses of 23vPPV are no longer required for Aboriginal and Torres Strait Islander children nor children with a risk condition.

ATAGI advice

2.6 The ATAGI provided pre-submission advice to the PBAC dated 2 May 2024, and post-submission advice in response to evaluator questions (for the November 2024 PBAC meeting) dated 7 August 2024. The ATAGI also gave advice on the optimum schedule for pneumococcal vaccination for Australian adults dated 2 July 2025. In the latter advice, ATAGI recommended that 21vPCV replace the current use of 13vPCV in the targeted NIP populations. ATAGI recommended a single dose of 21vPCV regardless of whether any other pneumococcal vaccines have been received previously. In adults who have previously received a pneumococcal vaccine, the recommended interval between the last pneumococcal vaccine dose and the 21vPCV dose is at least 12 months. The ATAGI's preference for 21vPCV was based on wider serotype coverage (the ATAGI advice did not specifically refer to 21vPCV possessing superior clinical effectiveness) compared to the existing pneumococcal vaccines on the NIP. ATAGI noted that implementation of a 21vPCV adult program alongside a 20vPCV paediatric program would further increase serotype coverage due to herd immunity arising from the 20vPCV paediatric program (while noting uncertainty in the extent of that wider coverage due to the lack of empiric evidence to support herd benefit). ATAGI also recommended the removal of 23vPPV from the adult schedule when the use of 13vPCV is replaced by 21vPCV (or 20vPCV).

2.7 The ATAGI provided post-submission advice to the PBAC dated 11 September 2025. In its latest advice, the ATAGI maintained that superiority of serotype coverage is time-dependent and that the dominant serotypes will change over time. The ATAGI reiterated the advice that use of 21vPCV will provide the broadest serotype coverage for adults, in the context of concurrent use of 20vPCV in the paediatric program with strong herd effects anticipated against 20v-non21vPCV serotypes. In terms of clinical

[4] https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2025-05/pbac-web-outcomes-05-2025.pdf

[5] https://ncirs.org.au/ncirs-fact-sheets-faqs-and-other-resources/pneumococcal-vaccines-frequently-asked-questions-faqs

effectiveness of 21vPCV against disease caused by the unique serotypes in the vaccine, ATAGI reaffirmed there will be uncertainty to a claim of superiority, given there are only immunogenicity data available, and these data do not bridge to any efficacy data. Data bridging immunogenicity data to efficacy data is particularly important as there is no established overall, nor serotype-specific, correlate of protection for key outcomes for adults (including IPD or CAP) and, as observed in children, the immune threshold for protection could vary by serotype. The ATAGI maintained its preference for 21vPCV over other vaccines, however also reiterated that it did not consider there is sufficient evidence to support a claim of superiority in clinical effectiveness for 21vPCV over 13vPCV or 20vPCV.

2.8 The September 2025 ATAGI advice also noted that when recommending the optimum vaccine strategy (20vPCV for paediatric populations and 21vPCV for adult populations), ATAGI considered the following programmatic matters were important:

- There would be limited further gain in terms of overall population benefits by using the same PCV in both adults and children
- There was sufficient anticipated direct and indirect population benefit from the recommended switching from 13vPCV to 20vPCV for the paediatric population
- The 11 unique serotypes in 21vPCV will broaden serotype coverage for adults
- The program will be simplified by having a single vaccine each for paediatric and adult population, rather than a PCV and 23vPPV.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

Name	Proposed Nationally Negotiated Price (NNP)	Formulation	Proprietary name and manufacturer
Pneumococcal (conjugate, 21-valent) vaccine	$[redacted] (weighted price)	Injection 0.5 mL	CAPVAXIVE, Merck Sharp & Dohme (Australia) Pty Ltd
Circumstances Vaccine may be provided in the following circumstances: (a) a dose of the vaccine may be provided to a person: (i) who is at least 18 years of age and has one or more of the following medical risk conditions: A. functional or anatomical asplenia including sickle cell disease, other haemoglobinopathies, congenital or acquired asplenia (e.g. splenectomy) or hyposplenia; or B. immunocompromising conditions including congenital or acquired immune deficiency including symptomatic IgG subclass or isolated IgA deficiency, haematological malignancies, solid organ transplant haematopoietic stem cell transplant (HSCT) or HIV infection; or C. chronic respiratory disease including suppurative lung disease, bronchiectasis and cystic fibrosis or chronic lung disease of prematurity; or D. chronic renal disease including: end stage renal disease – eGFR <15mL/min or relapsing or persistent nephrotic syndrome; or E. proven or presumptive cerebrospinal fluid (CSF) leak; or F. cochlear implants; or G. intracranial shunts; or H. previous episode of invasive pneumococcal disease (IPD) (b) a dose of the vaccine may be provided to a person: (i) who is an Aboriginal and/or Torres Strait Islander; and (ii) who is at least 25 years. (c) a dose of the vaccine may be provided to a person: (i) who is not an Aboriginal and/or Torres Strait Islander; and (ii) who is at least 70 years.			

Source: Table 1.1-6 p17, Table 1.4.1 p24 of the submission

CSF = cerebrospinal fluid; eGFR = estimated glomerular filtration rate HIV = human immunodeficiency virus; HSCT = haematopoietic stem cell transplant; IPD = invasive pneumococcal disease; NNP = Nationally Negotiated Price.

3.1 The submission proposed criteria for listing based on the November 2022 PBAC recommendation of 20vPCV, as reported in the associated Public Summary Document (20vPCV PSD, November 2022 PBAC Meeting).

3.2 The proposed NIP listing for 21vPCV includes:

- A single dose for non-Indigenous adults aged 70 years and over;
- A single dose for Aboriginal and Torres Strait Islander adults aged 25 years and over;
- A single dose in adults aged ≥18 years at increased risk of pneumococcal disease.

3.3 The July 2025 ATAGI Advice recommended lowering the age from 70 years to 65 years for non-Indigenous adults without risk conditions as it would capture 50%[6] more 21vPCV vaccine-type IPD cases in the target cohort and would increase the uptake of

[6] In 2023, 33% (n=48) of all 21vPCV-type-IPD cases in non-Indigenous adults without risk conditions aged ≥65 years occurred in the 65–69-year age cohort, suggesting that lowering the age threshold from 70 years to 65 years would potentially avert 50% more cases of IPD. ATAGI notes this would be the maximum number of cases potentially averted (i.e. assuming 100% vaccine coverage and vaccine effectiveness) (p11, ATAGI: Optimum schedule for pneumococcal vaccination for Australian adults, July 2025).

the vaccination as it programmatically aligns with the established NIP schedule (p3, ATAGI: Optimum schedule for pneumococcal vaccination for Australian adults, July 2025). The submission tested the impact of lowering the age to 65 years (for non-Indigenous adults without risk conditions) on incremental cost-effectiveness and net implication to the health budget.

3.4 Regarding the MaR populations, the submission noted that ATAGI has recognised that adults with chronic liver disease (CLD) and chronic obstructive pulmonary disorder (COPD) are at increased risk of pneumococcal disease and ATAGI currently recommends these adults receive two booster doses of 23vPPV following one dose of a PCV, however this usage is not funded on the NIP as CLD and COPD are not included in the list of currently funded conditions. The submission included specific assessment of the cost-effectiveness and financial impact of additional vaccination groups on the NIP for individuals with CLD and COPD. The Australian Immunisation Handbook (AIH) includes a table summarising risk conditions for pneumococcal vaccination and eligibility for NIP funding[7]. Adults with the risk conditions listed in the table are at increased risk of pneumococcal disease and are recommended by ATAGI to receive additional doses of pneumococcal vaccine. This includes COPD, and CLD, where the latter is defined as "Conditions with progressive deterioration of liver function for more than 6 months including cirrhosis and other advanced liver diseases". The pre-PBAC response stated that addition of CLD and COPD to the funded medically at-risk populations would simplify the adult pneumococcal program by reducing misalignment between the NIP-funded and ATAGI-recommended medically at-risk groups.

3.5 Consistent with ATAGI advice, the submission proposed a single dose of 21vPCV would replace 13vPCV in the non-Indigenous population ≥ 70 years, and replace 13vPCV and two booster doses of 23vPPV in the MaR and Indigenous populations. The submission stated this would simplify the adult pneumococcal schedule and should improve uptake and ultimately reduce vaccine-type disease in those populations.

3.6 In regard to booster doses of 23vPPV, the submission proposed that use of 21vPCV would negate the need for 23vPPV boosters on the pneumococcal schedule. The submission stated that 21vPCV would increase disease coverage to approximately 70% across all current adult cohorts in a single dose (Table 3). The serotype coverage estimates ranged from 66.7% in Aboriginal and Torres Strait Islander adults 25-49 to 78.3% in MaR non-Indigenous people 20-69 years, and was estimated to be 74.9% in the Non-Indigenous 70+ population, which is by far the largest proportion of the proposed NIP population (Table). ATAGI recommended the removal of 23vPPV from the adult schedule when the use of 13vPCV is replaced by 21vPCV (or 20vPCV) (p3, ATAGI: Optimum schedule for pneumococcal vaccination for Australian adults, July 2025).

[7] https://immunisationhandbook.health.gov.au/resources/tables/table-risk-conditions-for-pneumococcal-vaccination-and-eligibility-for-nip-funding

3.7 The proposed NIP listing of 21vPCV would allow a single dose per lifetime in the adult schedule. The proposed adult program would run in addition to the childhood vaccination program, which since 1 September 2025 includes 20vPCV as the only NIP-listed childhood vaccine for pneumococcal disease.

3.8 The submission proposed a catch-up program for those individuals eligible for vaccination with 13vPCV between 1 July 2020 and the commencement of 21vPCV on the NIP, regardless of whether they have received booster doses of 23vPPV. This was in line with the ATAGI recommendation of a single dose of 21vPCV for all adults in each target population regardless of whether they have previously received a dose of pneumococcal vaccine while maintaining the recommended interval of at least 12 months between any previous pneumococcal vaccine and their dose of 21vPCV (p15, ATAGI: Optimum Schedule for pneumococcal vaccination for Australian adults, July 2025). The rationale for this approach was based on broader disease coverage for 21vPCV compared to 13vPCV across all cohorts, the likelihood that the efficacy of 23vPPV has waned in those vaccinated prior to July 2020, and the low uptake of booster doses in those vaccinated after July 2020.

3.9 The submission proposed a Nationally Negotiated Price (NNP) for 21vPCV of $[redacted] per dose. The proposed NNP for 21vPCV was a weighted price (based on anticipated population proportions), comprising a requested price for non-Indigenous ≥ 70 years of $[redacted] (83.65%), Indigenous ≥ 50 years of $[redacted] (2.79%), $[redacted] (9.37%) for MaR adults 18-69 years, and $[redacted] (4.19%) for Indigenous 25-49 years of age.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 PD can be broadly divided into IPD (meningitis, bacteraemia and pneumonia associated with bacteraemia) and non-IPD (pneumonia, acute otitis media and sinusitis). In adults, non-IPD usually presents as community acquired pneumonia (CAP). Although this is often mild and treated in primary care, elderly or vulnerable patients can experience significant morbidity and mortality. IPD is a life-threatening condition with fatality rates between 14% and 27% in older Australians.

4.2 In Australia, there remains a substantial burden of disease in the proposed NIP populations, despite NIP listing of 13vPCV and 23vPPV. Based on notification rates from the NNDSS, 2016-2019 data the IPD incidence (cases per 100,000) in the targeted NIP populations was:

- non-Indigenous adults: 12.3 for 70 to 74 years to 35.9 for 85 years or older.
- Aboriginal and Torres Strait Islander adults: 73.7 for 50 to 54 years to 129.7 for 85 years or older.
- MaR: 12.2 for 20-24 years to 167.4 for 65-69 years.

4.3 The submission's estimates for vaccine serotype coverage were based on NNDSS data for 2016-2019. The submission stated that the 2016-2019 timeframe was selected as it excluded COVID-affected years, was more complete than 2022 data with regard to clinical manifestations, and reflected advice given by ATAGI and PBAC that a combination of years could be used to reduce data fluctuations (ATAGI Pre-submission Advice, para 6.62, 20vPCV PSD, November 2022 PBAC Meeting). Updated NNDSS data are available for 2023-24 (see Table 2).

4.4 The submission presented a comparison of incremental coverage with 21vPCV compared to 13vPCV and 20vPCV using the NNDSS IPD data from 2016-19 and 2022-23 (Table 2) and claimed there was no difference in disease coverage over the period. The incremental serotype coverage of 21vPCV using the 2023-24 NNDSS IPD data was estimated during the evaluation and compared with the submission's estimates based on 2016-19 data (Table 2). While the incremental coverage of 21vPCV over 13vPCV for the non-Indigenous 70+ cohort increased from 2016-19 to 2023-24 (favouring 21vPCV), it declined in the MaR population and was relatively unchanged for the Indigenous 50+ cohort. Similarly, incremental coverage for 21vPCV relative to 20vPCV remained relatively static for the non-Indigenous 70+ cohort but declined for the remaining cohorts. This indicates a possible shift in serotype distribution over this 8-year period (2016 to 2024).

Table 2: Difference in IPD coverage (21vPCV-13vPCV and 21vPCV –20vPCV) 2016-2019 and 2022-2023

	Non-Indigenous ≥ 70 years (% point difference)			Medically at-Risk 18 to 69[a] years (% point difference)			Aboriginal & Torres Strait Islander aged ≥ 50 years (% point difference)			Aboriginal & Torres Strait Islander aged 25-49 years (% point difference)		
Year (20XX)	**16/19**	**22/23**	**23/24**	**16/19**	**22/23**	**23/24**	**16/19**	**22/23**	**23/24**	**16/19**	**22/23**	**23/24**
Compare: 21vPCV-13vPCV	43.5	45.2	50.0	43.1	39.2	35.4	44.8	NR	45.5	NA	NA	NA
Compare: 21vPCV-20vPCV	22.6	20.7	21.4	17.7	8.9	5.2	17.5	10.8	9.0	-0.3	2.8	-1.4
Compare: 21vPCV-13vPCV+23vPPV	NA	NA	NA	6.0	0.3	5.2	8.9	6.2	9.0	-8.7	-0.9	-5.2

Source: Constructed during the evaluation based on Table 1.1-1 p3 of the submission and NNDSS IPD data for years 2023 and 2024
13vPCV = 13 valent-pneumococcal conjugate vaccine; 20vPCV = 20 valent-pneumococcal conjugate vaccine; IPD = invasive pneumococcal disease; NNDSS = National Notifiable Diseases Surveillance System; NR = not reported; 21vPCV = 21-valent-pneumococcal conjugate vaccine.
[a] non-Indigenous population aged 20-69 years used as a proxy for the MaR population.

4.5 The incidence of CAP events was derived from AIHW, 2018-2019 data using principal diagnosis hospital data (International Classification of Diseases, ICD-10-AM codes J12-J18) with a fraction attributable to *S. Pneumoniae* (20.6%; as per the ATAGI Pre-submission Advice (ATAGI Pre-submission Advice, May 2024)). The CAP inpatient incidence in non-Indigenous adults ≥ 70 years estimated by the submission ranged from 183.7 per 100,000 for those 70 to 74 years to 835.4 cases per 100,000 for those 85 years or older. In comparison, the rates for Aboriginal and Torres Strait Islander

adults ≥ 50 years ranged from 549.8 to 1,218.7 cases per 100,000, with a rate of 1,550.1 cases per 100,000 for the MaR population aged ≥ 18-69 years. The CAP outpatient incidence in non-Indigenous adults ≥ 70 years and Aboriginal and Torres Strait Islander adults ≥ 50 years ranged from 334.6 per 100,000 for those 70-74 years old to 686.7 per 100,000 for those 85 years and older, compared with 4,430.8 per 100,000 in the MaR 18-69 years population.

4.6 The submission claimed 21vPCV focuses on disease-causing strains of *S.pneumoniae* which are associated with the burden of residual pneumococcal disease in adults as well as problematic vaccine-type serotypes which benefit from direct protection. The submission based this claim on the NNDSS data (2016-2019), which report serotype distribution of IPD cases (see Table 3). The ATAGI Advice noted that 21vPCV can be considered to broaden coverage if 7-valent pneumococcal conjugate vaccine (7vPCV) serotypes are effectively controlled by infant vaccination (ATAGI Pre-submission Advice, May 2024). The ATAGI Advice noted that some serotypes not covered by 21vPCV (including those originally in 7vPCV) have not been eliminated in adults by the paediatric 13vPCV program; in 2022 one of these serotypes (19F) caused 7.9% of IPD in non-Indigenous adults ≥ 65 years. The future contribution of these serotypes to disease across the whole population is highly uncertain, as it is likely to be influenced by any introduction of extended valency conjugate vaccines to the paediatric population, which may provide different levels of direct protection to children and indirect immunity to adults than 13vPCV. If indirect protection were less under extended valency vaccines, the absence of 7vPCV serotypes from 21vPCV may lead to an increased risk of disease among adults from these serotypes. Serotype replacement by non-PCV serotypes could also result in a resurgence of IPD (ATAGI Pre-submission Advice, May 2024).

4.7 Serotype coverage for 21vPCV and other currently available pneumococcal vaccines is presented in Figure 1. This shows there is no overlap between serotypes covered by 7vPCV) and 21vPCV, and only 4 serotypes in common between 21vPCV and 13vPCV.

Figure 1: Vaccine serotype coverage

	Serotype Composition	Common STs to V116
PCV7	4 6B 9V 14 18C 19F 23F	0
PCV13	4 6B 9V 14 18C 19F 23F 1 3 5 6A 7F 19A	4
PCV15	4 6B 9V 14 18C 19F 23F 1 3 5 6A 7F 19A 22F 33F	6
PPSV23	4 6B 9V 14 18C 19F 23F 1 3 5 7F 19A 22F 33F 2 8 9N 10A 11A 12F 15B 17F 20	12
PCV20	4 6B 9V 14 18C 19F 23F 1 3 5 6A 7F 19A 22F 33F 8 10A 11A 12F 15B	10
V116	3 6A 7F 19A 22F 33F 8 9N 10A 11A 12F 17F 20 15A 15C 16F 23A 23B 24F 31 35B	

Source: Figure 1.1-3 p16 of the submission

PCV7 = 7-valent pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV15 = 15-valent pneumococcal conjugate vaccine; PCV20 = 20-valent pneumococcal conjugate vaccine; PPVS23 = 23-valent pneumococcal polysaccharide vaccine; 21vPCV = 21-valent pneumococcal conjugate vaccine.

