

**5.07 PNEUMOCOCCAL POLYSACCHARIDE CONJUGATE  
VACCINE, 20-VALENT ADSORBED,  
0.5 mL pre-filled syringe,  
Prevenar 20<sup>®</sup>,  
Pfizer Australia Pty Ltd.**

**1 Purpose of submission**

- 1.1 The Category 2 submission requested a National Immunisation Program (NIP) listing for 20-valent pneumococcal conjugate vaccine (20vPCV) for the prevention of pneumococcal disease in individuals with an at-risk condition ( $\geq 18$  years), non-Indigenous adults aged  $\geq 70$  years and Aboriginal and Torres Strait Islander adults aged  $\geq 25$  years. This is the first submission of 20vPCV for the proposed vaccination populations.
- 1.2 For the current NIP populations listing was requested on the basis of a cost-effectiveness analysis versus the currently listed 13-valent pneumococcal conjugate vaccine (13vPCV) and the near market 15-valent pneumococcal conjugate vaccine (15vPCV). For the proposed expanded population, Aboriginal and Torres Strait Islander adults aged 25-49 years, a cost-effectiveness analysis was presented versus 'no vaccine'.

**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: <u>Current NIP populations:</u> Non-Indigenous adults aged ≥ 70 years (regardless of risk conditions) Aboriginal and Torres Strait Islander adults aged ≥ 50 years (regardless of risk conditions) Adults (≥ 18 years) with NIP-funded risk conditions for pneumococcal disease. <u>Potential expanded NIP population:</u> Aboriginal and Torres Strait Islander adults aged 25-49 years (regardless of risk factors)	
Intervention	<b>Current NIP populations</b>	<b>Proposed program</b>
	Non-Indigenous adults aged ≥ 70 years (regardless of risk conditions)	20vPCV
	Aboriginal and Torres Strait Islander adults aged ≥ 50 years (regardless of risk conditions)	20vPCV + 2 x 23vPPV
	Adults (≥ 18 years) with NIP-funded risk conditions for pneumococcal disease.	20vPCV + 2 x 23vPPV
	<b>Expanded NIP populations</b>	
	Aboriginal and Torres Strait Islander adults aged 25-49 years (regardless of risk conditions)	20vPCV
Comparator	<b>Current NIP populations</b>	<b>Comparator</b>
	Non-Indigenous adults aged ≥ 70 years (regardless of risk conditions)	15vPCV or 13vPCV
	Aboriginal and Torres Strait Islander adults aged ≥ 50 years (regardless of risk conditions)	15vPCV + 2 x 23vPPV or 13vPCV + 2 x 23vPPV
	Adults (≥ 18 years) with NIP-funded risk conditions for pneumococcal disease.	15vPCV + 2 x 23vPPV or 13vPCV + 2 x 23vPPV
	<b>Expanded NIP populations</b>	<b>Comparator</b>
	Aboriginal and Torres Strait Islander adults aged 25-49 years (regardless of risk conditions)	No vaccine
Outcomes	<ul style="list-style-type: none"> <li>Efficacy (for 13vPCV, not 20vPCV): cases of invasive pneumococcal disease (IPD) and pneumococcal pneumonia (PP); sequelae of IPD cases; hospitalisations; deaths.</li> <li>Immunogenicity.</li> <li>Safety: local reactions; systemic reactions; serious adverse events; non-serious reactions; adverse events of special interest.</li> </ul>	
Clinical claim	<p><b>Efficacy Claim</b></p> <p>For non-Indigenous adults aged ≥ 70 years, Aboriginal or Torres Strait Islander adults aged ≥ 50 years and adults aged ≥ 18 years with NIP listed risk conditions:</p> <ul style="list-style-type: none"> <li>20vPCV has equivalent efficacy against IPD and PP to 13vPCV (15vPCV) for the shared serotypes and superior efficacy against IPD and PP for the additional 7 (5) serotypes.</li> </ul> <p>For Aboriginal and Torres Strait Islander adults aged 25-49 years:</p> <ul style="list-style-type: none"> <li>20vPCV has superior efficacy against IPD and PP to no vaccine.</li> </ul> <p><b>Safety Claim</b></p> <p>For non-Indigenous adults aged ≥ 70 years, Aboriginal or Torres Strait Islander adults aged ≥ 50 years and adults aged ≥ 18 years with NIP listed risk conditions:</p> <ul style="list-style-type: none"> <li>20vPCV has equivalent safety to 13vPCV and 15vPCV.</li> </ul> <p>For Aboriginal and Torres Strait Islander adults aged 25-49:</p> <ul style="list-style-type: none"> <li>20vPCV has inferior safety to no vaccine.</li> </ul>	

Source: Table 1.1.1, p4-5-S1 of the submission.

Abbreviations: 13vPCV, 13 valent pneumococcal conjugate vaccine; 15vPCV, 15 valent pneumococcal conjugate vaccine; 20vPCV, 20 valent pneumococcal conjugate vaccine; 23vPPV, 23 valent pneumococcal polysaccharide vaccine; IPD, invasive pneumococcal disease; NIP, National Immunisation Program; PP, pneumococcal pneumonia

## 2 Background

### Registration status

2.1 TGA status at time of PBAC consideration: not registered. The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the TGA Delegate’s Overview was available. The proposed TGA indication for 20vPCV was:

Active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* (*S. pneumoniae*) serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F in adults 18 years of age and older. Prevenar 20 should be used in accordance with official recommendations.

2.2 20vPCV received an accelerated approval by the United States Food and Drug Administration (FDA) in June 2021. Approval was based on immune responses as measured by opsonophagocytic activity (OPA) assay and was contingent upon verification of clinical benefit in a confirmatory trial. The European Medicines Agency (EMA) approved 20vPCV in December 2021. The EMA requested post-authorisation efficacy studies to confirm long-term effectiveness.

### Previous PBAC considerations

2.3 There have been no previous PBAC considerations for 20vPCV.

2.4 The PBAC has previously considered four submissions for 13vPCV and one for 15vPCV. A summary of these submissions is presented in the table below.