Serotype 20 has been subtyped to serotype 20A and 20B. As subtypes 20A and 20B, are not captured in the Australian IPD data, for the purposes of this submission, serotype 20 has been included in 21vPCV disease coverage rates. To be conservative, cross-reactive serotype 15B is also not included in 21vPCV disease coverage rates.

4.8 The serotype coverage for 21vPCV and the currently available vaccines is presented in Table 3. The disease coverage for 21vPCV ranges from 66.7% to 78.3% depending on the population. ATAGI noted that coverage is substantially higher for 21vPCV when compared to 13vPCV alone in Aboriginal and Torres Strait Islander adults ≥ 50 years and MaR adults, a small amount more than 20vPCV alone, and of a similar proportion as 13vPCV + 23vPPV (ATAGI Pre-Submission Advice, May 2024).

Table 3: IPD serotype coverage with 21vPCV, 20vPCV/15/13, and 23vPPV (2016-2019 NNDSS data excluding untyped and not available)

Vaccine	Non-Indigenous ≥ 70 years	MaR aged ≥ 18 years	Indigenous ≥ 50 years	Indigenous 25 to 49 years
21vPCV [a]	74.9%	78.3%	73.9%	66.7%
13vPCV	31.4%	35.2%	29.1%	NA
15vPCV	43.1%	48.3%	37.4%	NA
20vPCV	52.2%	60.7%	56.4%	67.0%
13vPCV+23vPPV	NA	72.3%	65.0%	75.4%
Difference 21vPCV -13vPCV	43.5%	43.1%	44.8%	NA
Difference 21vPCV -20vPCV	22.6%	17.7%	17.5%	-0.3%
Difference 21vPCV -13vPCV+23vPPV	NA	6.0%	8.9%	-8.7%
Difference 21vPCV -20vPCV+23vPPV	NA	6.0%	8.9%	-8.7%

Source: Table 1.1-1 p3 of the submission

15vPCV = 15-valent-pneumococcal conjugate vaccine; 13vPCV = 13-valent-pneumococcal conjugate vaccine; 23vPPV = 23 valent-pneumococcal polysaccharide vaccine; IPD = invasive pneumococcal disease; NA = neither on NIP nor PBAC approved; MaR = medically at risk; NNDSS = National Notifiable Diseases Surveillance System; 13vPCV = 13-valent-pneumococcal conjugate vaccine; 21vPCV = 21-valent-pneumococcal conjugate vaccine

[a] 21vPCV coverage includes serotype 20 (20A subtype not typed in Australia) and excludes potentially cross-reactive serotype 15B

Non-Indigenous adults 20 to 69 years was used as surrogate population for MaR ≥ 18 years

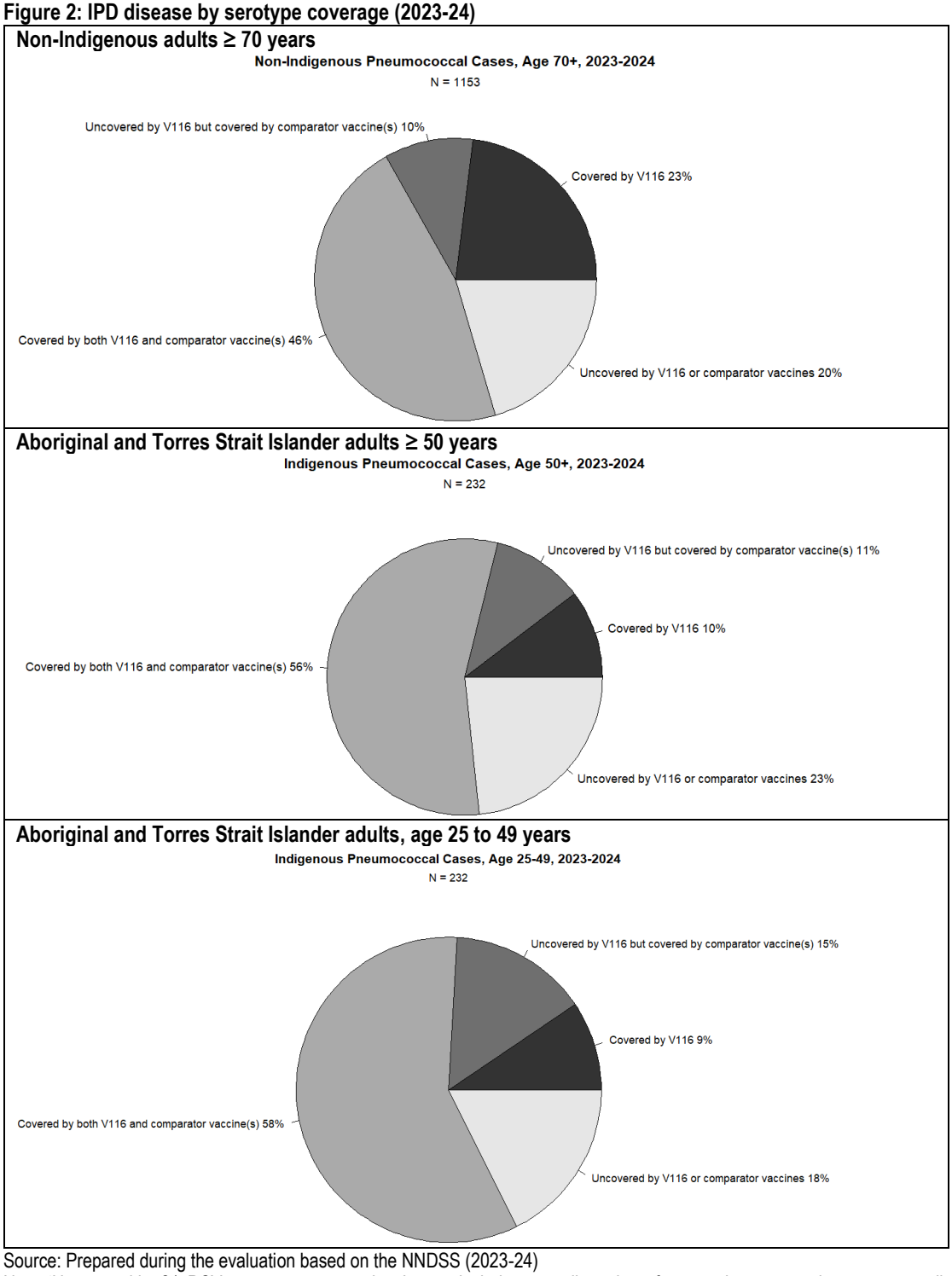
4.9 Though the listing of 21vPCV might increase the serotype coverage by inclusion of unique serotypes compared to the existing vaccines, it is possible that delisting 13vPCV from the NIP may increase the incidence of pneumococcal disease caused by serotypes not covered by 21vPCV (either overall, or as compared to 13vPCV) (ATAGI pre-submission advice to PBAC, May 2024). For the serotypes specific to 21vPCV, the rationale for the need for a new vaccine appears appropriate. Although 21vPCV covers more of the serotypes causing IPD in non-Indigenous adults aged ≥ 70 years than 13vPCV and 20vPCV (an increase of 43.5% and 22.6%, respectively), the incremental serotype coverage is comparatively lower in Aboriginal and Torres Strait Islander adults aged ≥ 50 years and MaR adults than 20vPCV alone (17.5% and 17.7% respectively), and similar in 13vPCV + 23vPPV (6% to 8.9% percentage points respectively). In Aboriginal and Torres Strait Islander adults 25 to 49 years, 13vPCV +23vPPV offered 8.7% higher serotype coverage compared to 21vPCV (75.4% versus 66.7%), i.e., 21vPCV offers less coverage in this population based on 2016-2019 NNDSS data (a similar estimate is seen with more recent data, Table 2).

4.10 A summary of recorded IPD cases (as available from the NNDSS), stratified by serotype coverage across 21vPCV and the comparator vaccines, is provided in Figure 2. These data indicate that despite the additional serotype coverage offered by 21vPCV, approximately 20% of IPD cases in non-Indigenous adults, 23% of cases in Aboriginal and Torres Strait Islander adults over 50, and 18% of cases in Aboriginal and Torres

Strait Islander adults 25 to 49 years are due to serotypes that would remain uncovered by any vaccines (including 21vPCV). The ESC noted that 21vPCV has increased coverage in terms of additional serotypes that are not covered by comparator vaccines; however, there is also a proportion of serotypes that are not covered by 21vPCV that are covered by comparator vaccines, which represents a decrease in protection from pneumococcal disease for those serotypes. The ESC noted that some serotypes absent from 21vPCV have not been eliminated in adults by the paediatric 13vPCV program and considered that ongoing childhood vaccination (including the removed serotypes) did not abrogate the risk of disease due to these serotypes in adults.

4.11 The Pre-Sub-Committee Response (PSCR) estimated the total coverage due to 21vPCV based on the 2023-2024 NNDSS data for IPD and estimated that the combination of 21vPCV in adults and 20vPCV in paediatrics could potentially lead to almost 90% coverage in adult populations (PSCR). The ESC noted that in producing these estimates, the sponsor had referred to the ATAGI post-submission advice to the PBAC, however it had assumed 100% protection for PCV20-non21vPCV (which ESC considered was overestimated). The ESC considered that the future magnitude of herd protection from the paediatric 20vPCV program was uncertain, and it would also take time to develop noting the paediatric program was implemented recently, on 1 Sep 2025.

Figure 2: IPD disease by serotype coverage (2023-24)



Source: Prepared during the evaluation based on the NNDSS (2023-24)
Note: 'Uncovered by 21vPCV or comparator vaccines' group includes a small number of cases where serotyping was not available & non-typable serotypes.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated 13vPCV which is currently listed on the NIP for adults aged ≥ 70 years, Aboriginal and Torres Strait Islander adults aged ≥ 50 years and at-risk adults aged ≥ 18 years as the primary comparator. 15vPCV and 20vPCV, which were recommended for NIP listing by the PBAC at the November 2021 and November 2022 meetings, respectively, were considered as near market comparators. The pre-PBAC response emphasised that the current NIP schedule, PCV13±2xPPV23, is the most relevant comparator as it is most likely to be replaced in the current NIP populations. The PBAC considered that 13vPCV (followed by 23vPPV boosters for MaR and Aboriginal and Torres Strait Islander adults) was the appropriate main comparator for the current NIP populations, noting that at the time of PBAC consideration, 15vPCV was not listed on the NIP, and 20vPCV was listed on the NIP for paediatric but not adult populations.

5.2 The nominated comparator for the proposed expanded population of Aboriginal and Torres Strait Islander adults aged 25 to 49 years was 20vPCV on the basis that 13vPCV is not listed for this population and 20vPCV was recommended for listing by the PBAC in this population in November 2022. The PBAC considered this was reasonable and noted it was consistent with ATAGI advice.

5.3 On the current NIP schedule, adults aged ≥ 18 years with an NIP-listed risk condition and Aboriginal and Torres Strait Islander adults aged ≥ 50 years are eligible to receive 2 subsequent doses of 23vPPV as booster doses (first booster dose at 12 months after the initial conjugate vaccine (range 2 to 12 months is acceptable); and second booster dose at least 5 years after the first booster dose). The same booster dose regimen was previously recommended by ATAGI for the expanded NIP population recommended for 20vPCV, Aboriginal and Torres Strait Islander adults 25-49 years (but is no longer recommended). In July 2025, the ATAGI recommended removal of 23vPPV from the adult schedule when the use of 13vPCV is replaced by 21vPCV (or 20vPCV).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer inputs

6.2 The PBAC noted and welcomed the input from health care professionals (2) and organisations (4) via the Office of Health Technology Assessment Consultation Hub. The PBAC noted the input was supportive of the listing of 21vPCV on the NIP for the prevention of pneumococcal disease. The inputs described a range of benefits of vaccination with 21vPCV, including broader serotype coverage and supporting

alignment of the age range with influenza (65+ years for non-indigenous Australians). The organisations supported the proposed NIP listing of 21vPCV, noting reasons including the significant burden of pneumococcal disease in older people (The Australian College of Nurse Practitioners), the disproportionate burden of IPD in First Nations populations (National Aboriginal Community Controlled Health Organisation; NACCHO), burden of disease and addressing unmet need (Lung Foundation Australia), and positive public health impacts (Immunisation Coalition).

Clinical trials

6.3 Details of the trials presented in the submission are provided in Table 4.

Table 4: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
21vPCV vs 20vPCV		
P003 (STRIDE-3) (Pivotal) (NCT05425732)	A phase 3 Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-Experienced Adults 50 Years of Age or Older.	CSR; 8 September 2023
	Platt HL, Bruno C, Buntinx E, Pelayo E, Garcia-Huidobro D, Barranco-Santana EA, Sjoberg F, Song JY, Grijalva CG, Orenstein WA, Morgan L, Fernsler D, Xu W, Waleed M, Li J, Buchwald UK; STRIDE-3 Study Group. Safety, tolerability, and immunogenicity of an adult pneumococcal conjugate vaccine, V116 (STRIDE-3): a randomised, double-blind, active comparator controlled, international phase 3 trial.	Lancet Infect Dis. 2024 Jul 1:S1473-3099(24)
21vPCV vs 15vPCV		
P007 (STRIDE-7) (HIV) (NCT05393037	A phase 3, Multicentre, Randomized, Double-blind, Active Comparator Controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Adults Living With HIV	CSR, 15 Dec 2023
P008 (STRIDE 8) At risk adults (NCT05696080)	A phase 3, Randomized, Double-blind, Active Comparator-controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-naïve Adults 18 to 64 Years of Age With Increased Risk for Pneumococcal Disease	CSR, 5 June 2024
Catch-up		
P006 (STRIDE-6) (Vaccine experienced) (NCT05420961)	A phase 3 Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-Experienced Adults 50 Years of Age or Older	CSR, 8 Sept 2023
Concomitantly with Influenza Vaccine		
P005 (STRIDE-5) (Concomitant flu) (NCT05526716)	A phase 3 Randomized, Double-blind, Placebo-Controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 When Administered Concomitantly with Influenza Vaccine in Adults 50 Years of Age or Older	CSR, 11 Sep 2023
Studies used for the ITC		
Essink 2022 (NCT03760146)	Essink B, Sabharwal C, Cannon K, Frenck R, Lal H, Xu X, Sundaraiyer V, Peng Y, Moyer L, Pride MW, Scully IL, Jansen KU, Gruber WC, Scott DA, Watson W. Pivotal Phase 3 Randomized Clinical Trial of the Safety, Tolerability, and Immunogenicity of 20-Valent Pneumococcal Conjugate Vaccine in Adults Aged ≥18 Years	Clin Infect Dis. 2022 Aug 31;75(3):390-398

Source: Table 2.2-1 p34 and Table 2.6-6 p113 of the submission.
CSR = clinical study report; ITC = indirect treatment comparison; HIV = human immunodeficiency virus; 21vPCV = 21-valent pneumococcal conjugate vaccine.

6.4 The proposed clinical claim for 21vPCV was based on 5 clinical trials (Table 5). The dosing of 20vPCV in P003 was consistent with the dosing for 20vPCV for the requested restriction and with the PBAC recommended restriction for 20vPCV in non-Indigenous adults ≥70 and indigenous adults 25 to 49 years (para 1.2, 20vPCV PSD, November

2022 PBAC Meeting). However, the dosing of 23vPPV in P007 and P008 was different from the dosing in the PBAC recommended restriction for 15vPCV and 20vPCV in Aboriginal and Torres Strait Islander adults ≥ 50 years and MaR ≥ 18 years (single dose at week 8 in P007 and P008 vs 2 doses in requested listing for 15/20vPCV) (para 1.2, 15vPCV PSD, November 2021 PBAC Meeting; para 1.2, 20vPCV PSD, November 2022 PBAC Meeting).

Table 5: Overview of clinical trials to support the clinical claim

Trial	NIP population	Intervention	Clinical claim
Main trials (NIP population)			
P003	Non-Indigenous adults ≥ 70	21vPCV vs 20vPCV	Non-inferior efficacy for 10 shared serotypes between 21vPCV and 20vPCV Superior efficacy for 10 of 11 serotypes unique to 21vPCV
	Aboriginal and Torres Strait Islander adults 25 to 49	21vPCV vs 20vPCV	Non-inferior efficacy for 10 common serotypes between 21vPCV and 20vPCV Superior efficacy for 11 unique to 21vPCV
P007	MaR ≥ 18	21vPCV vs 15vPCV + 1 dose of 23vPPV at week 8	Non-inferior efficacy for 13 common serotypes between 21vPCV and 15vPCV+23vPPV 23vPPV Superior efficacy for 8 unique serotypes to 21vPCV
P008	Aboriginal and Torres Strait Islander adults ≥ 50	21vPCV vs 15vPCV+1 dose of 23vPPV at week 8	
Supplementary trials			
P006	Catch up: Previously vaccinated with 13vPCV or 23vPPV	Cohort 1 (21vPCV vs 15vPCV) Cohort 2 (21vPCV vs 23vPPV) Cohort 3 (21vPCV)	NA
P005	Concomitant vaccination with QIV	21vPCV+QIV vs QIV +Placebo	NA

Source: Prepared during the evaluation based on Section 2.8, pp145-146; Table 1.1.8 p23 and Table 2.4-7, p55 of the submission
15vPCV = 15-valent pneumococcal conjugate vaccine; 20vPCV = 20-valent pneumococcal conjugate vaccine; 23vPPV = 23-valent pneumococcal polysaccharide vaccine; QIV = quadrivalent influenza vaccine; MaR = medically at risk; NA = not applicable; NIP = National Immunisation Program; 21vPCV = 21-valent pneumococcal conjugate vaccine.

6.5 The submission presented an indirect treatment comparison (ITC) as supportive evidence for the efficacy of 21vPCV compared to 4 common serotypes with 13vPCV (via 20vPCV as the common comparator). The evidence included the results from a randomised trial, Essink et al 2022, of 20vPCV vs 13vPCV, and P003 (21vPCV vs 20vPCV in adults > 50 years).

6.6 The submission based its claim of superior efficacy on an immunobridge between 21vPCV and its comparators. The submission relied on comparisons of immunogenicity data between 21vPCV and its comparators, including via an ITC for 13vPCV, acknowledging that efficacy data for the impact on pneumococcal disease cases has been demonstrated for 13vPCV. The submission stated that the proposed approach was justified due to broader serotype coverage for 21vPCV compared to 20vPCV, 15vPCV, 13vPCV and 23vPPV.

6.7 The ATAGI considered this rationale reasonable, although noted there may be uncertainty as to whether the relationship between the proposed immunogenicity to efficacy bridge (21vPCV immunogenicity was compared to 20vPCV, which was

compared to 13vPCV, which has efficacy data) will result in meaningful clinical protection for all unmatched serotypes. There is little overlap between the serotypes in 21vPCV and 13vPCV (4 shared serotypes) and whilst there are an additional 6 shared between 21vPCV and 20vPCV, 20vPCV has not been in use for long enough (and is not yet available on the NIP) to be certain that clinical protection is provided for these serotypes (ATAGI Pre-submission Advice, May 2024).

6.8 The TGA Clinical Evaluation Report (CER) noted that no evidence demonstrating clinical benefits of 21vPCV in preventing pneumococcal disease caused by the unique serotypes represented in 21vPCV in older adults and those at greater risk of pneumococcal disease due to underlying comorbidities was presented by the sponsor. The TGA CER noted that although immunogenicity data was accepted as a surrogate of clinical efficacy, it was important to collect epidemiological data on IPD and pneumococcal disease and monitor for vaccine-escape strains (TGA CER).

6.9 The key features of the randomised trials are summarised in Table 6.

Table 6: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Participant population	Outcomes	Use in modelled evaluation
21vPCV vs 20vPCV						
P003	2,663	R, DB, MC 6 mths	Low	Cohort 1: Pneumococcal vaccine-naïve participants ≥50 years of age;	OPA, IgG, Safety	Not used
				Cohort 2: Pneumococcal vaccine-naïve participants: 18 to 49 years of age	OPA, IgG, Safety	Not used
21vPCV vs 15vPCV						
P007	313	R, DB, MC 19 mths	Low	Adults living with HIV (≥18 years of age)	OPA, IgG, Safety	Not used
P008	518	R, DB, MC 14 mths	Low	Adults 18 to 64 years of age with at least 1 risk condition (e.g. diabetes, COPD, asthma, CHD, CKD)	OPA, IgG, Safety	Not used
Catch-up						
P006	717	R, DB, MC 6 mths	Low	Pneumococcal vaccine-experienced adults (≥50 years of age	OPA, IgG, Safety	Not used
Concomitant vaccination						
P005	1,080	R, DB, MC 9 mths	Low	Healthy male and female participants, ≥50 years of age	OPA, IgG, Safety	Not used

Source: Table 2.4-7 to Table 2.4-11, pp55-60 of the submission; Table 10-1, p42 P005 CSR; Section 6.3, p11 P005 Protocol
DB = double blind; IgG = immunoglobulin G; MC = multi-centre; OL = open label; OPA = opsonophagocytic activity; OS = overall survival; PFS = progression-free survival; R = randomised.

6.10 The key outcome to support the clinical claims was serotype-specific opsonophagocytic activity (OPA) at 30 days after vaccination measured as the geometric mean titre (GMT), from which geometric mean ratios (GMRs) were calculated. The submission stated that OPA can be used as an immunologic surrogate endpoint in adults to predict 21vPCV vaccine effectiveness. The PBAC has previously seen extrapolation of immunogenicity trials in terms of OPA to clinical effectiveness (immunobridging) and highlighted issues in assuming benefit in terms of disease prevention 'as there is no specific threshold of OPA titre that correlates with protection against IPD or pneumonia in adults', and the relationship to clinical

outcomes for the shared serotypes does not necessarily hold for non-shared serotypes (para 7.3, 20vPCV PSD, November 2022 PBAC meeting). These previous concerns from the PBAC are particularly relevant in the case of applying an immunobridge to 21vPCV from 13vPCV, given that only 4 serotypes are shared between the two vaccines (see paragraph 6.44).

6.11 The ATAGI Advice noted there was some uncertainty as to whether the immunobridging assumption from 13vPCV to 21vPCV will necessarily hold for all 17 serotypes in 21vPCV but not in 13vPCV and referred to the WHO Guidelines that state that "the limitations of these comparisons in predicting efficacy should be taken into account when considering the overall benefit/risk relationship for the new vaccine" (ATAGI Pre-Submission Advice, May 2024).

NIP Population-Main trials (P003, P007, P008)

Non-Indigenous adults ≥ 70 years

6.12 In P003, the primary objective was to demonstrate, in adults 50 years and older, non-inferiority of immune response (serotype specific OPA GMT 30 days after vaccination) for 10 common serotypes included in 21vPCV compared to 20vPCV, and superiority for the 11 unique serotypes included in 21vPCV compared to 20vPCV.

6.13 The submission presented a subgroup analysis of data from P003 Cohort 1 to support its claim of efficacy in non-Indigenous adults ≥ 70 years. This was an exploratory analysis; the subgroup analysis was not powered to determine noninferiority of the outcomes. Subgroup analysis by different ages was not pre-specified nor stratified at randomisation in P003. Moreover, P003 was not designed to evaluate efficacy of 21vPCV versus 13vPCV (OPA GMT/IgG GMC at Day 30 postvaccination). Thus, the results from this analysis should be interpreted with caution.

6.14 The non-inferiority criterion that defined the OPA GMR outcomes in P003 was the lower bound of the 2-sided 95% confidence interval (CI) of the OPA GMR > 0.50. This criterion for OPA GMR > 0.5 is lower than the World Health Organization (WHO) recommended lower bound of the 95% CI of 0.67. ATAGI considered a lower bound of 0.5 to be acceptable but noted concerns regarding the use of low thresholds that could result in acceptance of subsequent vaccines despite inferior immunogenicity to an originally licensed vaccine (ATAGI Pre-Submission Advice, May 2024).

6.15 Superiority criteria were pre-specified in P003 for OPA GMT and for the proportion of participants with a ≥ 4-fold rise in OPA responses at day 30. The superiority criteria that defined the OPA GMR at 30 days for the 11 unique serotypes in 21vPCV, were the lower bound of the 2-sided 95% CI of the OPA GMR > 2.0. The superiority criterion for serotype 15C in P003 was the lower bound of the 2-sided 95% CI of the OPA GMT ratio > 1.2. The superiority criteria that defined the proportion of participants with a ≥ 4-fold rise in OPA responses at day 30 for 21vPCV compared to 20vPCV in P003, was the lower bound of the 2-sided 95% CI for the difference (21vPCV – 20vPCV) being > 0.1.

MaR and Indigenous populations

6.16 The submission presented evidence from studies P007 and P008 comparing 21vPCV to 15vPCV followed by 23vPPV in high-risk populations human immunodeficiency virus (HIV) positive (P007) and at-risk adults (P008). This evidence was used by the submission to support use in the MaR population aged ≥ 18 years and Aboriginal and Torres Strait Islander adults aged ≥ 50 years; assuming that the P008 trial would be representative of health status in Aboriginal and Torres Strait Islander adults ≥ 50 years.

6.17 The submission presented a subgroup analysis of data from P003 Cohort 2 to support its claim of efficacy in Aboriginal and Torres Strait Islander adults aged 25-49 years.

Supplementary trials

6.18 The evidence from studies P005 and P006 was used to support concomitant administration of 21vPCV with other vaccines and the use of 21vPCV in the catch-up population respectively. While P006 evaluated the efficacy of 21vPCV postvaccination (OPA GMT ratio) with PCV, P005 evaluated the safety and tolerability of 21vPCV when administered concomitantly or sequentially with flu vaccine.

Applicability of the evidence

6.19 Although the clinical trials included participants that covered the relevant age groups for the proposed NIP listing, the following differences between the populations in the included studies and those in the proposed listing were noted:

- Evidence for non-Indigenous adults ≥ 70 years relied on a subgroup analysis (N = 568, 24%) from P003 Cohort 1 of adults ≥ 50 years (N = 2,362). The subgroup analysis was not powered to determine noninferiority outcomes.
- There was a lack of racial diversity across all the populations included in the trials. The trials included a small proportion of participants in Australia (< 5%) and there were no Indigenous Australian participants in the trials.
- Evidence for MaR adults ≥ 18 years (P007, N = 313) and Aboriginal and Torres Strait Islander adults ≥ 50 years (P008 = 518) did not include data for specific medical risk conditions listed on the NIP, for example, people with functional or anatomical asplenia, immunocompromising conditions (except HIV) and those with prior history of IPD (ATAGI pre-submission Advice, May 2024).

Comparative effectiveness

NIP Population-Main trials (P003, P007, P008)

6.20 A summary of evidence presented in the submission indicating if non-inferiority and superiority criteria were met in the comparisons of 21vPCV against 13vPCV, 15vPCV + 23vPPV and 20vPCV is presented in Table 7. The results in the table indicate whether non-inferiority or superiority was met for the vaccine comparison of interest for each 21vPCV serotype, as well as whether the results favoured 21vPCV, its comparator or neither (favours 21vPCV if the lower bound of the 95%CI were >1, favours comparator vaccine if the upper bound of the 95%CI were <1).

Table 7: **Results of immunogenicity across the trials: dichotomous data**

Sources of Results	Non-Indigenous ≥ 70			Aboriginal and Torres Strait Islander adults ≥50 years and MaR		Aboriginal and Torres Strait Islander adults 25 to 49 years
	21vPCV vs 20vPCV	21vPCV vs 20vPCV	21vPCV vs 13vPCV	21vPCV vs 15vPCV+23vPPV	21vPCV vs 15vPCV+23vPPV	21vPCV vs 20vPCV
	P003: Cohort 1≥50 years	P003: Subgroup Analysis ≥70 years	ITC: P003; Essink et al, 2020)	P007: HIV positive	P008: At risk adults aged 18 to 65 years	P003: Cohort 2 18 to 49 years
Common Serotypes (non-inferiority claim)						
3	Y (21vPCV)	Y (21vPCV)	Y (21vPCV)	Y	Y	Y (21vPCV)
6A	Y (20v)	Y	N	Y	Y (21vPCV)	N
7F	Y	Y	Y	Y	Y (21vPCV)	Y
8	Y (21vPCV)	Y	NA	Y	Y	Y (21vPCV)
9N	NA	NA	NA	Y	Y (21vPCV)	NA
10A	Y (20v)	Y	NA	Y	Y (21vPCV)	Y
11A	Y (21vPCV)	Y (21vPCV)	NA	Y (21vPCV)	Y (21vPCV)	Y (21vPCV)
12F	Y	Y	NA	Y	Y (21vPCV)	Y
17F	NA	NA	NA	Y (21vPCV)	Y (21vPCV)	NA
19A	Y (20v)	Y	N	Y	Y	Y (20v)
20A	NA	NA	NA	Y (21vPCV)	Y (21vPCV)	NA
22F	Y (20v)	Y	NA	Y	Y (21vPCV)	Y
33F	Y (21vPCV)	Y	NA	Y	Y (21vPCV)	Y (21vPCV)
Additional serotypes (superiority claim)						
9N	Y (21vPCV)	Y (21vPCV)	NA	NA	NA	Y (21vPCV)
15A	Y (21vPCV)	Y (21vPCV)	NA	Y (21vPCV)	Y (21vPCV)	Y (21vPCV)
15C	N	N	NA	N	Y (21vPCV)	N
16F	Y (21vPCV)	Y (21vPCV)	NA	Y (21vPCV)	Y (21vPCV)	Y (21vPCV)
17F	Y (21vPCV)	Y (21vPCV)	NA	NA	NA	Y (21vPCV)
20A	Y (21vPCV)	Y (21vPCV)	NA	NA	NA	Y (21vPCV)
23A	Y (21vPCV)	Y (21vPCV)	NA	Y (21vPCV)	Y (21vPCV)	Y (21vPCV)
23B	Y (21vPCV)	Y (21vPCV)	NA	Y (21vPCV)	Y (21vPCV)	Y (21vPCV)
24F	Y (21vPCV)	Y (21vPCV)	NA	Y (21vPCV)	Y (21vPCV)	Y (21vPCV)
31	Y (21vPCV)	Y (21vPCV)	NA	Y (21vPCV)	Y (21vPCV)	Y (21vPCV)
35B	Y (21vPCV)	Y (21vPCV)	NA	Y (21vPCV)	Y (21vPCV)	Y (21vPCV)

Source: Table 2.8-1 p142 of the submission

15vPCV = 15-valent pneumococcal conjugate vaccine; 20vPCV = 20-valent pneumococcal conjugate vaccine 23vPPV = 23-valent pneumococcal polysaccharide vaccine; CI = confidence interval; n = number of participants with event; N = total participants in group; NA = not applicable; 21vPCV = 21-valent pneumococcal conjugate vaccine.

(20v) favours 20vPCV as the upper bound of the 95%CI were <1

(21vPCV) favours 21vPCV as the lower bound of the 95%CI were >1

Y: non-inferiority/superiority was met but it straddles 1

N: non-inferiority/superiority was not met

6.21 Across the 10 shared serotypes for P003 Cohort 1, the OPA GMRs for 4 serotypes (3, 8, 11A and 33F) favoured 21vPCV, and 4 serotypes (6A, 10A, 19A and 22F) favoured 20vPCV. For the additional 8 serotypes (15A, 15C, 16F, 23A, 23B, 24F, 31 and 35B) 21vPCV met the superiority criterion except for serotype 15C.

6.22 The results of P007 showed the immune responses as assessed by OPA GMTs postvaccination with 21vPCV + Placebo at day 30 for the 13 common serotypes compared to 15vPCV +23vPPV were not different for 10 serotypes (3, 6A, 7F, 8, 9N, 10A, 12F, 19A, 22F, 33F) and were higher for three serotypes (11A, 17F, 20A). The OPA GMTs were higher with 21vPCV + Placebo than 15vPCV + 23vPPV for the 8 serotypes unique to 21vPCV. The non-inferiority/superiority criteria were not pre-specified in this trial.

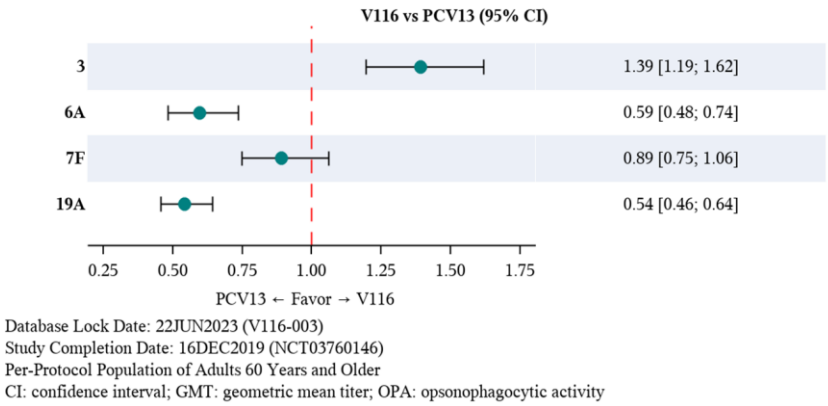
6.23 The results of P008 showed the immune responses as assessed by OPA GMTs postvaccination with 21vPCV + Placebo at day 30 for the 13 common serotypes compared to 15vPCV +23vPPV were not different for three serotypes (3, 8, 19A) and higher for 10 serotypes (6A, 7F, 9N, 10A, 11A, 12F, 17F, 20A, 22F, 33F). The OPA GMTs were higher with 21vPCV + Placebo than 15vPCV + 23vPPV for the 8 serotypes unique to 21vPCV. The non-inferiority/superiority criteria were not pre-specified in this trial.

ITC between 21vPCV vs 13vPCV

6.24 The ITC was based on trials NCT03760146 (N = 2,997) and P003 (N = 1,571) and applied a matching-adjusted indirect comparison (MAIC) supplemented by the Bucher method. The MAIC report only referred to matching based on age and gender. However, pre-existing comorbidities that affect the risk of complications with pneumococcal infection are important modifiers with respect to assessing vaccine efficacy in these populations. Information could not be located on whether the study populations have been matched for the presence of such risk factors, thereby potentially confounding the results of the ITC.

6.25 The results of the ITC for the 4 serotypes for participants aged ≥ 60 years between 21vPCV and 13vPCV are presented in Figure 3. The lower bound of the 2-sided 95% CI of the OPA GMT ratio for serotype 3 was above 1.00, in favour of 21vPCV, demonstrating stronger immune response to serotype 3 as compared to 13vPCV. However, the results from the ITC did not support the non-inferiority for two (6A and 19A favoured 13vPCV) of the 4 serotypes, while for serotype 7F the 95% CI spanned one, indicating no difference. Based on these results, superiority of 21vPCV over 13vPCV with respect to immunogenicity appears to be serotype-specific, and confined to one serotype, serotype 3, with the results favouring 13vPCV in 2 of the shared serotypes.

Figure 3: Serotype Specific OPA GMT Ratio Matching Adjusted Indirect Comparison Analysis (Anchored) 21vPCV vs 13vPCV



Source: Figure 2.6-5 p123 of the submission

13vPCV = 13-valent pneumococcal conjugate vaccine; CI = confidence interval; OPA GMT = opsonophagocytic activity geometric mean titre; 21vPCV = 21-valent pneumococcal conjugate vaccine.