**Table 2: Summary of PBAC considerations of pneumococcal vaccine for adults**

PBAC meeting	Population	Outcome
March 2015 (13vPCV)	Non-indigenous adults ≥ 65 years Aboriginal and Torres Strait Islander individuals ≥ 50 years	Not recommended. The PBAC considered the evidence provided was not sufficient for the PBAC to be confident that recommending 13vPCV at the requested price would be cost effective (paragraph 7.1).
July 2015 (13vPCV)	Non-indigenous adults ≥ 65 years Aboriginal and Torres Strait Islander individuals ≥ 50 years	Recommended on the basis of cost-minimisation to 23vPPV. In the absence of directly comparative evidence between 13vPCV and 23vPPV, the PBAC accepted that the effectiveness of 13vPCV against CAP is likely to be superior to that of 23vPPV, whereas effectiveness against IPD was likely to be at least equivalent to that of 23vPPV where IPD was caused by serotypes common to both vaccines but not where IPD was caused by serotypes contained only within 23vPPV (paragraph 7.6). The PBAC noted that the claim of 13vPCV superiority in prevention of VT pneumonia remained uncertain (paragraph 7.7).
July 2016 (13vPCV)	Non-indigenous adults ≥ 65 years Aboriginal and Torres Strait Islander individuals ≥ 50 years	The PBAC recommended a change to the circumstances under which 13vPCV is made available as a designated vaccine for the NIP for the prevention of pneumococcal pneumonia and IPD in adults on the basis of cost-effectiveness compared with 23vPPV. The PBAC noted that no new evidence on comparative effectiveness of 13vPCV and 23vPPV was presented (paragraph 7.5). The PBAC considered that the revised model, and the price reduction offered in the submission, enabled it to

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PBAC meeting	Population	Outcome
		have greater confidence that the requested listing would be cost effective compared with 23vPPV (paragraph 7.7).
November 2018 (13vPCV)	Children aged $\geq 5$ years to $< 15$ years Adults aged $\geq 15$ years and $< 65$ years with conditions increasing their risk of pneumococcal disease Aboriginal and Torres Strait Islander adults $\geq 25$ years	Not recommended on the basis of unacceptably high and uncertain estimated ICERs. The PBAC noted that the key evidence from CAPiTA was in immunocompetent individuals $\geq 65$ years. The submission relied on the application of immunogenicity results from immunocompromised individuals (GMFR) to infer the application of efficacy outcomes from CAPiTA to the immunosuppressed population (paragraph 7.4).
July 2019 (13vPCV)	Individuals at high risk of pneumococcal disease	The PBAC recommended the implementation of a whole-of-life NIP-funded pneumococcal vaccine schedule, in line with ATAGI's June 2019 advice (paragraph 4.1). Recommendations relevant to adult populations were as follows: <ul style="list-style-type: none"> <li>• Non-Aboriginal and Torres Strait Islander adults <math>\geq 70</math> years: 13vPCV (single dose)</li> <li>• Aboriginal and Torres Strait Islander adults <math>\geq 50</math> years: 13vPCV (single dose) and 23vPPV (two subsequent doses approximately five years apart)</li> </ul>
November 2021 (15vPCV)	Non-Aboriginal and Torres Strait Islander adults $\geq 70$ years Aboriginal and Torres Strait Islander adults $\geq 50$ years All persons $\geq 18$ years newly diagnosed with a condition putting them at-risk of pneumococcal infection	The PBAC recommended listing of 15vPCV was based on, among other matters, its assessment that the cost-effectiveness of 15vPCV would be acceptable if it were cost-minimised against 13vPCV (paragraph 7.1). The PBAC considered it reasonable that 15vPCV was non-inferior compared to 13vPCV based on data from one randomised, noninferiority immunogenicity trial (paragraph 7.5 and 7.6). The PBAC did not accept the claim of superior effectiveness for serotype 3, noting that a superiority threshold which correlates with additional clinical protection was uncertain (paragraph 7.7).

Source: Table 1.1.17, p 29-30-S1 of the submission and compiled during the evaluation.

Abbreviations: 13vPCV, 13 valent pneumococcal conjugate vaccine; 15vPCV, 15 valent pneumococcal conjugate vaccine; 20vPCV, 20 valent pneumococcal conjugate vaccine; 23vPPV, 23 valent pneumococcal polysaccharide vaccine; CAP, community acquired pneumonia; ICER, incremental cost-effectiveness ratio; IPD, invasive pneumococcal disease; VT, vaccine type; GMFR, geometric mean fold rise; NIP, National Immunisation Program; PBAC, Pharmaceutical Benefits Advisory Committee

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

### 3 Requested listing

Name, Restriction, Manner of administration and form	Proposed Nationally Negotiated Price	Proprietary Name and Manufacturer
PNEUMOCOCCAL POLYSACCHARIDE CONJUGATE VACCINE, 20-VALENT ADSORBED 0.5 mL, Injection, Prefilled syringe	Risk conditions: \$ Other adult NIP listings: \$	Prevenar 20 Pfizer
<b>Category/Program:</b>	<b>NIP</b>	
Groups eligible for the requested NIP listing of Prevenar 20	Adults aged 70 years and over Aboriginal and Torres Strait Islander adults aged 25 years and over Individuals aged ≥18 years at increased risk of pneumococcal disease <sup>a</sup>	
Number and timing of doses	A single 20vPCV (0.5 mL) injection	

Source: Table 1.4.1, p37-S1 of the submission

Abbreviations: 20vPCV, 20-valent pneumococcal conjugate vaccine; NIP, National Immunisation Program

<sup>a</sup> NIP-funded risk conditions for pneumococcal disease

- 3.1 The submission proposed a price for 20vPCV for Aboriginal and Torres Strait Islander adults and for non-Indigenous adults aged ≥ 70 years of \$ per dose. This compares with \$ per dose for 13vPCV. For adults aged ≥ 18 years with a NIP listed risk condition, the proposed price for 20vPCV was \$ per dose. This compares with \$ per dose for 13vPCV. The pre-PBAC response acknowledged in order to address uncertainties related to the clinical superiority of 20vPCV over 13vPCV and 15vPCV as raised during the evaluation of 20vPCV and by the ESC, that the PBAC may make a recommendation using a cost minimisation approach versus 13vPCV and 15vPCV. The PBAC noted this approach would result in the same price per dose for 20vPCV, 15vPCV and 13vPCV.
- 3.2 ATAGI noted it is unclear if the expanded population of Aboriginal and Torres Strait Islander adults aged 25-49 years would require another dose of pneumococcal vaccine in their lifetime. ATAGI recommended that the sponsor present a full cost-effectiveness analysis, including (at a minimum) a single dose of 20vPCV at 25 years old versus a single dose of 20vPCV at 50 years old among Aboriginal and Torres Strait Islanders (p11, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022). In this population the submission presented a cost-effectiveness analysis of a single dose of 20vPCV versus no vaccine which followed people until the age of 50 years (Table 9). The analysis did not enable the cost-effectiveness of additional doses, including additional doses of 23vPPV after the first dose of 20vPCV, to be assessed. The Pre-Sub-Committee Response (PSCR) stated the proposed program in the submission was for a single dose of 20vPCV in Aboriginal and Torres Strait Islander adults ≥ 25 years, in addition to the current NIP schedule of a dose of 20vPCV at ≥ 50 years followed by 2 doses of 23vPPV. The PSCR presented financial estimates including the cost of a subsequent dose of 23vPPV for the expanded population of Aboriginal and Torres Strait Islander persons aged 25-49 years to enable consideration of this regimen. The

cost-effectiveness of additional doses of 23vPPV for the expanded population were provided in the pre-PBAC response (see paragraph 6.77).