Note that the results presented in this figure are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of a pre-specified statistical plan for a clinical study. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.26 The submission stated that the ITC provided limited value in assessing the immunogenicity between 21vPCV and 13vPCV. The ITC has been deemed as supportive evidence only by ATAGI (ATAGI Pre-submission Advice, May 2024). In addition, there are differences in the characteristics and conduct of the trials used in the ITC that call the results of the indirect comparison into question:

- The pivotal studies in this analysis used different OPA assays; both intra-assay and inter-assay variability limit the ability to directly compare GMTs. While the use of the GMT ratio measure directly limits the impact on variability in assay differences, there may be other differences that are not accounted for that could not be corrected statistically.
- The analyses could only be performed in adults ≥ 60 years of age as this was the group for which published 13vPCV data were available. This is younger than the age of the proposed listing, and analysis for this age group was not pre-specified in P003.
- Other treatment effect modifiers (beyond age and gender, adjusted for in the matching) may exist which are not included in the ITC analyses. The unknown confounders assumption is not testable. Whether characteristics other than age and sex of participants were balanced across the included trials is unknown; therefore, the potential for differences in other factors affecting efficacy (such as comorbidities) cannot be discounted.
- Whether the design of P003 and Essink et al 2022 is comparable was not addressed by the submission. The Essink et al 2022 was a phase 3, randomised active controlled double blind multicentre study conducted in the USA and Sweden. The population in Essink et al 2022 comprised adults ≥ 18-year-olds in 3 cohorts based on age at enrolment (≥60, 50–59, and 18–49 years). While Essink et al 2022 included adults

aged ≥60 years, P003 included adults aged ≥50 years. Essink et al 2022 had a higher proportion of female participants compared to P003 which resulted in a reduction in the effective sample size of P003 after matching to the Essink et al 2022 sex distribution. Additionally, Essink et al 2022 had a higher proportion of participants in the 60-64 years age group compared to P003 further reducing the effective sample size for P003 after matching. This loss of sample size could impact the power and precision of comparisons between the studies in the ITC.

Supplementary trials:

6.27 In P006 (catch-up population), across all 3 cohorts previously vaccinated with 13vPCV or 23vPPV, 21vPCV was immunogenic for all 21 serotypes contained in the vaccine as assessed by serotype-specific OPA GMTs at 30 days postvaccination. Serotype-specific OPA GMTs and IgG GMCs were not different in the 21vPCV, 15vPCV, and 23vPPV groups for the common serotypes and higher in the 21vPCV group for the serotypes unique to 21vPCV. In Cohort 1 (prior 23vPPV; vaccinated with either 21vPCV or 15vPCV), 21vPCV elicited immune responses that were not different to 15vPCV for the 6 common serotypes and higher than 15vPCV for the 15 serotypes unique to 21vPCV, as assessed by OPA GMTs at 30 days postvaccination. In Cohort 2 (prior 13vPCV; vaccinated with either 21vPCV or 23vPPV), 21vPCV elicited immune responses that were not different to 23vPPV for the 12 common serotypes and higher than 23vPPV for the 9 serotypes unique to 21vPCV, as assessed by OPA GMT at 30 days postvaccination.

6.28 P005 showed that 21vPCV administered concomitantly with QIV (quadrivalent influenza vaccine) was non-inferior to 21vPCV administered sequentially with QIV as assessed by serotype-specific OPA GMTs at 30 days postvaccination with 21vPCV. The lower bound of the 2 sided 95% CI of the OPA GMT ratio (concomitant/sequential) > 0.5 for 20 of the 21 pneumococcal serotypes at 30 days postvaccination with 21vPCV. ATAGI noted that while co-administration is largely acceptable based on the non-inferiority criteria in P005, the reduced immune response to QIV and 21vPCV, may favour separate administration. Where sequential administration is logistically challenging/not feasible, co-administration is acceptable to facilitate vaccination uptake (ATAGI pre-submission advice to PBAC, May 2024).

Comparative harms

6.29 The proportion of participants with systemic AEs and vaccine-related systemic AEs (up to day 5 post vaccination) was generally comparable across 21vPCV and 20vPCV (P003) and 15vPCV + 23vPPV (P007/P008), see Table 8. The proportions of participants who experienced serious adverse events (SAEs) were low (≤ 2%) in the study and comparable across intervention groups, and none of the SAEs were considered to be vaccine related. No deaths were considered by the investigator to be vaccine related. The ATAGI advised “Phase 3 safety data indicated that 21vPCV has a similar safety profile to 20vPCV and 23vPPV. This is likely to be acceptable, although no safety data were available for at-risk people as defined on the NIP, or for Aboriginal and Torres

Strait Islander populations. Safety risks are likely to be similar to 13vPCV, which is on the NIP for these populations" (ATAGI Pre-submission Advice, May 2024).

Table 8: Adverse Event Summary (All Participants as Treated Population), Main trials (P003, P007, P008)

	P003 Cohort 1 (≥ 50 years)		P003, Cohort 2 (18 to 49 years)		P007		P008	
	21vPCV	20vPCV	21vPCV	20vPCV	21vPCV + Placebo	15vPCV + 23vPPV	21vPCV + Placebo	15vPCV + 23vPPV
	n (%), N=1,177	n (%), N=1,175	n (%), N=200	n (%), N=100	n (%), N=155	n (%), N=155	n (%), N=386	n (%), N=130
One or more AE	685 (58.2)	778 (66.2)	164 (82.0)	79 (79)	111 (71.6)	141 (91.0)	265 (68.7)	118 (90.8)
Systemic AEs	461 (39.2)	470 (40.0)	118 (59.0)	50 (50)	98 (63.2)	92 (59.4)	199 (51.6)	89 (68.5)
Vaccine-related[a] AE	609 (51.7)	715 (60.9)	159 (79.5)	78 (78)	96 (61.9)	136 (87.7)	241 (62.4)	112 (86.2)
Injection-site	505 (42.9)	642 (54.6)	146 (73.0)	75 (75)	79 (51.0)	130 (83.9)	206 (53.4)	107 (82.3)
Systemic	322 (27.4)	316 (26.9)	102	42 (42)	67 (43.2)	70 (45.2)	154 (39.9)	70 (53.8)
Serious AE	19 (1.6)	24 (2.0)	1 (0.5)	3 (3)	4 (2.6)	6 (3.9)	10 (2.6)	7 (5.4)
Serious vaccine-related AE	0 (0.0)	0 (0.0)	0	0 (0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	4 (0.3)	2 (0.2)	0	0 (0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
One or more solicited AE	600 (51.0)	708 (60.3)	161 (80.5)	78 (78.0)	96 (61.9)	136 (87.7)	243 (63.0)	113 (86.9)
Solicited injection site AE	487 (41.4)	630 (53.6)	144 (72.0)	75 (75.0)	79 (51.0)	130 (83.9)	203 (52.6)	113 (86.9)
Injection site erythema	64 (5.4)	74 (6.3)	31 (15.5)	13 (13.0)	6 (3.9)	17 (11.0)	35 (9.1)	17 (13.1)
Injection site pain	464 (39.4)	607 (51.7)	143 (71.5)	74 (74.0)	78 (50.3)	128 (82.6)	200 (51.8)	107 (82.3)
Injection site swelling	71 (6.0)	98 (8.3)	28 (14.0)	14 (14.0)	11 (7.1)	32 (20.6)	31 (8.0)	33 (25.4)
Solicited systemic AE	334 (28.4)	323 (27.5)	107 (53.5)	44 (0)	67 (43.2)	67 (43.2)	157 (40.7)	102 (78.5)
Fatigue	237 (20.1)	230 (19.6)	81 (40.5)	34 (34.0)	47 (30.3)	53 (34.2)	117 (30.3)	46 (35.4)
Headache	135 (11.5)	152 (12.9)	59 (29.5)	24 (24.0)	34 (21.9)	30 (19.4)	86 (22.3)	72 (55.4)
Myalgia	70 (5.9)	79 (6.7)	33 (16.5)	14 (14.0)	19 (12.3)	24 (15.5)	42 (10.9)	59 (45.4)
Pyrexia	15 (1.3)	15 (1.3)	7 (3.5)	1 (1.0)	3 (1.9)	5 (3.2)	12 (3.1)	34 (26.2)

Source: Table 2.5-15 p88 of submission; Table 2.5-16 p89, Table 2.5-26 p95, Table 2.8-3 p144 of the submission, Table 12-4 P003 CSR
20vPCV = pneumococcal 20-valent conjugate vaccine; 21vPCV = pneumococcal 21-valent conjugate vaccine
[a] Determined by the investigator to be related to the vaccine.
Notes: Reported adverse events include nonserious adverse events within 30 days of vaccination and serious adverse events occurring day 1 through the duration of participation in the study
MedDRA version 26.0 was used in the reporting of this study
Every subject is counted a single time for each applicable row and column.
Injection site erythema, injection site pain, and injection site swelling, fatigue, headache, and myalgia were solicited from Day 1 to Day 5 following vaccination. Pyrexia was defined as maximum temperature ≥100.4F (38.0C) solicited from Day 1 through Day 5 postvaccination.

Benefits/harms

6.30 Given the submission's claim was based on immunogenicity data, a comparative benefits and harms table has not been provided.

Clinical claim

6.31 The submission claimed that in adults ≥ 18 years, 21vPCV has superior effectiveness against pneumococcal disease compared to 13vPCV and 20vPCV in current NIP populations and non-inferior effectiveness in Aboriginal and Torres Strait Islander adults aged 25-49 years. The claims for superiority should be interpreted with caution as they were not supported by evidence demonstrating clinical effectiveness. For all populations, the ESC considered there was uncertainty with respect to significance of immunogenicity results for non-shared serotypes, and uncertainty with respect to linking immunogenicity results with clinical outcomes.

Comparison of immunogenicity outcomes

6.32 The specific efficacy claims (based on immunogenicity outcomes) were:

Non-Indigenous 70+:

- For the 4 common serotypes compared to 13vPCV, 21vPCV has a higher immune response for serotype 3, and no different immune response for 7F. The submission did not establish non-inferiority for 2 of the 4 common serotypes (6A and 19A).
- For the 10 common serotypes, 21vPCV is non-inferior to 20vPCV.
- For 10 of the 11 unique serotypes 21vPCV is superior to 20vPCV (15C did not achieve superiority due to likely cross reactivity with 15B from 20vPCV). The submission did not establish superiority for 1 of the 11 unique serotypes.

Aboriginal and Torres Strait Islander adults ≥ 50 years and MaR aged ≥18 years:

- For the 13 common serotypes 21vPCV is non-inferior to 15vPCV followed by 23vPPV.
- For 8 unique serotypes 21vPCV is superior to 15vPCV, except for 15C in study P007 due to likely cross reactivity with 15B from 23vPPV. The submission did not establish superiority for 1 of the 8 unique serotypes.

Aboriginal and Torres Strait Islander adults 25 to 49 years:

- For the 10 common serotypes, 21vPCV is non-inferior to 20vPCV.
- For the 11 unique serotypes 21vPCV is superior to 20vPCV. The submission presented a comparison of 21vPCV with 20vPCV alone in this population and did not present a comparison of 21vPCV with the comparator regimen recommended previously by the PBAC in November 2022, which included 20vPCV plus 23vPPV booster doses. There are 11 additional serotypes in the comparator regimen that are not found in 21vPCV. The ESC noted ATAGI's advice to remove the 23vPPV doses from the recommendation for 20vPCV.

6.33 The ESC agreed with the evaluation that based on the ITC for the 4 shared serotypes, the claim of superior efficacy of 21vPCV compared to 13vPCV was not reasonable as it was only met for 1 out of 4 serotypes shared with 13vPCV. The submission's claim assumed the immunogenicity to efficacy bridge will hold for all serotypes, however, 21vPCV shares only 4 serotypes with 13vPCV, for which there are efficacy data, noting that 2 out of 4 serotypes had lower immune response with 21vPCV compared to 13vPCV. The future contribution of these serotypes to disease across the whole population is highly uncertain (ATAGI Pre-submission Advice, May 2024).

6.34 The ESC agreed with the evaluation that on the basis of the comparisons presented, the claim of non-inferiority of 21vPCV against 20vPCV and 15vPCV appears reasonable in the context of shared serotypes. ATAGI raised concerns about the incrementally lower immune responses (i.e., downward drift) when comparing between PCVs from 13vPCV to 20vPCV/15vPCV to 21vPCV for shared serotypes; it is uncertain whether the observed immunogenicity findings will translate into differences in clinical protection between vaccines (p8, ATAGI: Optimum Schedule for pneumococcal vaccination for Australian adults, July 2025). The ATAGI Advice noted that the clinical claim of 21vPCV superiority compared to 20vPCV in non-Indigenous adults ≥ 65 years and 20vPCV in MaR adults ≥ 18 years made by the submission was based on vaccine serotype coverage only, not on non-inferiority/superiority of 21vPCV immunogenicity, although predefined immunogenicity criteria were specified in the pivotal trial P003 comparing 21vPCV and 20vPCV (see paragraphs 6.14 and 6.15).

6.35 For the non-shared serotypes, the ATAGI Advice noted that while a clinical claim of non-inferiority of shared serotypes, based on trial data, may be acceptable, any claim of superiority for additional serotypes is subject to uncertainty, as correlates of protection are different for different serotypes (ATAGI Pre-submission Advice, May 2024). The ESC agreed with the evaluation, that the claim of superiority of 21vPCV against 13vPCV, 20vPCV and 15vPCV for non-shared serotypes was not adequately supported. The ATAGI Advice stated that comparing serotype specific responses with a vaccine that does not contain those serotypes is problematic (ATAGI pre-submission Advice, May 2024). In addition, the ATAGI Advice noted that some of the 21vPCV individual serotypes do not match the summary VE of 75% for IPD and 45% for pneumococcal CAP, and the serotype distribution in CAP in Australia is not known (ATAGI Pre-submission Advice, May 2024). The submission included sensitivity analyses in the economic evaluation in which VE for non-13vPCV serotypes in 21vPCV were decreased by 45% (relative reduction) as recommended by the ATAGI. For those sensitivity analyses, the assumed VE for 21vPCV was 41.3% for IPD (compared with 75% in the base case), and 24.8% for CAP (compared with 45% in the base case).

6.36 The OPA GMTs for non-shared serotypes were higher with 21vPCV than the comparator vaccines. It is possible that having higher GMTs may confer a longer duration of protection, but without data on waning, this is hard to confirm. Therefore, a higher immune response may not necessarily result in increased disease protection.

Comparison of serotype coverage

6.37 For the current NIP populations (non-Indigenous adults aged ≥ 70 years; MaR aged ≥ 18 years; and Aboriginal and Torres Strait Islander adults aged ≥ 50 years), the submission claimed that 21vPCV was superior in clinical effectiveness against pneumococcal disease compared to 13vPCV and 20vPCV, based on increased serotype coverage with 21vPCV and its translation to a reduction in IPD and CAP. The ESC considered the claim of overall superior effectiveness uncertain, noting that serotype coverage varied between populations as discussed below:

- For the Non-Indigenous ≥70 years population, the assumed increase in disease coverage for 21vPCV was 43.5% compared with 13vPCV and 22.6% compared with 20vPCV. Based on these estimates, the ESC considered there was likely greater serotype disease coverage with 21vPCV than either 13vPCV or 20vPCV alone.
- For the MaR aged ≥18 years population, the assumed increase in disease coverage for 21vPCV was 6.0% when 21vPCV was compared with 13vPCV (or 20vPCV) plus 23vPPV booster doses. The submission estimated equal coverage for both regimens after additional coverage associated with the booster was considered. Based on these estimates, the ESC considered there was a slight increase in serotype disease coverage with 21vPCV over these regimens, but the significance was unclear as it was modest based on these estimates and likely to change over time. The ESC noted ATAGI's recommendation to remove the booster doses and considered there was likely greater serotype disease coverage with 21vPCV than either 13vPCV or 20vPCV alone.
- For the Indigenous ≥50 years population, the assumed increase in disease coverage for 21vPCV was 8.9% when 21vPCV was compared with 13vPCV (or 20vPCV) plus 23vPPV booster doses. The submission estimated equal coverage for both regimens after additional coverage associated with the booster was considered. Based on these estimates, the ESC considered there was a slight increase in serotype disease coverage with 21vPCV over these regimens, but the significance was unclear as it was modest based on these estimates and likely to change over time.

6.38 For the Indigenous 25 to 49 years population, the submission claimed that 21vPCV was non-inferior in clinical effectiveness against pneumococcal disease compared to 13vPCV and 20vPCV, based on serotype coverage. The change in disease coverage for 21vPCV was negative, with a change of 0.3% compared with 20vPCV alone, and -8.7% when 21vPCV was compared with 20vPCV plus 23vPPV booster doses. Based on these estimates, the ESC considered there was similar serotype coverage compared with 20vPCV alone, but if the booster is considered then serotype coverage is lower with 21vPCV. The ESC noted ATAGI's recommendation to remove the booster doses and considered the coverage of 21vPCV and 20vPCV were similar. As for the other populations, there may be a change in the estimates over time.

6.39 The PSCR argued that the broader direct and indirect protection with 21vPCV compared to both 13vPCV and 20vPCV, as acknowledged by ATAGI, should constitute sufficient evidence to support a claim of superiority in clinical effectiveness.

Overall interpretation

6.40 In terms of comparative effectiveness, the ESC considered that there was significant uncertainty regarding prevalence of disease serotypes over time, the impact of herd immunity afforded by paediatric vaccines, and the relative vaccine efficacy. The pre-PBAC response noted ATAGI's preferential recommendation for 21vPCV and suggested this was consistent with a claim of superior public health outcomes for 21vPCV over 13vPCV and 20vPCV, as 21vPCV will prevent more cases of pneumococcal disease than the alternatives, especially given 20vPCV is now the incumbent paediatric vaccine. The pre-PBAC response stated that 21vPCV would provide a significant improvement over alternatives in terms of a reduction in pneumococcal disease, including reductions in hospitalisations and deaths.

6.41 The PBAC considered the claim of superior comparative effectiveness was partly supported by the data, noting that 21vPCV has higher serotype coverage compared with 13vPCV and 20vPCV based on current data, however the magnitude of the translation from immunogenicity outcomes to clinical effectiveness was uncertain. The PBAC noted ATAGI's advice that a 21vPCV program will provide the greatest impact on pneumococcal disease compared to other currently available pneumococcal vaccines. This advice was based on 21vPCV providing the broadest serotype coverage, particularly in the context of the existing 20vPCV program for children (implemented on 1 Sep 2025), and ATAGI acknowledged uncertainties associated with this. The PBAC agreed with ATAGI that it was reasonable to accept that 21vPCV will provide a significant improvement in efficacy if implemented on the NIP as proposed. The PBAC agreed with the ESC that the uncertainties described above relating to serotype coverage and immunobridging evidence, could be explored with relevant sensitivity analyses and managed with a conservative approach in the economic model (e.g. lower vaccine efficacy for non-shared serotypes, and shorter time horizon, see paragraph 6.62).

6.42 In terms of safety, the submission described 21vPCV as non-inferior to 13vPCV, 15vPCV, 20vPCV and 23vPPV. The PBAC agreed with the ESC that this was reasonable.

Economic analysis

6.43 The submission presented results from a separate CUA with results expressed as the cost per quality-adjusted life year (QALY) gained ($/QALY) for the current NIP populations for 13vPCV ± 23vPPV and the near-market comparator 20vPCV. The PBAC considered that 13vPCV ± 23vPPV was the appropriate main comparator for the current NIP populations (paragraph 5.1). The submission presented a CMA for the Indigenous population aged 25 to 49. The submission relied on the superior efficacy claim to justify the CUA. The submission stated that there is no bridge to efficacy for non-13vPCV serotypes in 21vPCV, but it is likely that the immune responses observed with 21vPCV for non-13vPCV serotypes will translate to clinical protection. There was no evidence presented in the submission that translated the comparative treatment effects for immunogenicity (a surrogate outcome) to pneumococcal disease cases avoided.

Cost-utility analysis

6.44 The submission presented a Markov model that was not informed by the clinical studies presented in the submission. The CAPiTA study, a double-blind RCT of 13vPCV vs no vaccine, was used to model VE and the subsequent impact on prevention of IPD and CAP of the additional vaccine-specific serotype coverage for 21vPCV versus 13vPCV or 20vPCV. This approach aligned with the methodology reviewed by the PBAC for 20vPCV, where VE for 20vPCV was based on the CAPiTA study for serotypes shared with 13vPCV and the additional serotypes in 20vPCV (paragraph 7.6, 20vPCV PSD, November 2022 PBAC meeting). However, 13vPCV and 20vPCV increased the number of serotypes offered by 7vPCV and 13vPCV respectively, unlike 21vPCV, where the majority of serotypes shared with 13vPCV have been dropped and new serotypes are proposed (4 and 10 serotypes are shared between 21vPCV and 13vPCV and 20vPCV, respectively). Therefore, as noted by ATAGI, 'there is uncertainty as to whether the immunogenicity to efficacy bridge (21vPCV immunogenicity was compared to 20vPCV, which was compared to 13vPCV, which has efficacy data) will result in meaningful clinical protection for all unmatched serotypes' (ATAGI Pre-submission Advice, April 2024).

6.45 Additionally, the CAPiTA study included individuals that were not fully representative of the broader population included in the CUA, particularly relevant when considering the MaR population. The MaR population in the CUA encompassed younger individuals who were immune compromised due to one or more severe comorbidities. In contrast, the older adult population included in CAPiTA generally had less serious underlying health issues and specifically excluded immune deficient individuals.

6.46 The key components of the economic evaluation are presented in Table 9.

Table 9: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	21vPCV vs 13vPCV ± 23vPPV[a].
Time horizon	Lifetime (ranging from 30 years for non-Indigenous adults ≥ 70 years, to 70 years for MaR adults ≥ 18 years) in the model base case versus 4 years in the CAPiTA trial.
Outcomes	IPD cases, CAP inpatient and outpatient cases, PMS cases, IPD and CAP inpatient deaths, LYs and QALYs.
Methods used to generate results	Static Markov model
Health states	A total of 3 health states and four infection events resolved within 1 model cycle. Health states: (1) No PD; (2) PMS; (3) Death. Infection events: (1) IPD meningitis; (2) IPD non-meningitis (includes bacteraemia, invasive pneumonia, other, and unknown); (3) Inpatient CAP; (4) Outpatient CAP.
Cycle length	1 year
Transition probabilities and event rates	The model assumed a fixed distribution of serotypes based on NNDSS data. The incidence of IPD events by patient population were derived from IPD notifications 2016-2019 NNDSS data. The incidence of CAP inpatient events was derived from reported pneumonia cases using ICD hospital codes J12-J18 from 2018-2019 AIHW, with a fraction attributable to *S. pneumoniae* (20.6%) as advised by ATAGI. The incidence of CAP events managed by GPs was from an Australian economic model of 13vPCV versus no vaccination (Dirmesropian et al. (2017)), with a fraction attributable to *S. pneumoniae* (20.6%) as advised by ATAGI. Probability of sequelae or fatality from *S. pneumoniae* events (Dirmesropian et al. (2019)). IPD fatality rates were based on NNDSS combined death data (2008-2019 – longer time frame used due to small number of cases). CAP fatality rates are derived from data reported in Dirmesropian et al. (2019). Permanent disability (modelled as hearing loss and neurological disorder) associated with meningitis was derived from Rubin et al. (2010). Background mortality: ABS 2019.
Extrapolation	The waning profiles of all PCVs and 23vPPV were based on assumptions used for 20vPCV (paragraph 6.60, 20vPCV PSD, November 2022 PBAC meeting) that were deemed acceptable by ATAGI (ATAGI Pre-submission Advice).
Health related quality of life	Literature-based utility values. Utility values: No PD: 0.84-0.7 (based on Hawthorne 2013) Neurological disorder: 0.68 (based on Rubin 2010) Hearing loss: 0.73 (based on Rubin 2010) Utility decrements (based on Mangen 2015): IPD: 0.0709 CAP inpatient: 0.0709 CAP outpatient: 0.0045 The ESC considered that the submission's approach potentially overestimated the disutility for post-meningitis sequalae (PMS), as the source was an economic evaluation (Rubin 2010) which used data from other studies using methods that are considered less reliable (e.g. proxy reporting by clinicians), however due to the low number of meningitis cases predicted in the model, this input had a small impact on the model's results.
Costs	Vaccines (21vPCV, 13vPCV, 20vPCV, 23vPPV), vaccine administration (MBS item 3), Hospitalisations related to bacteraemia, meningitis, invasive pneumonia, and CAP. CAP outpatient cost (MBS item 44), PMS costs (Rubin et al. (2010)) The ESC considered that the submission's approach potentially overestimated the costs of post- PMS, however due to the low number of meningitis cases predicted in the model, this input had a small impact on the model's results.

Component	Summary
Serotype distribution	Fixed serotype distribution throughout the time horizon

Source: Table 3.1-1, pp153-154 of the submission.
13vPCV = 13-valent pneumococcal conjugate vaccine; 23vPPV = 23-valent pneumococcal polysaccharide vaccine; ABS = Australian Bureau of Statistics; AIHW = Australian Institute of Health and Welfare; ATAGI = Australian Technical Advisory Group on Immunisation; CAP = community-acquired pneumonia; GP = general practitioner; ICD = International Classification of Diseases; IPD = invasive pneumococcal disease; LY = life year; MaR = medically at-risk; NNDSS = National Notifiable Diseases Surveillance System; PBAC = Pharmaceutical Benefits Advisory Committee; PCV = pneumococcal conjugate vaccine; PD = pneumococcal disease; PMS = post meningitis sequelae; QALY = quality-adjusted life year; 21vPCV = 21-valent pneumococcal conjugate vaccine.
[a] The model assumed 80% of the alive cohort of Indigenous and MaR population receive 2 doses of 23vPPV with a 5-years gap between 1st and 2nd dose.

6.47 The submission adopted a 3-step approach to assess the comparative benefits of 21vPCV against 13vPCV ± 23vPPV or 20vPCV:

- Identify prevalent serotypes in Australia that cause IPD and CAP.
- Compare the serotype coverage of all vaccines being considered.
- Estimate the efficacy of each vaccine in preventing IPD and CAP cases by serotype.

6.48 The submission applied serotype-specific VE as a percentage reduction in baseline incidence of IPD and CAP due to administration of a vaccine as summarised in Table 10. For both 21vPCV and the comparator(s), the base case analysis assumed 0% effectiveness for serotypes they did not cover, and 0% effectiveness for non-vaccine serotypes (i.e., NVTs). The ESC considered this was reasonable. Serotype-specific VE as reported by the CAPiTA study was assumed to be the same across all PCV vaccines. This approach was consistent with the ATAGI advice (ATAGI Pre-submission advice, April 2024). For 23vPPV, ATAGI accepted VE of 61.0% for IPD as 'these values are consistent with previous PCV models' and 5.6% for CAP (ATAGI Pre-submission Advice, April 2024). The ESC noted the VE estimates remain uncertain, noting there was no evidence to support the estimates of VE against IPD and CAP for non-shared 13vPCV STs.

Table 10: Serotype-specific VE inputs used in the economic model

	21vPCV	13vPCV	20vPCV	23vPPV
IPD				
Shared 13vPCV STs (excl. ST3)	75.0%	75.0%	75.0%	61.0%
ST 3	26.0%	26.0%	26.0%	61.0%
Non-shared 13vPCV STs (excl. ST3)	75.0%	-	75.0%	61.0%
CAP				
Shared 13vPCV STs (excl. ST3)	45.0%	45.0%	45.0%	5.6%
ST 3	15.6%	15.6%	15.6%	5.6%
Non-shared 13vPCV STs (excl. ST3)	45.0%	-	45.0%	5.6%

Source: Table 3.4-17, p181 of the submission.
13vPCV = 13-valent pneumococcal conjugate vaccine; 20vPCV = 20-valent pneumococcal conjugate vaccine; 23vPPV = 23-valent pneumococcal polysaccharide vaccine; CAP = community acquired pneumonia; IPD = invasive pneumococcal disease; ST = serotype; 21vPCV (V116) = 21-valent pneumococcal conjugate vaccine; VE = vaccine effectiveness.

6.49 The coverage of IPD and CAP cases across vaccine-specific serotypes by population, as detailed in Table 11, was based on the serotypes covered in each vaccine (see Figure 1) and the distribution of IPD and CAP cases by serotypes. The distribution of IPD cases

by serotypes was directly obtained from NNDSS (2016-2019) data. The submission presented a sensitivity analysis using data from the NNDSS from 2022-2023 (Table 14).

Table 11: Vaccine serotype coverage (NNDSS 2016-2019) attributed to IPD and CAP by population

Vaccine comparison	Non-Indigenous ≥ 70 years		Indigenous ≥ 50 years		MaR 18 to 69[a] years	
	n	%	n	%	n	%
21vPCV vs. 13vPCV ± 23vPPV						
21vPCV only[b]	274	53.0%	14	16.9%	132	19.5%
In both	113	21.9%	47	57.1%	399	58.9%
In 13vPCV ± 23vPPV only	49	9.5%	7	8.0%	91	13.5%
In neither (NVTs)	81	15.6%	15	18.1%	56	8.2%
Total	517	100%	82	100.0%	678	100.0%
21vPCV vs. 20vPCV						
In 21vPCV only[b]	176	34.0%	21	25.5%	211	31.1%
In both	211	40.8%	40	48.5%	320	47.3%
In 20vPCV only	59	11.4%	7	8.0%	91	13.4%
In neither (NVTs)	71	13.7%	15	18.1%	56	8.3%
Total	517	100%	82	100%	678	100.0%

Source: Table 3.4-14, p176 of the submission; estimated in the evaluation from Attachment 3 to the submission (Model inputs and calculations).

13vPCV = 13-valent pneumococcal conjugate vaccine; 20vPCV = 20-valent pneumococcal conjugate vaccine; CAP = community acquired pneumonia; IPD = invasive pneumococcal disease; MaR = Medically at-risk; NNDSS = National Notifiable Diseases Surveillance System; NVT = non-vaccine type; 21vPCV = 21-valent pneumococcal conjugate vaccine.

[a] non-Indigenous population aged 20 to 69 years used as a proxy for the MaR population.

[b] Excluding potential cross reactivity to 15B serotypes.

6.50 As the serotype distribution for CAP events in Australia is not known, the submission assumed the same distribution as for IPD events. The non-Indigenous population aged 20 to 69 years was used as a proxy for the MaR population given the lack of data in this population. The ESC considered these assumptions were reasonable.

6.51 CAP rates used in the model were based on hospitalisation rates for all-cause pneumonia (International Classification of Diseases, ICD-10-AM codes, ICD-10-AM codes J12-J18) from the National Hospital Morbidity Database (NHMD) in 2018-2019. The ESC considered that CAP incidence was potentially overestimated as the submission included codes J12 and J14-J18 which also capture viral pneumonia and non-PD bacterial pneumonia. The ATAGI Advice recommended the use of principally coded pneumococcal disease pneumonia (J13) plus lobar pneumonia (J18.1) plus 11.1% of unspecified pneumonia (J18 minus J18.1) to estimate true CAP incidence due to pneumococcal disease. The submission provided only aggregated NHMD data, preventing assessment of this alternative estimate.

6.52 The ESC noted the submission's estimates reflected NNDSS 2016-2019 data, and that more recent data yielded somewhat different estimates (Table 2). The ESC considered it was reasonable to apply the 2016-2019 estimates in the base case, however it was important to consider the impact of reducing the time horizon to mitigate the impact of potentially significant rates of serotype replacement (discussed further in paragraph 6.54). The ESC noted that ATAGI recommended the use of a 5-year or 10-year time horizon to mitigate the impact of serotype shift. The ESC considered that a

ten-year time horizon may be reasonable, noting that changes were observed in the distribution of disease by vaccine serotype between 2009/18 and 2023/24.

6.53 For the PCV vaccines, the waning profile (reduction in VE) in the submission was assumed to be 0% for the first 5 years, 5% per annum for the next 5 years (years 6-10), 10% per annum for the next 5 years (years 11-15) and 15% per annum thereafter until no VE remains (years 16+). For the 23vPPV booster vaccine, the waning profile was assumed to be 0% for the first 2 years, and linear waning to 100% over the next 3 years (years 3-5). The waning profiles were based on the assumptions used for 20vPCV (paragraph 6.60, 20vPCV PSD, November 2022 PBAC meeting) that were deemed acceptable by ATAGI (ATAGI Pre-submission Advice). Conjugated pneumococcal vaccines 21vPCV, 13vPCV and 20vPCV use the common CRM197 carrier protein designed to elicit immune response and production of memory B cells and long-lasting antibodies. Given the similarities in production and mechanism of action between these vaccines, similar immunogenicity and waning profiles could be expected. However, data presented in the submission showed differences in immunogenicity responses, even for shared serotypes. This suggests the waning profile may not be equivalent across vaccines, particularly for non-shared serotypes where comparative data is lacking. A sensitivity analysis was conducted using waning values previously used in the 20vPCV evaluation (paragraph 6.75, 20vPCV PSD, November 2022, PBAC Meeting) of 0% in years 0-5, 50% in years 6-10, and 100% in years > 10 (Table 14).

6.54 The ESC noted that the model was sensitive to the waning assumptions applied. The ESC noted that greater waning was assumed for 23vPPV (0% benefit at 5 years) compared with PCVs (0% benefit at 17 years) and noted this was consistent with earlier PBAC considerations of PCVs. However, the ESC considered that the waning profile of 21vPCV remained uncertain, as there was no evidence provided to support this. The ESC noted that differences were noted in immunogenicity responses for common serotypes in the PCVs, and this may flow into longevity of effect. The ATAGI advice indicated this remained uncertain, however it would be reasonable to assume that waning would be similar for 21vPCV and other PCVs, in the absence of data to the contrary. The ESC considered it was reasonable to apply these estimates in the base case, however considered that the sensitivity analyses of waning were informative.

6.55 Serotype distribution was assumed to remain constant over time, although ATAGI noted that serotype distribution will likely change over time and sensitivity analyses (5-10 year time horizon) were required to test this uncertainty (ATAGI Pre-submission Advice, April 2024). The submission presented a sensitivity analysis using a 10-year time horizon as advised by ATAGI to address serotype shift (Table 14). The ESC considered it unlikely that serotype distribution would remain unchanged over time as assumed by the submission. The potential for serotype replacement (where non-vaccine serotypes may increase in prevalence following widespread vaccination) could substantially alter the effectiveness and cost-effectiveness of vaccination strategies over time. As noted in paragraph 6.49, the model was sensitive to using NNDSS 2022-2023 values, which was post the expansion in July 2020 of 13vPCV NIP eligibility for non-Indigenous adults ≥ 70 years, Aboriginal and Torres Strait Islander adults ≥ 50, and

MaR adults 18-69 years showing the potential effect of serotype replacement. A further sensitivity analysis conducted in the evaluation based on the experience after the introduction of 13vPCV into Sweden's national-immunisation program in 2009[8]. The ESC considered this analysis was informative as it showed that after the introduction of 13vPCV there was considerable serotype shift and if a similar situation occurred in Australia after introduction of 21vPCV, this would reduce the cost-effectiveness of 21vPCV.

6.56 The key drivers of the results of the economic model are summarised in Table 12.

Table 12: Key drivers of the model

Description	Method/Value	Impact[a]
Base case	**-**	**ICER vs 13vPCV, 21vPCV was dominant for all populations)**
Vaccine waning for PCVs	Years 0-5: 0% Years 6-10: 5% Years 11-15: 10% Years 16+: 15%	High, favoured 21vPCV. Using waning values previously recommended by ATAGI, for use in sensitivity analyses, of 0% in years 0-5, 50% in years 6-10, and 100% in years > 10 worsened cost-effectiveness: 13vPCV - Remained dominant for all populations
Serotype distribution	NNDSS (2016-2019)	High, favoured 21vPCV. Sensitivity analysis presented by the submission using 2022-2023 data worsened cost-effectiveness: 13vPCV - Remained dominant for all populations.
Vaccine effectiveness	IPD: 75% CAP: 45% Assumed same efficacy as 13vPCV in the CAPiTA for non-shared ST.	High, favoured 21vPCV. Decreasing 21vPCV VE to prevent IPD and CAP cases of non-shared 13vPCV STs by 45% (relative reduction), worsened cost-effectiveness: 13vPCV • non-Indigenous adults ≥ 70 years: $[redacted]/QALY • Remained dominant for Aboriginal and Torres Strait Islander adults ≥ 50, and MaR adults 18-69 years.
Time horizon	Lifetime[b]	Moderate, favoured 21vPCV. Decreasing the time horizon to 10 years decreased incremental QALYs and increased incremental costs for all populations and comparators. 13vPCV - Remained dominant for all populations.