- 3.3 The requested restriction is consistent with the proposed TGA indication.

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

## 4 Population and disease

- 4.1 Pneumococcal disease is caused by the bacterium *S. pneumoniae*. It can be broadly categorised into invasive pneumococcal disease (IPD: meningitis, bacteraemia and bacteraemia associated pneumonia) and non-invasive pneumococcal disease, including community acquired pneumonia (CAP) and hospital acquired pneumonia (HAP).

- 4.2 In Australia, there remains a substantial burden of disease in the proposed NIP populations and the incidence of IPD among Aboriginal and Torres Strait Islander Australians is higher than among non-Indigenous Australians for all age groups (risk ratios of up to 13.4 based on notification rates from the National Notifiable Diseases Surveillance System, 2011-2014).

- 4.3 Pneumococcal disease can be fatal. It was estimated that in 2015, the IPD burden was 3,795 disability adjusted life years (DALYs), with 82% of this attributed to fatal burden (AIHW 2019). Pneumococcal disease was associated with 2,434 hospital admissions in 2016 and 622 deaths between 1997 and 2016 (AIHW 2018).

- 4.4 The currently available pneumococcal vaccines (and serotype coverage) are:

- 13-valent pneumococcal conjugate vaccine, 13vPCV [non-23vPPV in purple font] (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F);
- 15-valent pneumococcal conjugate vaccine, 15vPCV [non-13vPCV in green font; non-23vPPV in purple font] (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F); and
- 23-valent pneumococcal polysaccharide vaccine, 23vPPV [non-15vPCV in blue font; 15vPCV-non13vPCV in green font; non-20vPCV in red font] (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F).

- 4.5 The proposed vaccine (and serotype coverage) is:

- 20-valent pneumococcal conjugate vaccine, 20vPCV [non-15vPCV in blue font; 15vPCV-non13vPCV in green font; non-23vPPV in purple font] (1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F)

- 4.6 The 20vPCV is based on the same technology and platform as 13vPCV. The 20vPCV vaccines modifies immune response to the polysaccharide from a T-cell independent response to a T-cell dependent response. The T-cell dependent response leads to both an enhanced antibody response and generation of memory B-cells, allowing for an anamnestic (booster) response on re-exposure to the bacteria. Vaccination with

20vPCV induces serum antibody production and immunologic memory against the serotypes contained within the vaccine.

- 4.7 The vaccination schedules proposed for 20vPCV in the submission were based on the currently funded NIP schedules for 13vPCV. The submission proposed that 20vPCV will replace 13vPCV for all eligible NIP populations. The submission proposed an expansion to the current NIP schedule to include Aboriginal and Torres Strait Islander adults aged 25-49.
- 4.8 The serotype coverage for 20vPCV and the currently available vaccines is presented in Table 3. The coverage for 20vPCV ranges from 43% to 72% depending on the population. The PBAC noted that this compares with 25% to 38% for 13vPCV, 29% to 51% for 15vPCV and 51% to 80% for 23vPPV.

**Table 3: Serotype coverage of 20cPCV and comparators**

Component	Input	Adults aged > 18 years with risk conditions		Non-indigenous adults		Aboriginal and Torres Strait Islander adults (with or without risk conditions)	
		Additional risk	Existing NIP	65-69 years	≥ 70 years	25-49 years	≥ 50 years
Serotype coverage	20vPCV	66% <sup>a</sup>	66% <sup>a</sup>	43% <sup>b</sup>	53% <sup>b</sup>	72% (50%) <sup>b</sup>	64% (51%) <sup>b</sup>
		70% <sup>a</sup> (with cross reactive serotypes 6C and 15C)	70% <sup>a</sup> (with cross reactive serotypes 6C and 15C)	48% <sup>b</sup> (with cross reactive serotypes 6C and 15C)	62% <sup>b</sup> (with cross reactive serotypes 6C and 15C)	72% (50%) <sup>b</sup> (with cross reactive serotypes 6C and 15C)	65% (52%) <sup>b</sup> (with cross reactive serotypes 6C and 15C)
	13vPCV	38% <sup>a</sup>	38% <sup>a</sup>	27% <sup>b</sup>	32% <sup>b</sup>	32% (25%) <sup>b</sup>	34% (27%) <sup>b</sup>
	15PCV	51% <sup>a</sup>	51% <sup>a</sup>	36% <sup>b</sup>	44% <sup>b</sup>	38% (29%) <sup>b</sup>	45% (36%) <sup>b</sup>
	23vPPV	76% <sup>a</sup>	76% <sup>a</sup>	51% <sup>b</sup>	59% <sup>b</sup>	80% (54%) <sup>b</sup>	70% (56%) <sup>b</sup>

Source: p28-29, Table 2.4.3, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022. Compiled during ESC evaluation.

a From National Notifiable Disease Surveillance System – IPD Public dataset using 2019 data from NSW,VIC,QLD,NT,SA,TAS and 2019 IPD data provided by WA Health; excludes untyped cases

b From National Notifiable Disease Surveillance System – IPD Public dataset using 2019 data from NSW,VIC,QLD,NT,SA,TAS; excludes untyped cases.

- 4.9 Based on 2016-2019 IPD surveillance data, in Aboriginal and Torres Strait Islander adults aged 25-49, the serotypes covered by 20vPCV would be responsible for 64% of IPD (p17, Table 2.2.4, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022). Based on the same data, in non-Indigenous Australians aged 5-69, the serotypes covered by 20vPCV would be responsible for 56% of IPD of which the 7 (or 5) additional serotypes covered by the 20vPCV would be responsible for 23.9% (11.2%) of IPD (p22, Table 2.2.10 PART B, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022).

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

## 5 Comparator

- 5.1 The submission nominated 13vPCV as primary comparator which is currently listed on the NIP for adults aged  $\geq 70$  years, Aboriginal and Torres Strait Islander adults aged  $\geq 50$  years and at-risk adults aged  $\geq 18$  years. 15vPCV, which was recommended for NIP-listing by the PBAC at the November 2021 meeting, was considered as a near market comparator. The nominated comparator for the expanded population of Aboriginal and Torres Strait Islander adults aged 25-49 years was 'no vaccine'. The ESC considered the proposed comparators were appropriate, noting the comparators were consistent with the ATAGI advice.
- 5.2 On the current NIP schedule, adults aged  $\geq 18$  years with an NIP listed risk condition and Aboriginal and Torres Strait Islander adults aged  $\geq 50$  years receive 2 subsequent doses of 23vPPV within 2 months and 5 years of the initial conjugate dose. These subsequent doses are relevant for both the intervention and the comparator for both populations.

*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 comments**

- 6.2 The PBAC noted and welcomed the input from a consumer group/organisation (1) via the Consumer Comments facility on the PBS website. The PBAC noted Lung Foundation Australia was supportive of the listing of 20vPCV on the NIP for the prevention of pneumococcal disease. The comments described a range of benefits of treatment with 20vPCV including providing an alternative vaccine to 13vPCV; a potential reduction in the risk of disease, disability, death and treatment costs associated with pneumococcal disease, and the economic and social burden experienced by those with the disease; and strengthening the respiratory health of the Australian community.

### **Clinical trials**

- 6.3 The proposed clinical claim for 20vPCV was based on two sets of clinical evidence:
- 20vPCV immunogenicity data to demonstrate the comparability of the immune response for the 13 serotypes shared between 20vPCV and 13vPCV and for the additional 7 serotypes shared between 20vPCV and 23vPPV ('immunobridge'). This evidence was used to directly support the clinical and safety claims of 20vPCV made by the submission.
  - 13vPCV efficacy, effectiveness and immunogenicity data included as supportive evidence for the efficacy of 20vPCV via the indirect extrapolation to 13vPCV

effectiveness studies. The evidence included one randomised trial, CAPiTA (2015), 7 observation studies, 16 immunogenicity studies in healthy adults, and 18 immunogenicity studies in individuals at increased risk of IPD. In these studies, 13vPCV was compared to either placebo (or not vaccinated) or 23vPPV. The CAPiTA trial has previously been reviewed by the PBAC in the March 2015, July 2015, July 2016, and November 2018 13vPCV submissions and all 13vPCV immunogenicity studies have been presented in past PBAC submissions for 13vPCV.

- 6.4 The submission stated that the proposed approach was justified because 20vPCV is based on the same technology and platform as 13vPCV. It was agreed by the FDA and EMA that licensure for the proposed indication could be granted based on demonstration of an adequate safety profile of the vaccine, as well as by establishing an ‘immunobridge’ between 20vPCV and 13vPCV for the 13vPCV matched serotypes and between 20vPCV and 23vPPV for the 7 additional serotypes. The ATAGI considered this reasonable, although noted there may be uncertainty as to whether the relationship to clinical outcomes will necessarily hold for the 7 unmatched serotypes (p30, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022).
- 6.5 The submission presented the following immunogenicity trials to directly support the clinical and safety claims of 20vPCV:
- One pivotal head-to-head, randomised, non-inferiority trial (B7471007) comparing 20vPCV to 13vPCV for the ‘13 matched’ serotypes and 23vPPV for the 7 additional serotypes (N=3,889).
  - Four randomised trials designed to demonstrate: Batch consistency (B7471008) evaluating 20vPCV immune response across three different lots (N=1,708), 20vPCV immune response in those previously vaccinated (B7471006) (N=873), impact of concurrent seasonal flu vaccination (B7471004) (N=1791) and COVID-19 booster dose (B7471026) (N=559). These studies were descriptive in nature and were not designed or powered to assess comparative efficacy and were therefore considered supplementary in the evaluation. However, results from B7471008 were included in the indirect comparison versus 15vPCV.
  - An indirect treatment comparison (ITC) comparing 20vPCV with 15vPCV using 13vPCV as the common comparator. The evidence base for 15vPCV included one pivotal head-to-head, randomised, non-inferiority trial (PNEU-AGE) comparing 15vPCV to 13vPCV (N=1,202) and supplementary trials (PNEU-DAY (N=1,515), PNEU-PATH (N=652), PNEU-TRUE (N=2,221)).
- 6.6 The ATAGI noted that while correlation of immunogenicity with clinical protection has not been documented for adults, this approach has been used previously for 13vPCV in Australia and is accepted by the FDA and EMA. However, the WHO cautioned that in comparison of vaccines in general, serotype specific correlates of protection may vary and the limitations of these comparisons in predicting efficacy should be

considered when assessing the overall benefit/risk relationship for the new vaccine (p30, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022).