Source: Compiled during evaluation.

13vPCV = 13-valent pneumococcal conjugate vaccine; CAP = community acquired pneumonia; CFR = case fatality rate; ICER = incremental cost-effectiveness ratio; IPD = invasive pneumococcal disease; PCV = pneumococcal conjugate vaccine; QALY = quality-adjusted life year; VE = vaccine efficacy; ST = serotypes; 21vPCV = 21-valent pneumococcal conjugate vaccine.

[a] ICERs shown are those for the populations with the greatest impact.

[b] As per Section 5.1, p64 of ATAGI Pre-submission Advice, a 10-year time horizon could minimise the likely effects of serotype replacement.

The redacted values correspond to the following ranges:

[1] $5,000 to < $15,000

6.57 The model base case results presented in the submission (Table 13) showed 21vPCV was the dominant option across all targeted populations when compared to 13vPCV ± 23vPPV. This result should be interpreted with caution as: (1) the model base case assumed a lifetime time horizon, even though ATAGI noted increased uncertainty beyond 5 to 10 years; (2) the model fixed the serotype distributions causing IPD

[8] Bergman K, Härnqvist T, Backhaus E, Trollfors B, Dahl MS, Kolberg H, Ockborn G, Andersson R, Karlsson J, Mellgren Å, Skovbjerg S. Invasive pneumococcal disease in persons with predisposing factors is dominated by non-vaccine serotypes in Southwest Sweden. BMC Infect Dis. 2021 Aug 4;21(1):756

throughout the time horizon, without incorporating the potential for serotype replacement over time; (3) the model base case results assumed that all non-shared serotypes between 21vPCV and 13vPCV would have the same efficacy in avoiding IPD cases, however, there was no immunobridging evidence presented in the submission to support this assumption; and (4) the submission used a lower price ($[redacted]) in the MaR population to achieve the ICER presented.

Table 13: Results of the economic evaluation (per 1,000 population)[a]

Non-Indigenous ≥ 70 years			
Component	**21vPCV**	**13vPCV**	**Increment**
Costs	$[redacted]	$[redacted]	-$[redacted]
QALY	8,088	8,085	2.65
LY	17,034	17,026	7.09
Incremental cost/extra QALY gained		**Dominant**	
Incremental cost/extra LY gained		Dominant	
Indigenous ≥ 50 years [b]			
Component	**21vPCV**	**13vPCV ± 2x23vPPV**	**Increment**
Costs	$[redacted]	$[redacted]	-$[redacted]
QALY	7,367	7,364	2.28
LY	13,529	13,523	5.30
Incremental cost/extra QALY gained		**Dominant**	
Incremental cost/extra LY gained		Dominant	
MaR ≥ 18 to 69 years [b,c]			
Component	**21vPCV**	**13vPCV ± 2x23vPPV**	**Increment**
Costs	$[redacted]	$[redacted]	-$[redacted]
QALY	15,379	15,378	1.43
LY	48,186	48,180	5.52
Incremental cost/extra QALY gained		**Dominant**	
Incremental cost/extra LY gained		Dominant	

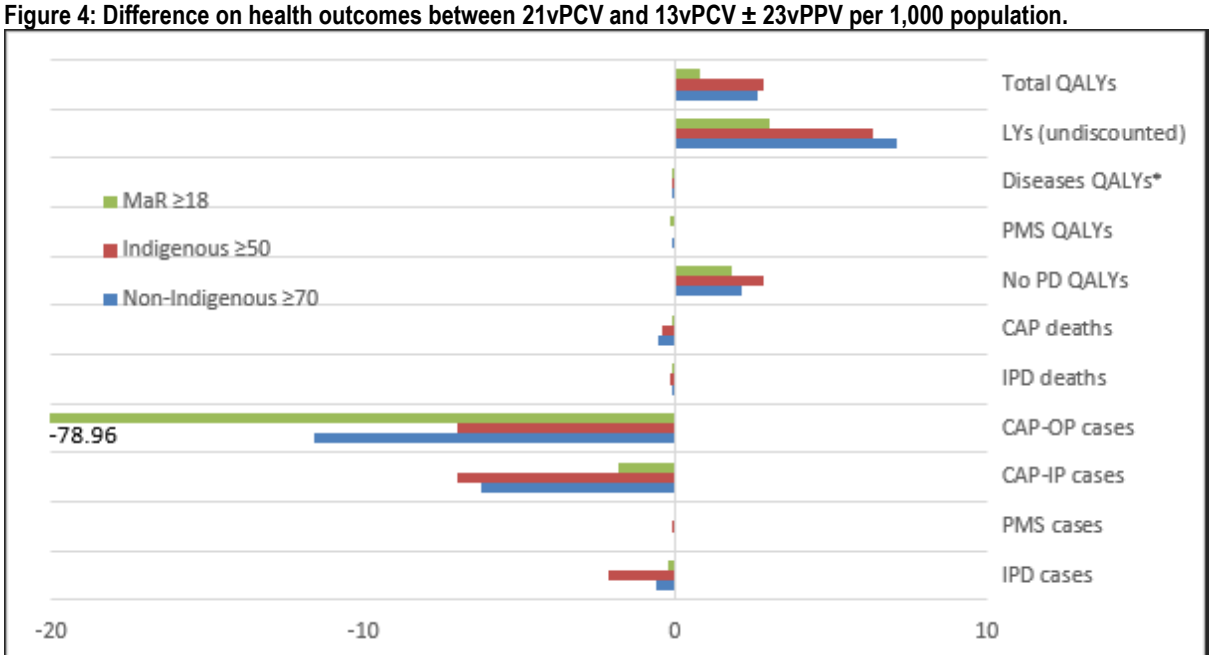
Source: Compiled in the evaluation using Table 3.8-2, p202, Table 3.8-3, p204 and Table 3.8-4, p206 of the submission.
13vPCV = 13-valent pneumococcal conjugate vaccine; 23vPPV = 23-valent pneumococcal polysaccharide vaccine; LY = life years; MaR = medical at risk; QALY = quality adjusted life years; 21vPCV = 21-valent pneumococcal conjugate vaccine.
[a] All analyses use the comparator prices assumed by the submission.
[b] Two-doses of 23vPPV were considered after 13vPCV vaccine. The completion rate of individuals in the model who received 13vPCV followed by 23vPPV was 80%. First 23vPPV booster is administered within a year and the second 23vPPV booster after 5 years.
[c] Non-Indigenous population aged 20 to years used as a proxy for the MaR population.

6.58 The model results indicated that the overall economic impact of the vaccination program was primarily driven by the incidence and cost associated with treating CAP inpatients across the current NIP populations. While the efficacy applied against CAP (and IPD) was the same for both vaccines, 21vPCV was assumed to cover a higher proportion of serotypes causing CAP (and IPD) than 13vPCV, therefore resulting in a higher number of cases avoided (and hence a higher number of QALYs accumulated). A similar pattern was observed with the number of CAP outpatient cases, particularly among the MaR population (Figure 4). The MaR population was assumed to be at high risk of developing CAP outpatient events, with an estimated incidence of 4,431 cases per 100,000/year. However, given the relatively low cost of treating CAP outpatient

cases ($244.30 per patient) compared to CAP inpatient cases ($8,501 per patient), the results are not sensitive to the avoidance of CAP outpatient cases.

6.59 The comparator for non-indigenous ≥ 70 is 13vPCV. The comparator for Aboriginal and Torres Strait Islander adults ≥ 50 is 13vPCV ± 23vPPV. The comparator for MaR adults ≥ 18 to 69 years vs 13vPCV ± 23vPPV. The analyses including 23vPPV boosters assume 80% of patients receive 2 boosters

Figure 4: Difference on health outcomes between 21vPCV and 13vPCV ± 23vPPV per 1,000 population.



Source: compiled during the evaluation.

13vPCV = 13-valent pneumococcal conjugate vaccine; 23vPPV = 23-valent pneumococcal polysaccharide vaccine; CAP = community acquired pneumonia; IP = inpatient; IPD = invasive pneumococcal disease; LY = life-years; MaR = medically at-risk; OP = outpatient; PD = pneumococcal disease; PMS = post-meningitis sequalae; QALY = quality adjusted life-year; 21vPCV = 21-valent pneumococcal conjugate vaccine.

[a] Disease QALYs correspond to the QALYs accumulated during infectious events (IPD and CAP).

6.60 The results of univariate sensitivity analyses are summarised in Table 14. The submission included sensitivity analyses in the economic evaluation in which VE for non-13vPCV serotypes in 21vPCV were decreased by 45% (relative reduction) as recommended by the ATAGI. For those sensitivity analyses, the assumed VE for 21vPCV was 41.3% for IPD (compared with 75% in the base case), and 24.8% for CAP (compared with 45% in the base case). The results from the ITC did not support the non-inferiority for two) of the 4 serotypes shared between 21vPCV and 13vPCV (6A and 19A favoured 13vPCV. A multi-way sensitivity analysis conducted in the evaluation was tested incorporating lower VE for 21vPCV for non-shared 13vPCV STs (excl. ST3), and reduction for shared serotypes 6A and 19A (45% relative reduction) and a shorter time horizon (10 years). All analyses use the comparator prices assumed by the submission.

Table 14: Economic evaluation 21vPCV vs 13vPCV ± 23vPPV sensitivity analyses (per total population)[b]

Variable/ assumption	Base-case value	Sensitivity value	Incremental cost ($)	Incremental QALY	ICER ($/QALY)
Non-Indigenous ≥ 70 vs 13vPCV (requested price = $[redacted])					
Base-case	-	-	-$[redacted]	554	Dominant
Age at vaccination	70 years	65 years [a]	-$[redacted]	520	Dominant
Evaluation MSA: VE reduction (-45% relative reduction) for non-shared 13vPCV STs (excl. ST3), and reduction for shared serotypes 6A and 19A, and time horizon[c]	IPD: 75% CAP: 45% 30 years	-45% [a] -45% [a] 10 years [a]	$[redacted]	77	$[redacted] [1]
Alternative MSA: VE reduction for non-shared 13vPCV STs (excl. ST3) and time horizon[c] (45% reduction on 6A and 19A removed)	IPD: 75% CAP: 45% 30 years Decrease 45%	-45% [a] -45% [a] 10 years [a] 0%	$[redacted]	89	$[redacted] [2]
PBAC Scenario 1 (reflects Evaluation MSA with 65-year threshold): VE reduction for non-shared 13vPCV STs (excl. ST3), and reduction for shared serotypes 6A and 19A, time horizon[c] and age 65	IPD: 75% CAP: 45% 30 years 70 years	-45% [a] -45% [a] 10 years [a] 65 years [a]	$[redacted]	51	$[redacted] [3]
Indigenous ≥ 50 vs 13vPCV ± 23vPPV (requested price = $[redacted])					
Base-case	-	-	-$[redacted]	19	Dominant
PBAC Scenario 2 (reflects Evaluation MSA): Evaluation MSA: VE reduction (-45% relative reduction) for non-shared 13vPCV STs (excl. ST3), and reduction for shared serotypes 6A and 19A, and time horizon[c]	IPD: 75% CAP: 45% 30 years	-45% [a] -45% [a] 10 years [a]	-$[redacted]	3	Dominant
Alternative MSA: VE reduction for non-shared 13vPCV STs (excl. ST3) and time horizon[c] (45% reduction on 6A and 19A removed)	IPD: 75% CAP: 45% 30 years Decrease 45%	-45% [a] -45% [a] 10 years [a] 0%	-$[redacted]	3	Dominant
MaR adults ≥ 18 to 69 years vs 13vPCV ± 23vPPV (requested price = $[redacted])					
Base-case	-	-	-$[redacted]	482	Dominant
PBAC Scenario 3 (reflects Evaluation MSA): Evaluation MSA: VE reduction (-45% relative reduction) for non-shared 13vPCV STs (excl. ST3), and reduction for shared serotypes 6A and 19A, and time horizon[c]	IPD: 75% CAP: 45% 30 years	-45% [a] -45% [a] 10 years [a]	-$[redacted]	3	Dominant
Alternative MSA: VE reduction for non-shared 13vPCV STs (excl. ST3) and time horizon[c] (45% reduction on 6A and 19A removed)	IPD: 75% CAP: 45% 30 years Decrease 45%	-45% [a] -45% [a] 10 years [a] 0%	-$[redacted]	11	Dominant

Source: Table 3.9-1, p212 of the submission.

13vPCV = 13-valent pneumococcal conjugate vaccine; CAP = community acquired pneumonia; CFR = case fatality rate; ICER = incremental cost-effectiveness ratio; IPD = invasive pneumococcal disease; PCV = pneumococcal conjugate vaccine; QALY = quality-adjusted life year; VE = vaccine efficacy; ST = serotypes; 21vPCV = 21-valent pneumococcal conjugate vaccine.

[a] Recommended by ATAGI. Note, 45% relative reduction in assumed VE corresponds to VE of 41.3% for IPD (compared with 75% in the base case), and VE of 24.8% for CAP (compared with 45% in the base case).

[b] all analyses use the comparator prices assumed by the submission.

[c] M16, M17, and N16, 'Inputs - Efficacy_waning' all set to 45%, and F37, 'Model Settings' set to 10
The redacted values correspond to the following ranges:
[1] *$55,000 to < $75,000*
[2] *$45,000 to < $55,000*
[3] *$115,000 to < $135,000*

6.61 The submission presented a sensitivity analysis changing the age of vaccination of the non-Indigenous population from 70 years to 65 consistent with ATAGI's recommendation. For the submission base case, the model was not sensitive to changing the age threshold for non-Indigenous adults ≥ 70 to ≥ 65 and was also not sensitive when changing the MaR age range from 69 to 64 as a consequence of changing the age threshold for non-Indigenous adults.

6.62 The ESC considered that the submission's estimates were optimistic and advised that revisions to the assumed VE and time horizon would be appropriate to inform the PBAC's consideration of the cost-effectiveness of 21vPCV. The ESC considered that the evaluation's multi-way sensitivity analyses which tested the impact of reduced VE for 21vPCV (45% relative reduction in VE for non-shared serotypes as there is no direct clinical efficacy data) and reduced time horizon to 10 years (to limit the impact of serotype shift) were informative. The pre-PBAC response disagreed with this analysis, noting that lower VE (45% reduction) was also applied to the shared 13vPCV serotypes 6A and 19A in the 21vPCV arm. The evaluators clarified that in this analysis, IPD and CAP efficacy was reduced by 45% for 21vPCV, on the basis that the submission did not establish non-inferiority for 2 of the 4 common serotypes (6A and 19A).

6.63 The pre-PBAC response disagreed with the reduction in time horizon to ten years, stating that the inclusion of 20vPCV on the NIP for children would create serotype shift towards, rather than away from, the serotypes unique to 21vPCV.

Additional populations

6.64 The submission proposed 21vPCV for immunisation of additional populations not covered by the NIP as follows:

- Aboriginal and Torres Strait Islander adults 25 to 49 years, noting 20vPCV is the only PCV that has been recommended by the PBAC for this population (the submission presented a CMA against 20vPCV).
- Catch-up program for individuals within the requested populations that were vaccinated prior to implementation of 21vPCV on the NIP (see paragraph 3.7). The submission provided scenario analyses assessing the impact of catch-up doses for non-Indigenous adults aged > 70, but not for any of the other proposed populations.
- Non-funded NIP at-risk conditions: MaR adults aged ≥ 18 to 69 years with chronic disease not currently NIP funded (COPD and CLD).

6.65 In the scenario analysis for the catch-up program proposed in non-Indigenous adults aged > 70 years, the submission assumed they were previously vaccinated with either a dose of 13vPCV or 23vPPV at 70 years followed by 21vPCV at 73 and 75 years,

respectively (i.e. 3 and 5 years after the previous vaccine, respectively). Therefore, the comparator was 'no additional vaccination' (the effectiveness of the prior vaccine remained according to its waning profile). The evaluation considered this was reasonable. Results are presented in Table 15.

Table 15: Results of the model for the catch-up program for non-Indigenous adults aged >70 years (per population)

21vPCV vs no vaccine	13vPCV + 21vPCV[a]	13vPCV	Incremental	23vPPV + 21vPCV[b]	23vPPV	Incremental
QALYs	1,692,833	1,692,164	670	1,692,720	1,691,952	767
Total costs	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	-$[redacted]
ICER ($/QALY)			**$[redacted][1]**			**Dominant**

Source: compiled during evaluation.

13vPCV = 13-valent pneumococcal conjugate vaccine; 23vPPV = 23-valent pneumococcal polysaccharide vaccine; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; 21vPCV = 21-valent pneumococcal conjugate vaccine.

[a] Patients were vaccinated with 13vPCV at 70 years and followed by 21vPCV after 3 years.

[b] Patients were previously vaccinated with 23vPPV at 70 years and followed by 21vPCV after 5 years.

The redacted values correspond to the following ranges:

[1] $0 to < $5,000

6.66 Catch-up results were driven by the additional disease coverage provided by 21vPCV among older adults (21vPCV: 74.9%; 13vPCV: 31.4%; 23vPPV: 59.2%; see Table 3) coupled with the assumption that 23vPPV effectiveness was fully waned after 5 years. The evaluation noted it was a simplified approach to the question of cost-effectiveness of the proposed catch-up program given that each comparison assumed vaccination at a single point in time (3 years after 13vPCV or five years after 23vPPV) and had a baseline age, which may not reflect the proposed population.

6.67 The submission did not present results for catch-up programs for Aboriginal and Torres Strait Islander adults and MaR adults, yet they were accounted for in the financial estimates.