6.7 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
<b>20vPCV immunogenicity trials</b>		
B7471004	Protocol B7471004. A phase 3, randomized, double-blind trial to evaluate the safety and immunogenicity of a 20-valent pneumococcal conjugate vaccine (20vPCV) when coadministered with seasonal inactivated influenza vaccine (SIIV) in adults ≥65 years of age.	2 November 2021.
B7471006	Protocol B7471006. Final report: a phase 3, randomized, open-label trial to evaluate the safety and immunogenicity of a 20-valent pneumococcal conjugate vaccine in adults ≥65 years of age with prior pneumococcal vaccination. Cannon K, Elder C, Young M et al. A trial to evaluate the safety and immunogenicity of a 20-valent pneumococcal conjugate vaccine in populations of adults ≥65 years of age with different prior pneumococcal vaccination.	25 July 2020.  <i>Vaccine</i> 2021; 39(51): 7494–7502.
B7471007	Protocol B7471007. Final report: a phase 3, randomized, double-blind trial to evaluate the safety and immunogenicity of a 20-valent pneumococcal conjugate vaccine in pneumococcal vaccine-naïve adults 18 years of age and older. Essink B, Sabharwal C, Cannon K et al. Pivotal phase 3 randomized clinical trial of the safety, tolerability, and immunogenicity of 20-valent pneumococcal conjugate vaccine in adults 18 years and older.	11 June 2020.  <i>Clinical Infectious Disease</i> 2021 Epub ahead of print.
B7471008	Protocol B7471008. Final report: a phase 3, randomized, double-blind trial to evaluate the safety and immunogenicity of 3 lots of 20-valent pneumococcal conjugate vaccine in pneumococcal vaccine-naïve adults 18 through 49 years of age. Klein NP, Peyrani P, Yacism K et al. A phase 3, randomized, double-blind study to evaluate the immunogenicity and safety of 3 lots of 20-valent pneumococcal conjugate vaccine in pneumococcal vaccine-naïve adults 18 through 49 years of age.	30 June 2020.  <i>Vaccine</i> 2021; 39(38): 5428–5435.
B7471007 and B7471008	Sabharwal C, Yacisin K, Sundaraiyer V, et al. Serotype 15C immune responses to a 20-valent pneumococcal conjugate vaccine in pneumococcal vaccine-naïve adults.	European Congress of Clinical Microbiology and Infectious Diseases 2021.
B7471006, B7471007 and B7471008	Sabharwal C, Sundaraiyer V, Peng Y, et al. Immunogenicity of a 20-valent pneumococcal conjugate vaccine in adults 18 years and older with medical conditions and other factors that increase risk of pneumococcal disease.	European Congress of Clinical Microbiology and Infectious Diseases 2021.
B7471026	Protocol B7471026. A phase 3, randomized, double-blind trial to describe the safety and immunogenicity of 20-valent pneumococcal conjugate vaccine when coadministered with a booster dose of BNT162b2 in adults 65 years of age and older.	17 March 2022
<b>15vPCV immunogenicity trials</b>		
PNEU-AGE	Platt HL, Cardona JF, Haranaka M, et al. A phase III trial of safety, tolerability, and immunogenicity of V114, 15-valent pneumococcal conjugate vaccine, compared with 13-valent pneumococcal conjugate vaccine in adults 50 years of age and older (PNEU-AGE).	European Congress of Clinical Microbiology and Infectious Diseases 2021.

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Trial ID	Protocol title/ Publication title	Publication citation
	Platt HL, Cardona JF, Haranaka M, et al. A phase 3 trial of safety, tolerability, and immunogenicity of V114, 15-valent pneumococcal conjugate vaccine, compared with 13-valent pneumococcal conjugate vaccine in adults 50 years of age and older (PNEU-AGE).	<i>Vaccine</i> 2022; 40(1): 162-172.
PNEU-DAY	Hammit L, Quinn D, Janczewska E, et al. Immunogenicity, safety, and tolerability of V114, a 15-valent pneumococcal conjugate vaccine, in immunocompetent adults aged 18–49 years with or without risk factors for pneumococcal disease: a randomized Phase 3 Trial (PNEU-DAY). Published by Oxford University Press on behalf of Infectious Diseases Society of America. 2021 Hammit LL, Quinn D, Janczewska E, et al. Phase 3 trial to evaluate safety, tolerability and immunogenicity of V114 followed by 23-valent pneumococcal polysaccharide vaccine 6 months later in at-risk adults aged 18-49 years (PNEU-DAY).	<i>Open Forum Infectious Diseases</i> 2022; 9(3).  European Congress of Clinical Microbiology 2021.
PNEU-PATH	Song JY, Chang CJ, Andrews C, et al. Safety, tolerability, and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine, followed by sequential 23vPPV vaccination in healthy adults aged ≥50 years: a randomized phase III trial (PNEU-PATH).	<i>Vaccine</i> 2021; 39(43): 6422-6436.
PNEU-TRUE	Simon JK, Staerke NB, Hemming-Harlo M, et al. Lot-to-lot consistency, safety, tolerability, and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine, in healthy adults aged ≥50 years: A randomized phase 3 trial (PNEU-TRUE. <i>Vaccine</i> 2022 Simon JK, Staerke NB, Hemming-Harlo M, et al. A phase III, randomised, double-blind, active comparator-controlled, lot-to-lot consistency study to evaluate the safety and immunogenicity of V114 in healthy adults ≥50 years of age (PNEU-TRUE).	<i>Vaccine</i> 2022; 40(9): 1342-1351.  European Congress of Clinical Microbiology & Infectious Diseases 2021.

Source: Table 2.2.1, pp12-14 of the submission.

Abbreviations: 15vPCV 15-valent pneumococcal conjugate vaccine; 20vPCV 20-valent pneumococcal conjugate vaccine

Note: Trials B7471006, B7471004, and B7471026 were not directly relevant to supporting the proposed clinical claims.

Note: Among the presented 15vPCV trials, the PBAC previously considered that only PNEU-AGE was powered to compare efficacy between 15vPCV and 13vPCV and the remaining trials were considered supplementary evidence (paragraph 6.8, Vaxneuvance, PSD, November 2021 PBAC Meeting).

6.8 The key features of the randomised trials used to directly support the clinical and safety claims are summarised in Table 5.

Table 5: Key features of the included evidence

Trial	N	Design	Risk of bias	Population	Outcome(s)	Use in modelled evaluation
<b>20vPCV (immunogenicity studies)</b>						
B7471007	3,889	Phase III, MC, R, DB	Low	Pneumococcal vaccine-naïve adults aged ≥ 18 years	Serotype-specific OPA GMTs, Safety	Not used
B7471008	1,708	Phase III, MC, R, DB	Low	Pneumococcal vaccine-naïve adults aged 18-49 years	Serotype-specific OPA GMTs, Safety	Not used
<b>15vPCV (immunogenicity studies)</b>						
PNEU-AGE	1,205	Phase III, R, DB, MC 6 mths	Low	Pneumococcal vaccine-naïve adults aged ≥ 50 years	Serotype-specific OPA GMTs, Safety	Not used
PNEU-DAY	1,515	Phase III, R, DB, MC 6 mths	Low	Pneumococcal vaccine-naïve immunocompetent adults aged 18-49 years	Serotype-specific OPA GMTs, Safety	Not used
PNEU-PATH	652	Phase III, R, DB, MC 13 mths	Low	Pneumococcal vaccine-naïve adults aged ≥ 50 years	Serotype-specific OPA GMTs, Safety	Not used
PNEU-TRUE	2,340	Phase III, R, DB, MC 6 mths	Low	Pneumococcal vaccine-naïve adults aged ≥ 50 years	Serotype-specific OPA GMTs, Safety	Not used

Source: Compiled during the evaluation using information from Sections 2.3-2.5 of the submission

Abbreviations: 13vPCV, 13-valent pneumococcal conjugate vaccine; 15vPCV, 15-valent pneumococcal conjugate vaccine; 20vPCV, 20-valent pneumococcal conjugate vaccine; DB, double blind; MC, multi-centre; mths, months; R, randomised.

6.9 The key outcome to support the clinical claims was serotype-specific OPA at 1 month after vaccination measured as geometric mean titre (GMT). Based on this, OPA geometric mean ratios (GMRs) were calculated.

#### **Pivotal randomised head-to-head 20vPCV vs 13vPCV and 23vPPV trial (B7471007): immunogenicity**

6.10 In study B7471007, the primary objectives were to demonstrate, in adults aged ≥ 60 years (Cohort 1), non-inferiority of immune responses (serotype-specific OPA GMT one month after vaccination) induced by 20vPCV compared to:

- 13vPCV for the shared 13 serotypes in 13vPCV (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F); and
- 23vPPV for the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F).

6.11 Evidence to support clinical claims (non-inferiority/superiority) of 20vPCV to 13vPCV and 23vPPV for populations aged 18 to 59 years were based on secondary objectives to demonstrate non-inferiority of immune response to the 20 serotypes in 20vPCV (i) between adults ≥ 60 years (Cohort 1) and adults 50 to 59 (Cohort 2) and (ii) between adults ≥ 60 years (Cohort 1) and adults 18 to 49 (Cohort 3).

6.12 Across both objectives, the non-inferiority criteria that defined the OPA GMR outcome were the lower bound of the 2-sided 95% confidence interval (CI) of the OPA GMR > 0.50. OPA GMR > 0.5 is lower than the World Health Organisation (WHO) recommended lower bound of the 95% CI of 0.67. ATAGI has considered 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 (“downward drift”) and that this concern may need to be considered alongside any future use of the ‘totality of evidence’ approach (p31, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022). The PSCR noted that ‘downward drift’ is less applicable to adult pneumococcal vaccines as 13vPCV was the first pneumococcal conjugate vaccine licensed in adults. The PSCR further noted that it would be difficult to achieve the large sample sizes required to assess non-inferiority of vaccines with multiple antigens.

- 6.13 Superiority criteria or thresholds were not specified in the submission or the B7471007 Clinical Study Report. The PSCR provided additional information regarding the pre-specified statistical plans to test and demonstrate superiority. The PSCR indicated that superiority for the 7 additional serotypes would only be tested after non-inferiority was achieved for the 7 serotypes. The results presented in B7471007 showed that lower bound of the 95% CI for serotype 8 was 0.49, therefore, did not meet non-inferiority criteria. Therefore, superiority for the 7 additional serotypes could not be tested and it would be reasonable to exercise caution when interpreting these results.
- 6.14 Although the trial included participants that covered the relevant age groups for the proposed NIP listing, the following differences to the proposed listing were noted:
- Non-indigenous adults aged  $\geq 70$  years. Only 12.9% of participants in Cohort 1 were aged  $\geq 70$  years.
  - Aboriginal and Torres Strait Islander adults aged  $\geq 50$  years and aged 25-49 years (expanded NIP population). There is a lack of racial diversity across all 3 age cohorts. Although native populations such as American Indian or Alaska Native were included in the trial, these represented less than 0.7% across all 3 cohorts. The majority ( $> 82.7\%$ ) of the participants were white.
  - Adults aged  $> 18$  years with NIP-funded risk conditions for pneumococcal disease. 33.1% of individuals across all 3 age cohorts had one or more risk factors for serious pneumococcal infection. However, none of these risk factors reflect the NIP-funded risk conditions for pneumococcal disease.

**Indirect treatment comparisons between 20vPCV and 15vPCV: immunogenicity**

- 6.15 The submission performed four meta-analyses (20vPCV vs 13vPCV and 15vPCV vs 13vPCV across two age groups: age  $\geq 50$  years, and age 18-49 years) to generate data used in the indirect comparisons versus 15vPCV.
- 6.16 The submission conducted ITCs comparing serotype specific OPA GMRs between 20vPCV and 15vPCV, using 13vPCV as a common comparator, across nominated age groups: indirect comparison 1 (IC1) age  $\geq 50$  years, and indirect comparison 2 (IC2) age 18-49 years. The submission used the Bucher method to perform the indirect comparisons.

- 6.17 Data used for IC1 were obtained from B7471007 Cohorts 1 and 2 for 20vPCV and PNEU-AGE, PNEU-PATH and PNEU-TRUE for 15vPCV. For IC2, data were from B7471007 Cohort 3 and B7471008 for 20vPCV and PNEU-DAY for 15vPCV.
- 6.18 Only a small proportion of participants in B7471007 Cohort 1 were aged  $\geq 70$  (12.9%). Further, it was observed that OPA GMTs of those in younger age groups (Cohorts 2 and 3) were often higher than those of older participants in Cohort 1. Therefore, including data from a younger age group ( $\geq 50$  years) to represent those over 70 years may overestimate the effect.
- 6.19 The submission combined data from studies that were designed for different purposes; for example, B7471008 and PNEU-TRUE were designed to evaluate batch consistency. Only the pivotal trials, B7471007 and PNEU-AGE, were designed for comparative assessment while the remaining trials were descriptive studies without formal hypothesis testing. Additionally, ATAGI had cautioned that ‘while inclusion and exclusion criteria were otherwise similar across the studies, specific differences in subject populations across studies were not controlled. Cross-study comparative conclusions must be drawn with caution, as the uncontrolled factors could impact on the immune responses and confound the interpretation of cross-study results’ (p69, 20vPCV TGA Clinical Evaluation Report, 2021). For example, although the mean ages of B7471007 (Cohort 3) and B7471008 (Cohort 3) were similar (34.0 vs 35.4 years), the distribution of race across these studies varied.
- 6.20 The submission stated that indirect comparisons were not specifically conducted for the following requested NIP populations due to a lack of data specific to these populations and for the required combination of vaccination schedule: non-Indigenous adults  $\geq 70$  years, Aboriginal and Torres Strait Islander populations and adults ( $\geq 18$  years) with specified risk conditions for pneumococcal disease. Evidence to support these populations were proxied using the indirect comparisons conducted by age groups.
- 6.21 The submission nominated the non-inferiority margin as the lower bound of the 95% CI  $> 0.5$  as it was used by both the 20vPCV and 15vPCV pivotal trials.