6.68 For non-NIP funded MaR conditions, the submission applied population specific risk factors to baseline IPD and CAP incidence rates. 21vPCV was dominant over no vaccine in adults aged 50 to 64 years with COPD and CLD. The ICER for 21vPCV in younger adults aged 18 to 49 years with CLD was $5,000 to < $15,000. The submission did not present results for adults aged 18 to 49 years with COPD, yet they were accounted for in the financial estimates. The more favourable results in the 50 to 64 years cohorts were driven by the higher IPD and CAP incidence risks of this age group compared to the younger cohort aged 18 to 49 years. The ESC noted this was a simplified approach to the question of cost-effectiveness of the proposed expansion to include COPD and CLD, that relied on estimates of increased risk in the proposed cohorts drawn from previous ATAGI advice (Table 15). The ESC noted that cost-effectiveness scenarios reflecting these conditions resulted in ICERs as shown in Table 15, however the scenarios applied some optimistic assumptions as per the submission base case analyses, and therefore the results should be considered with caution.

Table 16: Non-funded NIP conditions in MaR population: scenario analyses

Non-NIP funded Condition	Risk factor	ICER ($/QALY)[c]
Adults aged 18 to 49 years[a]		
Chronic liver disease	8.4	$ [redacted]
Adults aged 50 to 64 years[b]		
Chronic obstructive pulmonary disease	3.8	Dominant
Chronic liver disease	3.2	Dominant

Source: Table 3.8-7, p210 of the submission.
ICER = incremental cost-effectiveness ratio; MaR = medically at-risk; NIP = National Immunization Program; QALY = quality adjusted life year.
[a] Age at vaccination: 20 years; Time horizon: 30 years.
[b] Age at vaccination: 50 years; Time horizon: 15 years.
[c] Applies proposed price for 21vPCV in MaR of $[redacted] per dose.
The redacted values correspond to the following ranges:
[1] *$5,000 to < $15,000*

Cost-minimisation approach

6.69 On the basis that NNDSS data 2016-2019 for Aboriginal and Torres Strait Islander adults 25 to 49 years showed similar disease coverage for serotypes in 21vPCV and 20vPCV (Table 17), the submission presented a CMA for 21vPCV to 20vPCV for the proposes listing for Aboriginal and Torres Strait Islander adults 25 to 49 years. The submission requested a price of $[redacted] per dose for this population.

Table 17: ST disease coverage in 21vPCV vs. 20vPCV for Aboriginal and Torres Strait Islander adults 25 to 49 years

Vaccine	VT serotype coverage % (NNDSS 2016-2019)
20vPCV	67.0%
21vPCV	66.7%

Source: Table 3.8-6, p209 of the submission.
20vPCV = 20-valent pneumococcal conjugate vaccine; NNDSS = National Notifiable Diseases Surveillance System; PCV = pneumococcal conjugate vaccine; ST = serotype; VT = vaccine type; 21vPCV = 21-valent pneumococcal conjugate vaccine.

6.70 The submission proposed that 1 dose of 21vPCV was therapeutically equivalent to 1 dose of 20vPCV in Indigenous adults 25 - 49 years. The key components and assumptions used in the CMA are described in Table 18.

Table 18: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Serotype coverage between 21vPCV and 20vPCV are not different among Indigenous 25 to 49 years.
Therapeutic claim: safety	No safety data was assessed in the CMA
Evidence base	IPD and CAP cases caused by serotypes covered in 20vPCV and 21vPCV.
Equi-effective doses	1 dose/lifetime of 21vPCV = 1 dose/lifetime of 20vPCV
Direct medicine costs	Same cost per dose for 21vPCV and 20vPCV
Other costs or cost offsets	No

Source: p209 of the submission.
20vPCV = 20-valent pneumococcal conjugate vaccine; CAP = community acquired pneumonia; CMA = cost minimisation approach; IPD = invasive pneumococcal disease; 21vPCV = 21-valent pneumococcal conjugate vaccine.

6.71 The equi-effective dose estimated in the submission was based on a single dose of 21vPCV and 20vPCV per lifetime, which was consistent with the clinical studies presented in the submission. This approach also aligned with previous PBAC evaluations for other PCVs using a single dose per lifetime. No additional costs or cost

offsets were assumed for this population. The result of the CMA is presented in Table 19.

Table 19: Results of the cost-minimisation approach

Component	Proposed medicine	Comparator
Cost per dose	$[redacted] (requested price)	$[redacted] (assumed by submission)
Dose duration	1 per lifetime	1 per lifetime
Total medicine cost per lifetime	$[redacted]	$[redacted]
Difference in cost per week	$0	$0

Source: compiled during the evaluation.

Estimation of the weighted price

6.72 The estimation of the weighted price of 21vPCV based on the requested price per dose for each population is presented in Table 20. The weighted price was based on eligible populations and did not consider the uptake rate. Revised estimates including the proposed expansions of the populations are also shown.

Table 20: Estimation of weighted price of 21vPCV per dose based on requested prices per population

NIP population	Requested price per dose	Weighting based on anticipated population over 6 years
Submission Estimates		
Non-Indigenous ≥70 years	$[redacted]	83.65%
Indigenous ≥50 years	$[redacted]	2.79%
MaR 18-69 years	$[redacted]	9.37%
Indigenous 25-49 years	$[redacted]	4.19%
Overall price	**$[redacted]**	**100%**
Revised Estimates		
Non-Indigenous ≥65 years	$[redacted][a]	78.21%[a]
Indigenous ≥50 years	$[redacted]	1.09%
MaR ≥18 years	$[redacted][b]	3.65%[b]
Additional MaR, COPD and CLD (≥18 years)	$[redacted][c]	15.42%[c]
Indigenous 25-49 years	$[redacted]	1.63%
Overall price	**Not specified**	**100%**

Source: Table 3.6-2, p189 of the submission, and (Budget Impact tab, Attachment 10 to the submission, cells I10:J15).

a. The population size would increase by 40% based on data provided for 2025 to 2027 (V116 Regimen tab, Attachment 10 to the submission, cells AC161:AF168), calculated from Non-ATSI population, 65-69 cohort as a proportion of summed cohorts corresponding to 70+ population (includes all cohorts from 70 years to 100+ years). The requested price for 65+ population is equal to the price requested for 70+ population consistent with the pre-PBAC response which stated that lowering the non-indigenous age threshold to 65 has a minimal impact on cost-effectiveness, "thus should not impact the price".

b. Unchanged from submission values. The population size is unchanged from the submission estimates for 18-69 cohort for simplicity, noting this population is a small proportion of the total, and these individuals would remain eligible for vaccination with 21vPCV after the change to the age threshold.

c. Population estimated to correspond to 700,000 to < 800,000additional adults (Budget Impact tab, Attachment 10 to the submission, cell I25+ cell I29). Requested price $[redacted] sourced from Table 3.8-7 p 210 of the submission.

21vPCV cost/patient/course

6.73 The proposed vaccine cost per person was $[redacted], assuming a single dose of 21vPCV per lifetime in the adult schedule.

Estimated PBS usage & financial implications

6.74 This submission was not considered by the DUSC.

6.75 The submission used an epidemiological approach in estimating the potential utilisation of 21vPCV on the NIP. It included the three current NIP-funded populations, an expanded Indigenous 25-49 cohort already recommended for 20vPCV, and an expansion scenario for currently non-NIP funded MaR conditions, CLD and COPD. The populations for which estimates were presented were mostly consistent with the CUA and CMA in the submission, with the exception that the submission did not present cost-effectiveness results for individuals 18-49 years with COPD (in the MaR population 18 to 69 years), and catch-up programs for Aboriginal and Torres Strait Islander adults ≥ 50 and MaR adults. The key inputs relied on in the financial estimates are outlined in Table 21.

Table 21: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incidence/prevalence for Indigenous and non-Indigenous population	Based on ABS projections series 3222.0 for non-Indigenous and 3238.0 for Aboriginal and Torres Strait Islander adults, 2024 and 2023 projections respectively.	The evaluation considered this was reasonable.
Incidence/prevalence for MaR population	a) Stem cell and solid organ transplant and patients with previous IPD used a 5 x arbitrary conversion factor. b) Asplenia: Dendle et al. (2012) c) Cochlear implants: provider website d) Incidence and prevalence of COPD and prevalence of CLD consistent with ATAGI advice. CLD prevalence from Wu et al. (2024)	a) ATAGI criticised the arbitrary 5 x conversion factor due to lack of support. b) Asplenia incidence was uncertain given it was unclear if Dendle et al. (2012) remains valid with data from 1998-2006. c) The Cochlear implant incidence was underestimated as it used an unreferenced claim from a single provider. d) The evaluation considered the COPD and CLD estimates were reasonable.
Uptake rate for 21vPCV	Non-Indigenous adults 70 years ([redacted]%) sourced from ATAGI advice. Catch-up: The cumulative uptake rate (over 3 years) was assumed to be [redacted]%, except for Aboriginal and Torres Strait Islander adults > 50 years, for whom the rate was assumed to be [redacted]% over 3 years. The [redacted]% figure was based on the 13vPCV PSD, while the [redacted]% was derived from the uptake rate of the flu vaccine among Indigenous populations.	The evaluation considered this was reasonable. Sensitivity analyses suggested by ATAGI were conducted by the submission (**Error! Reference source not found.**.)
Uptake rate for second dose of the 23vPPV booster	80% uptake assumed for second dose of 23vPPV booster dose after 13vPCV (based on 20vPCV PSD).	The financial impact is likely underestimated as the second dose of 23vPPV was assumed to start in Year 1. The estimates in the 20vPCV PSD did not include a second 23vPPV dose (para 6.85, 20vPCV PSD, November 2022, PBAC Meeting) as it was assumed to be received beyond the financial forecast period.
Administration cost	MBS item 3	MBS costs might be overestimated as a proportion of the Indigenous population may receive vaccines through ACCHOs (para 6.89, 20vPCV PSD, November 2022 PBAC Meeting).

Source: Compiled in the evaluation from Section 4.

13vPCV = 13-valent pneumococcal conjugate vaccine; 20vPCV = 20-valent pneumococcal conjugate vaccine; 23vPPV = 23-valent pneumococcal polysaccharide vaccine; ABS = Australia Bureau of Statistics; ACCHO = Aboriginal Community Controlled Health; ATAGI = Australian Technical Advisory Group on Immunisation; MaR = medically at risk; MBS = Medicare Benefits Schedule; PBAC = Pharmaceutical Benefits Advisory Committee; PSD = public summary document; 21vPCV = 21-valent pneumococcal conjugate vaccine.

6.76 The estimated use and financial implication of incorporating 21vPCV in the NIP for the targeted populations, as well as populations with CLD and COPD, are outlined in Table 22. All analyses use the comparator prices assumed by the submission.

Table 22: Estimated use and financial implications of listing 21vPCV in the NIP

	Year 1 (2026)	Year 2 (2027)	Year 3 (2028)	Year 4 (2029)	Year 5 (2030)	Year 6 (2031)
Estimated extent of use						
Naïve						
Non-Indigenous ≥ 70	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]

	Year 1 (2026)	Year 2 (2027)	Year 3 (2028)	Year 4 (2029)	Year 5 (2030)	Year 6 (2031)
Indigenous 25 to 49	[redacted][3]	[redacted][3]	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][5]
Indigenous ≥ 50	[redacted][4]	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
MaR 18+	[redacted][6]	[redacted][7]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]
Total Naïve	[redacted][8]	[redacted][1]	[redacted][1]	[redacted][9]	[redacted][9]	[redacted][9]
Catch-up						
Non-Indigenous ≥ 70	[redacted][9]	[redacted][10]	[redacted][11]	0	0	0
Indigenous ≥ 50	[redacted][4]	[redacted][4]	[redacted][12]	0	0	0
MaR 18+	[redacted][3]	[redacted][4]	[redacted][12]	0	0	0
Total Catch-up	[redacted][1]	[redacted][10]	[redacted][13]	0	0	0
Total estimated doses of 21vPCV	[redacted][14]	[redacted][15]	[redacted][1]	[redacted][9]	[redacted][9]	[redacted][9]
Estimated financial implications						
Naïve						
Non-Indigenous ≥ 70	$[redacted][16]	$[redacted][16]	$[redacted][16]	$[redacted][17]	$[redacted][17]	$[redacted][17]
Indigenous 25 to 49	$[redacted][18]	$[redacted][18]	$[redacted][18]	$[redacted][18]	$[redacted][18]	$[redacted][18]
Indigenous ≥ 50	$[redacted][18]	$[redacted][18]	$[redacted][18]	$[redacted][18]	$[redacted][18]	$[redacted][18]
MaR 18+	$[redacted][18]	$[redacted][18]	$[redacted][18]	$[redacted][18]	$[redacted][18]	$[redacted][18]
Total	$[redacted][21]	$[redacted][16]	$[redacted][16]	$[redacted][16]	$[redacted][16]	$[redacted][16]
Catch-up						
Non-indigenous ≥ 70	$[redacted][16]	$[redacted][17]	$[redacted][18]	$-	$-	$-
Indigenous ≥ 50	$[redacted][18]	$[redacted][18]	$[redacted][18]	$-	$-	$-
MaR 18+	$[redacted][18]	$[redacted][18]	$[redacted][18]	$-	$-	$-
Total	$[redacted][16]	$[redacted][17]	$[redacted][18]	$-	$-	$-
Combined total cost 21vPCV (naïve+ catch-up)	**$**[redacted][19]	**$**[redacted][20]	**$**[redacted][16]	**$**[redacted][16]	**$**[redacted][16]	**$**[redacted][16]
Estimated cost-offsets to the NIP (13vPCV ± 2x23vPPV)	$[redacted][16]	$[redacted][17]	$[redacted][17]	$[redacted][17]	$[redacted][17]	$[redacted][17]
Total cost to NIP	**$**[redacted][21]	**$**[redacted][16]	**$**[redacted][17]	**$**[redacted][18]	**$**[redacted][18]	**$**[redacted][18]
Total cost to MBS[a]	$[redacted][18]	$[redacted][18]	$[redacted][18]	-$[redacted][18]	-$[redacted][18]	-$[redacted][18]
Total cost to Government	**$**[redacted][20]	**$**[redacted][16]	**$**[redacted][17]	**$**[redacted][18]	**$**[redacted][18]	**$**[redacted][18]
Non-Funded MaR populations						
COPD	$[redacted][16]	$[redacted][17]	$[redacted][18]	$[redacted][18]	$[redacted][18]	$[redacted][18]
CLD	$[redacted][18]	$[redacted][18]	$[redacted][18]	$[redacted][18]	$[redacted][18]	$[redacted][18]
Total cost to government (including COPD & CLD)	**$**[redacted][22]	**$**[redacted][20]	**$**[redacted][16]	**$**[redacted][17]	**$**[redacted][17]	**$**[redacted][17]
Sensitivity analysis for proposed change to age threshold						
Total cost to government (Current NIP	$[redacted][17]	$[redacted][17]	$[redacted][18]	$[redacted][18]	$[redacted][18]	$[redacted][18]

	Year 1 (2026)	Year 2 (2027)	Year 3 (2028)	Year 4 (2029)	Year 5 (2030)	Year 6 (2031)
schedule and non-Indigenous ≥ 65)[b]						

Source: Compiled from Section 4 of the submission. All analyses use the comparator prices assumed by the submission.
13vPCV = 13-valent pneumococcal conjugate vaccine; 23vPPV = 23-valent pneumococcal polysaccharide vaccine; CLD = chronic liver disease; COPD = chronic obstructive pulmonary disease; MaR = medically at-risk; NIP = National Immunization Program; 21vPCV = 21-valent pneumococcal conjugate vaccine.
[a] The cost to the MBS reflects the assumed administration cost per dose ($19.60 for MBS Item 3).
[b] The PSCR stated that this scenario was assessed relative to the current NIP schedule, which includes 23vPPV for high-risk cohorts but excludes indigenous individuals aged 25-49.
The redacted values correspond to the following ranges:
[1] *300,000 to < 400,000*
[2] *200,000 to < 300,000*
[3] *20,000 to < 30,000*
[4] *10,000 to < 20,000*
[5] *5,000 to < 10,000*
[6] *60,000 to < 70,000*
[7] *30,000 to < 40,000*
[8] *400,000 to < 500,000*
[9] *200,000 to < 300,000*
[10] *100,000 to < 200,000*
[11] *40,000 to < 50,000*
[12] *500 to < 5,000*
[13] *50,000 to < 60,000*
[14] *700,000 to < 800,000*
[15] *500,000 to < 600,000*
[16] *$20 million to < $30 million*[17] *$10 million to < $20 million*
[18] *$0 to < $10 million*
[19] *$60 million to < $70 million*
[20] *$40 million to < $50 million*
[21] *$30 million to < $40 million*
[22] *$70 million to < $80 million*

6.77 The total cost to Government was estimated at $40 million to < $50 million in Year 1 and $0 to < $10 million in Year 6, for a total cost of $100 million to < $200 million across the first 6 years of listing, of which 41% ($40 million to < $50 million) corresponded to catch-up doses. When including CLD and COPD, the total cost to Government increased to $100 million to < $200 million in the first 6 years of listing. This was an increase of $60 million to < $70 million, with over 90% of this for the COPD population.

6.78 The financial estimates were sensitive to the expansion of the listed population to include non-Indigenous adults 65-69 years. Based on the submission's estimates, this expansion would increase the total cost to NIP by $40 million to < $50 million over six years and cost to government by $50 million to < $60 million over 6 years compared with the current scenario (13vPCV replaced).

6.79 The ESC noted that the financial estimates were sensitive to the uptake rates assumed, although considered the rates assumed by the submission were reasonable.

Quality Use of Medicines

6.80 The submission proposed developing educational materials through stakeholder input to provide the latest information to healthcare professionals and the community

about 21vPCV, its place in clinical practice, and how to identify and manage potential vaccine-related adverse events. Provider education would also be carried out to ensure appropriate dosing for different populations and proper implementation of ATAGI's catch-up vaccination program advice when using 21vPCV in clinical practice. Specific education would be required in relation to the requirements for booster doses consistent with ATAGI's recommendation that 23vPPV be removed from the adult schedule when the use of 13vPCV is replaced by 21vPCV (or 20vPCV) (p3, ATAGI: Optimum schedule for pneumococcal vaccination for Australian adults, July 2025).

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended that 21-valent pneumococcal conjugate vaccine (21vPCV, Capvaxive) be a designated vaccine for the purposes of the *National Health Act 1953*, for the prevention of pneumococcal disease in individuals with an at-risk condition aged ≥ 18 years, non-Indigenous adults aged ≥ 65 years and Aboriginal and Torres Strait Islander adults aged ≥ 25 years. Consistent with ATAGI advice, the submission proposed that 21vPCV be listed on the NIP as a single dose for all populations. The PBAC noted this would simplify the adult pneumococcal schedule in comparison with the current schedule which recommended 13vPCV followed by booster doses of 23vPPV in the Medically at Risk (MaR) and Aboriginal and Torres Strait Islander populations. The PBAC recommended reducing the age threshold for non-indigenous adults to 65 years (from 70 years) as proposed by the ATAGI. The PBAC also recommended expanding the eligibility of the adult MaR population to include chronic obstructive pulmonary disease (COPD) and chronic liver disease (CLD), noting that adults with CLD and COPD are at increased risk of pneumococcal disease. The PBAC advised, in the context of no clinical outcomes data for 21vPCV and the potential for coverage of 21vPCV to change over time, that more conservative assumptions should be applied in the economic evaluation, and that a price reduction would be required for 21vPCV to be considered cost-effective.

7.2 The PBAC considered there is a clinical need for alternative pneumococcal vaccines as there remains a substantial burden of disease in the proposed NIP populations, despite NIP listing of 13vPCV and 23vPPV. The PBAC noted the proposed listing of 21vPCV was supported by the consumer comments received for this submission.

7.3 The PBAC considered that a 21vPCV program will provide a greater impact on pneumococcal disease compared to the current adult NIP schedule and noted this was consistent with ATAGI's preferential recommendation for 21vPCV over other available vaccines. On this basis, the PBAC was satisfied that 21vPCV will provide, for some patients, a significant improvement in efficacy over the main comparator, 13vPCV, followed by booster doses of 23vPPV in the MaR populations aged ≥ 18 years, and Aboriginal and Torres Strait Islander population aged ≥ 50 years.

7.4 The nominated comparator for the proposed expanded population of Aboriginal and Torres Strait Islander adults aged 25 to 49 years was 20vPCV on the basis that no vaccine is currently listed for this population and 20vPCV was recommended for listing by the PBAC in November 2022. The PBAC considered this was reasonable and noted it was consistent with ATAGI advice.

7.5 The PBAC noted and welcomed the advice from the ATAGI that was provided to the PBAC to assist with consideration of this submission. The PBAC acknowledged the work undertaken by the ATAGI to define the optimum schedule for pneumococcal vaccination for Australian adults which was completed in July 2025. The PBAC noted ATAGI's advice regarding the desire to simplify the pneumococcal schedule by having a single vaccine for the adult population, rather than a PCV and 23vPPV. The PBAC noted ATAGI's advice that a 21vPCV program will provide the greatest impact on pneumococcal disease compared to other currently available pneumococcal vaccines. This advice was based on 21vPCV providing the broadest serotype coverage, particularly in the context of the existing 20vPCV program for children (implemented on 1 Sep 2025).

7.6 With regard to the requested listing, the ATAGI advised that lowering the age threshold for non-Indigenous adults from 70 to 65 years would enable alignment with other NIP-funded vaccination programs such as influenza and herpes zoster. This would be programmatically simpler for providers as implementation would align with the well-established schedule point of 65 years of age. A simpler program is expected to improve provider compliance and vaccine coverage. The PBAC advised that the proposed change to the age of vaccination of the non-Indigenous population from 70 years to 65 years was appropriate, noting that the submission provided sensitivity analyses to assess the impact of this change on the cost-effectiveness evaluation and financial estimates which allowed the impact of this change to be assessed.

7.7 The PBAC recommended that the MaR population should be expanded to include CLD and COPD populations as proposed by the submission, noting this was supported by ATAGI, and that the submission had provided sensitivity analyses to assess the impact of this change on the cost-effectiveness evaluation and financial estimates. However, there was limited evidence presented in the submission to support the analyses, and the PBAC therefore considered the results uncertain. The PBAC acknowledged that adults 18 years and above, with these conditions are at increased risk of pneumococcal disease and are recommended by ATAGI to receive a PCV followed by 23vPPV boosters. It was noted that current funding arrangements vary by age, which would impact the vaccine replaced by 21vPCV for CLD and COPD patients, i.e. 13vPCV is NIP-funded for non-indigenous adults 70 years or above, however 23vPPV is not NIP-funded for this group; for younger patients, no vaccines are currently NIP-funded if aged younger than 70 years (non-indigenous adults) or younger than 50 years (Aboriginal and Torres Strait Islander adults).

7.8 The PBAC considered that the appropriate age threshold for Aboriginal and Torres Strait Islander adults was 25 years, in recognition of the disproportionately high

burden of pneumococcal disease in this population. The PBAC noted this expansion to include younger adults, in comparison with the current threshold of 50 years for Aboriginal and Torres Strait Islander adults, was supported by ATAGI. The PBAC recalled that it had previously recommended 20vPCV for this group in November 2022 (see paragraph 2.4).

7.9 The PBAC noted the clinical claims presented in the submission were based on serotype specific opsonophagocytic activity (OPA) from immunogenicity trials and extrapolation to clinical effectiveness (immunobridging). However, there was little overlap between the serotypes in 21vPCV and 13vPCV (4 shared serotypes out of 21 serotypes covered by 21vPCV), resulting in uncertainty regarding the clinical protection for the 17 unmatched serotypes. The PBAC considered the submission's claim that VE results from the CAPiTA trial which assessed 13vPCV compared with no vaccine (VE of 75% for IPD and 45% for pneumococcal CAP) are applicable to 21vPCV is highly uncertain given the limited overlap in serotype coverage.

7.10 The PBAC noted that the submission presented an indirect treatment comparison (ITC) of serotype-specific opsonophagocytic geometric mean ratios between 21vPCV and 13vPCV, using 20vPCV as a common comparator, in non-Indigenous adults ≥ 70 years of age. Unaddressed confounders in the ITC rendered the results uncertain (in both magnitude and significance). The results from the ITC did not support non-inferiority for 2 (6A and 19A favoured 13vPCV) of the 4 serotypes, while for serotype 7F the 95% CI spanned one, indicating no significant difference. The result for the fourth shared serotype (3) favoured 21vPCV.

7.11 In terms of comparative effectiveness, the PBAC considered there was significant uncertainty regarding prevalence of disease serotypes over time, the impact of herd immunity afforded by paediatric vaccines, and the relative vaccine efficacy. The PBAC noted that 21vPCV has higher serotype coverage compared with 13vPCV and 20vPCV based on current data, however the magnitude of the translation from immunogenicity outcomes to clinical effectiveness was uncertain. Overall, the PBAC considered it was reasonable to accept that 21vPCV will provide a significant improvement in efficacy if implemented on the NIP as proposed. The PBAC agreed with the ESC that the abovementioned uncertainties relating to serotype coverage and immunobridging evidence, could be managed with a conservative approach in the economic model.

7.12 In terms of comparative safety, the submission described 21vPCV as non-inferior to 13vPCV, 15vPCV, 20vPCV and 23vPPV. The PBAC considered this was reasonable.

7.13 With regard the economic evaluation, the effectiveness of 21vPCV applied in the CUA was based on the assumed serotype distribution of IPD and CAP cases, the serotype coverage of the vaccine and the vaccine efficacy. The efficacy of 21vPCV in preventing IPD and CAP cases was assumed to be the same as reported for 13vPCV in the CAPiTA randomised, clinical outcomes trial. The CAPiTA trial included individuals that were not fully representative of the broader population included in the CUA. This was particularly relevant when considering the MaR population, as the CUA modelled

younger individuals who were immune compromised whereas CAPiTA included older adults with less serious underlying health issues and excluded individuals who were immune deficient. The PBAC considered it would be appropriate to apply reduced VE for 21vPCV (45% relative reduction in VE for non-shared serotypes) in the economic evaluation as there is no direct clinical efficacy data. This corresponds to VE of 41.3% for IPD (compared with 75% in the base case), and 24.8% for CAP (compared with 45% in the base case).

7.14 The PBAC compared the results of the MSA with and without the assumed reduction in VE for ST 6A and 19A that had been applied during the evaluation (Table 14). The PBAC advised it was appropriate to apply the conservative assumption of 45% reduction on 6A and 19A, consistent with ATAGI's concerns about incrementally lower immune responses (i.e., downward drift) when comparing between PCVs from 13vPCV to 20vPCV/15vPCV to 21vPCV for shared serotypes (see paragraph 6.34).

7.15 The CUA model fixed the serotype distributions causing IPD and CAP throughout the time horizon. This approach did not consider the potential for serotype replacement altering the prevalence of serotypes responsible for pneumococcal disease after the introduction of vaccines covering new serotypes. Sensitivity analyses demonstrated that the model was sensitive to assumptions in relation to serotype replacement, although limited data were available to inform these analyses. The PBAC considered that a ten-year time horizon was appropriate, consistent with ESC's advice that future serotype prevalence is uncertain.

7.16 Overall, the PBAC considered the submission's estimates of clinical benefits uncertain due to a lack of evidence supporting the relationship between serotype coverage and clinical benefits and overestimated due to the assumption that PD serotype prevalence will remain unchanged over time. The PBAC considered that the submission overestimated the benefits of 21vPCV and advised that revisions to the assumed VE (relative reduction of 45% for non-13vPCV serotypes in 21vPCV; and for shared serotypes 6A and 19A) and time horizon (reduction to 10 years) would be appropriate to inform the PBAC's consideration of the cost-effectiveness of 21vPCV. The PBAC gave advice in relation to the cost-effectiveness of 21vPCV for each proposed population as described in the following paragraphs.

Non-Indigenous adults aged 65 years and above

7.17 The PBAC considered the appropriate comparator for this group was 13vPCV. The PBAC noted that the economic evaluation corresponding to PBAC advice for non-indigenous adults aged 65 years or older is identified as PBAC Scenario 1 in Table 14. An ICER no more than $5,000 to < $15,000 /QALY, would be required to demonstrate cost-effectiveness.

Adults with COPD and CLD aged ≥ 18 years

7.18 The PBAC recommended that the MaR population should be expanded to include CLD and COPD as discussed in paragraph 7.7. The PBAC noted that the submission had provided scenario analyses for CLD and COPD, and that the submission's analyses suggested that expansion to these indications would be cost-effective at the price

proposed by the submission. However, the PBAC agreed with the concerns raised by the ESC regarding these analyses (paragraph 6.68). The PBAC considered that the scenario analyses were uncertain and not reliable for decision-making. The PBAC considered that the cost-effectiveness of this expansion should be informed by the economic evaluation of non-indigenous adults aged 65 years or older (identified as PBAC Scenario 1 in Table 14) as a proxy for cost-effectiveness in this group. An ICER no more than $5,000 to < $15,000 /QALY, would be required to demonstrate cost-effectiveness.

Aboriginal and Torres Strait Islander adults aged ≥ 50 years

7.19 The PBAC considered the appropriate comparator for this group was 13vPCV followed by 23vPPV boosters. The PBAC noted that the economic evaluation corresponding to PBAC advice for Aboriginal and Torres Strait Islander adults aged ≥ 50 years is identified as PBAC Scenario 2 in Table 14. An ICER no more than $5,000 to < $15,000 /QALY, would be required to demonstrate cost-effectiveness.

Adults with a NIP-listed risk condition aged ≥ 18 years

7.20 The PBAC considered the appropriate comparator for this group was 13vPCV followed by 23vPPV boosters. The PBAC noted that the economic evaluation corresponding to PBAC advice for adults with a NIP-listed condition is identified as PBAC Scenario 3 in Table 14. An ICER no more than $5,000 to < $15,000 /QALY, would be required to demonstrate cost-effectiveness.

Aboriginal and Torres Strait Islander adults aged 25 to 49 years

7.21 The PBAC considered that the requested price ($[redacted] per dose) was cost-effective for the Indigenous 25 to 49 years population, noting it had previously given advice regarding the cost-effectiveness of 20vPCV in this population in November 2022.

Catch-up program

7.22 The PBAC noted that the submission requested a catch-up program for 21vPCV that would run for three years. The PBAC noted that 21vPCV offered broader serotype coverage compared to 13vPCV for all cohorts, and that the ATAGI supported a catch-up program that would allow a single dose of 21vPCV for adults, regardless of previous adult pneumococcal vaccination, noting that denying access to 21vPCV based on previous vaccination would be inequitable. The PBAC noted that the submission had provided scenario analyses assessing the impact of catch-up doses for non-Indigenous adults aged > 70, but not for any of the other proposed populations. The PBAC noted the analyses for non-Indigenous adults aged >70 years suggested that catch-up doses would be cost-effective for individuals that had previously received 13vPCV or had received 23vPPV (Table 15). However, the PBAC considered that the scenario analyses were a simplified approach to the question of cost-effectiveness of the proposed catch-up program given that each comparison assumed vaccination at a single point in time (3 years after 13vPCV or five years after 23vPPV) and had a baseline age, which may not reflect the proposed population. The PBAC considered the proposed catch-up program was appropriate because it would provide equitable access to the vaccine, and maximise protection within the eligible populations,

however the scenario analyses presented in the submission were not reliable for decision-making. The PBAC considered that the cost-effectiveness of 21vPCV was likely to be less favourable in the catch-up populations (previously vaccinated as an adult) in comparison to naïve populations (not vaccinated as an adult), however the PBAC agreed with the ATAGI that the proposed catch-up program would be appropriate to maximise protection from pneumococcal disease, and not disadvantage individuals vaccinated prior to implementation of a 21vPCV program. As such, the PBAC recommended acceptance of the catch-up program. The PBAC advised that the population-specific advice above in paragraphs 7.18 to 7.21 should be used to determine the cost-effective price for each population, including catch-up doses.

7.23 The PBAC noted that the submission had requested a weighted price and that this would need to be recalculated, taking into account the PBAC's advice concerning the eligible populations, and the cost-effective price for each population. The PBAC advised that the weighted price should be calculated with the population weightings as shown in Table 20 and apply the cost-effective prices as determined for each population and described above in paragraphs 7.18 to 7.21.

7.24 With regard to the financial estimates, the PBAC advised that the methods used to derive the utilisation and financial estimates and the structure of the estimates model were reliable for decision-making, noting that the estimates would need to be recalculated to incorporate the change to the age threshold for non-Indigenous adults from ≥ 70 to ≥ 65 years, and the expansion of the MaR population to include CLD and COPD, and applying the recommended price.

7.25 The PBAC recommended the listing of 21vPCV on the basis that it should be available through the National Immunisation Program (NIP) under the circumstances specified in Section 8 below (for the prevention of pneumococcal disease in individuals with an at-risk condition aged ≥ 18 years, non-Indigenous adults aged ≥ 65 years and Aboriginal and Torres Strait Islander adults aged ≥ 25 years). The PBAC recommended that the MaR population should be expanded to include chronic liver disease (CLD) and chronic obstructive pulmonary disease (COPD).

7.26 Consistent with ATAGI advice, the PBAC advised that a catch-up program should be implemented, that would allow eligible adults to receive 21vPCV through the NIP, regardless of previous vaccination with other pneumococcal vaccines.

7.27 The PBAC noted ATAGI's advice that recommended removal of 23vPPV from the adult schedule when the use of 13vPCV is replaced by 21vPCV and considered that the Determination should be updated accordingly to indicate that 23vPPV booster doses are not funded through the NIP for adults vaccinated with 21vPCV.

7.28 The PBAC noted that the Australian Immunisation Handbook[9] list of risk conditions for pneumococcal vaccination was recently updated with editorial changes.

[9] https://immunisationhandbook.health.gov.au/resources/tables/table-risk-conditions-for-pneumococcal-vaccination-and-eligibility-for-nip-funding

Corresponding editorial changes may be appropriate for the Determination for consistency.

7.29 The PBAC noted that this submission is not eligible for an Independent Review because it is only relevant to submissions requesting a listing (or change to a listing) on the PBS.

Outcome:
Recommended

8 Recommended listing

8.1 The recommended listing in paragraph 8.2 includes the populations explicitly requested by the submission and the extensions to the populations that were recommended by the PBAC. This includes addition of two further risk factors (chronic obstructive pulmonary disease and chronic liver disease) to the list of medical risk conditions, and a decrease in the minimum age requirement from 70 years to 65 years for persons who are not Aboriginal and/or Torres Strait Islanders.

8.2 Add new item to the Determination:

Vaccine and the circumstances in which vaccine may be provided	***Brand***	***Formulation***	***Active ingredient and strength***	***Number and timing of doses***
Pneumococcal (conjugate, 21-valent) vaccine	*Capvaxive*	*Injection (0.5mL)*	*84 mcg of pneumococcal purified capsular polysaccharide antigen (4 mcg each of polysaccharide serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B) conjugated to approximately 65 mcg of diphtheria CRM197 protein.*	*1 dose*

Circumstances
Vaccine may be provided in the following circumstances:
(a) a dose of the vaccine may be provided to a person:
(i) who is at least 18 years of age and has one or more of the following medical risk conditions:
(A) functional or anatomical asplenia including sickle cell disease, other haemoglobinopathies, congenital or acquired asplenia (e.g. splenectomy) or hyposplenia; or
(B) immunocompromising conditions including congenital or acquired immune deficiency including symptomatic IgG subclass or isolated IgA deficiency, haematological malignancies, solid organ transplant haematopoietic stem cell transplant (HSCT) or HIV infection; or
(C) chronic respiratory disease including suppurative lung disease, bronchiectasis and cystic fibrosis or chronic lung disease of prematurity or chronic obstructive pulmonary disease (COPD); or
(D) chronic renal disease including: end stage renal disease – eGFR <15mL/min or relapsing or persistent nephrotic syndrome; or
(E) proven or presumptive cerebrospinal fluid (CSF) leak; or
(F) cochlear implants; or
(G) intracranial shunts; or
(H) previous episode of invasive pneumococcal disease (IPD); or
(I) chronic liver disease.
(b) a dose of the vaccine may be provided to a person:
(i) who is an Aboriginal and/or Torres Strait Islander; and
(ii) who is at least 25 years.
(c) a dose of the vaccine may be provided to a person:
(i) who is not an Aboriginal and/or Torres Strait Islander; and
(ii) who is at least 65 years.

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.