## Comparative effectiveness

6.22 A summary of the OPA GMRs in adults aged  $\geq 60$  years for the 13 shared and 7 additional serotypes is presented in Table 6.

**Table 6: Result of OPA GMT and GMR for 13 shared and 7 additional serotypes from Cohort 1 of B7471007**

Sero type	Vaccine group (as randomised)						Vaccine comparison		
	Vaccination 1 20vPCV/saline			Vaccination 1 13vPCV/23vPPV					
	n <sup>a</sup>	GMT <sup>b</sup>	(95% CI) <sup>b</sup>	n <sup>a</sup>	GMT <sup>b</sup>	(95% CI) <sup>b</sup>	GMR <sup>c</sup>	(95% CI) <sup>c</sup>	P-Value <sup>d</sup>
<b>Shared (20vPCV versus 13vPCV)</b>									
1	1430	123.4	(112.3, 135.5)	1419	153.8	(140.2, 168.8)	0.80	(0.71, 0.90)	NA
3	1415	40.7	(38.0, 43.6)	1411	47.8	(44.7, 51.2)	0.85	(0.78, 0.93)	NA
4	1415	508.7	(456.5, 566.9)	1409	626.9	(563.5, 697.4)	0.81	(0.71, 0.93)	NA
5	1418	91.6	(83.4, 100.5)	1395	109.7	(100.1, 120.3)	0.83	(0.74, 0.94)	NA
6A	1403	889.0	(795.0, 994.1)	1390	1165.1	(1043.3, 1301.0)	0.76	(0.66, 0.88)	NA
6B	1413	1115.2	(1003.1, 1239.8)	1401	1341.3	(1208.5, 1488.8)	0.83	(0.73, 0.95)	NA
7F	1409	968.8	(887.0, 1058.3)	1391	1129.2	(1034.7, 1232.4)	0.86	(0.77, 0.96)	NA
9V	1399	1455.5	(1317.5, 1608.0)	1391	1567.8	(1420.5, 1730.5)	0.93	(0.82, 1.05)	NA
14	1418	746.7	(679.0, 821.2)	1408	746.7	(679.8, 820.1)	1.00	(0.89, 1.13)	NA
18C	1420	1252.6	(1123.1, 1397.0)	1403	1482.3	(1330.5, 1651.5)	0.85	(0.74, 0.97)	NA
19A	1420	517.9	(472.2, 568.0)	1398	645.3	(588.9, 707.1)	0.80	(0.71, 0.90)	NA
19F	1421	265.8	(240.2, 294.1)	1403	333.3	(301.5, 368.3)	0.80	(0.70, 0.91)	NA
23F	1424	276.5	(242.5, 315.2)	1409	335.1	(294.4, 381.4)	0.83	(0.70, 0.97)	NA
<b>Additional<sup>e</sup> (20vPCV versus 23vPPV)</b>									
8	1374	465.6	(422.5, 513.1)	1319	848.1	(769.1, 935.2)	0.55	(0.49, 0.62)	>0.999
10A	1310	2007.6	(1808.0, 2229.1)	1263	1079.9	(972.1, 1199.7)	1.86	(1.63, 2.12)	<0.001
11A	1198	4426.8	(3965.5, 4941.8)	1209	2534.9	(2276.8, 2822.3)	1.75	(1.52, 2.01)	<0.001
12F	1294	2538.7	(2255.3, 2857.7)	1222	1716.6	(1521.8, 1936.3)	1.48	(1.27, 1.72)	<0.001
15B	1283	2398.2	(2090.6, 2751.2)	1249	768.5	(669.7, 881.9)	3.12	(2.62, 3.71)	<0.001
22F	1274	3666.2	(3244.4, 4143.0)	1227	1846.2	(1636.6, 2082.6)	1.99	(1.70, 2.32)	<0.001
33F	1157	5125.9	(4611.3, 5698.0)	1201	3720.6	(3356.2, 4124.6)	1.38	(1.21, 1.57)	<0.001

Source: Table 2.5.1 and 2.5.2, p64 and 72 of the submission

Abbreviations: 13vPCV, 13-valent pneumococcal conjugate vaccine; 20vPCV, 20-valent pneumococcal conjugate vaccine; 23vPPV, 23-valent pneumococcal conjugate vaccine; CI, confidence interval; LS, least squares; NR, not available; OPA, opsonophagocytic activity; GMR, geometric mean ratio; GMT, geometric mean titre

<sup>a</sup> n = Number of subjects with valid and determinate OPA titres for the specified serotype.

<sup>b</sup> GMTs and 2-sided CIs were calculated by exponentiating the LS means and the corresponding CIs based on analysis of log-transformed OPA titres using a regression model with vaccine group, sex, smoking status, age at vaccination in years (continuous), and baseline log transformed OPA titres.

<sup>c</sup> GMRs (ratio of GMTs 20vPCV/saline to 13vPCV/23vPPV) and 2-sided CIs were calculated by exponentiating the difference of LS means and the corresponding CIs based on the same regression model as above.

<sup>d</sup> Nominal 1-sided p-value for superiority based on the same regression model.

<sup>e</sup> The comparison consists of 20vPCV followed by saline compared to 13vPCV followed by 23vPPV at one month post 23vPPV vaccination

6.23 Across the 13 shared serotypes, the OPA GMRs comparing the 20vPCV and 13vPCV OPA titres in adults  $\geq 60$  years ranged from 0.76 (serotype 6A) to 1.00 (serotype 14) (Table 6). The lower bounds of the 95% CI were above 0.5 for all 13 serotypes, therefore the non-inferiority criteria were met. The ESC noted that the OPA GMRs for 11 of the 13 matched serotypes had the upper bound of the 95% CI  $< 1$ , thus favouring 13vPCV. The pre-PBAC response noted that ATAGI stated that 'While GMRs for 11 of 13 serotypes had confidence intervals below 1 (favouring 13vPCV) observed

differences are considered to have a low likelihood of resulting in a loss in protection of clinical significance' (p2, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022).

- 6.24 For the additional 7 serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F), the OPA GMRs in adults  $\geq 60$  years ranged from 0.55 (serotype 8) to 3.12 (serotype 15B). The ESC noted that the lower bound of the 95% CI for serotype 8 was 0.49, therefore did not meet the non-inferiority criteria. The PSCR stated that as non-inferiority was not met for serotype 8, additional analyses to further characterise the immune responses to this serotype were performed and they suggest that the immune response is expected to be similarly protective to the other 19 vaccine serotypes in 20vPCV that met non-inferiority. The lower bound of the 95% CI for the OPA GMRs for the remaining 6 serotypes were  $> 1$  with nominal p-values for superiority  $< 0.001$ . The PSCR provided additional information (including a redacted Statistical Analysis Plan) verifying that superiority for the 7 additional serotypes could not be formally tested as non-inferiority was not achieved for all 7 serotypes. Claims for superiority should be interpreted with caution.
- 6.25 The secondary objectives of demonstrating non-inferiority of immune responses to the 20 serotypes in 20vPCV in adults 50 to 59 (Cohort 2) and adults 18 to 49 (Cohort 3) were met (the lower bound of the 95% CI were above 0.5). The submission concluded that clinical claims made based on results from Cohort 1 can be translated to those aged 18 to 59 years vaccinated with 20vPCV. The ATAGI considered it acceptable to infer non-inferiority of immunogenicity in the younger age groups for the 13 shared serotypes, although there may be some uncertainty regarding the 7 additional serotypes (p48, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022).

### **Results from meta-analyses comparing 20vPCV or 15vPCV with 13vPCV**

#### **Age $\geq 50$ years**

- 6.26 In the comparisons between 20vPCV and 13vPCV, the upper bounds of the 95% CI were  $< 1$  for 11 of the 13 shared serotypes (except for serotypes 9V and 14), favouring 13vPCV. Overall, in the pooled results, none of the lower bounds of the 95% CI were  $< 0.5$ , thus meeting the non-inferiority criteria. Heterogeneity across trials ranged from 0% to 80% and was statistically significant at the 5% level for serotypes 5 and 9V and at the 10% level for serotypes 7F, 19A and 19F.
- 6.27 In the comparisons between 15vPCV and 13vPCV, the lower bound of the 95% CI was  $> 1$  for serotypes 3, 6B, 18C and 23F, thus favouring 15vPCV, while the upper bound of the 95% CI was  $< 1$  for serotypes 4 and 7F, favouring 13vPCV. In the overall pooled results, none of the lower bounds of the 95% CI was  $< 0.5$  therefore meeting the non-inferiority criteria. Heterogeneity across trials ranged from 0% to 73% and was statistically significant at the 5% level for serotype 7F.

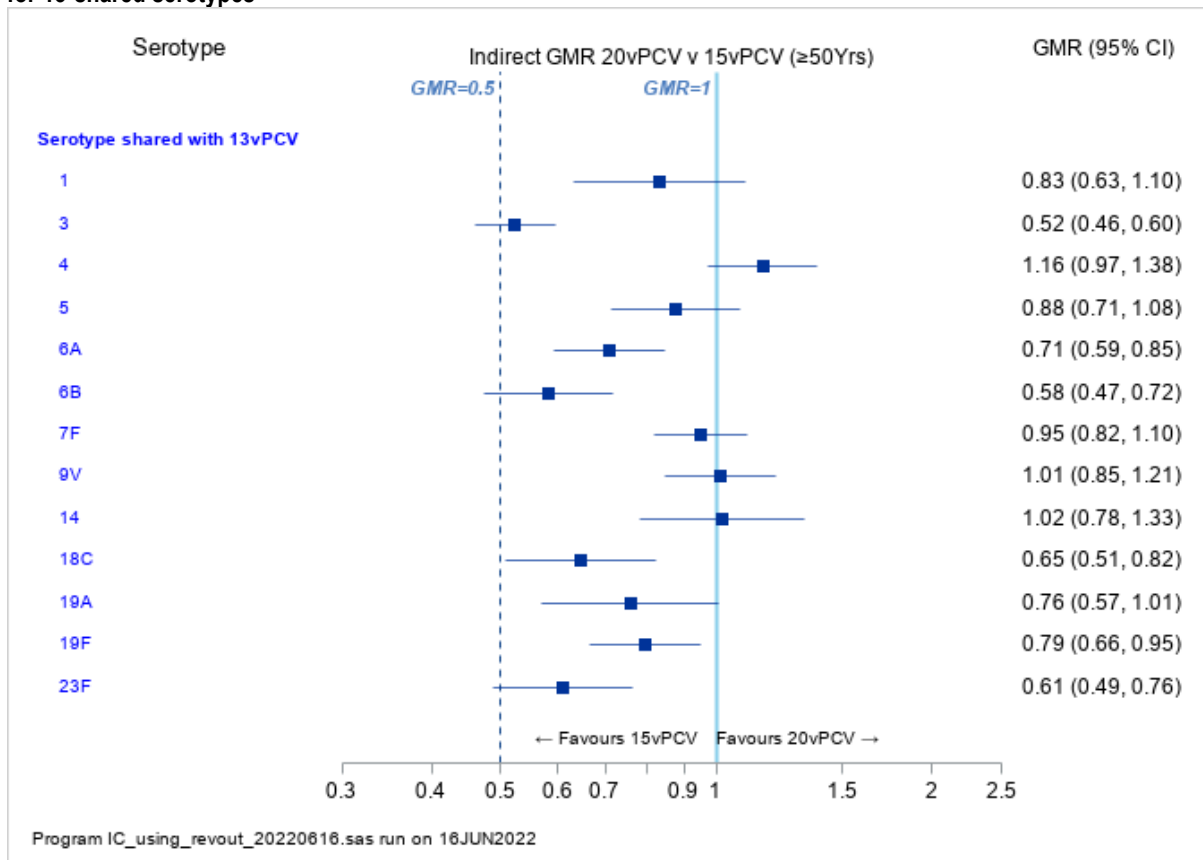
**Age 18-49 years**

- 6.28 In the comparisons between 20vPCV and 13vPCV, the results showed that across all 13 shared serotypes the pooled OPA GMRs were  $< 1$ . The upper bounds of the 95% CI were  $< 1$  for serotypes 1, 4, 5, 19A and 19F, favouring 13vPCV. For the additional two serotypes 22F and 33F not covered by the 13vPCV, the upper bounds of the 95% CI were  $> 1$ . The submission claimed that for these serotypes 20vPCV was superior to 13vPCV because the upper bounds of the 95% CI were far greater than 1. The GMR (95% CI) were 56.02 (40.99, 76.57) for 22F and 8.59 (6.73, 10.95) for 33F. Claims for superiority should be interpreted with caution as the analysis was conducted to demonstrate non-inferiority and there is no specific OPA threshold that has been identified which correlates to clinical efficacy. Heterogeneity across trials ranged from 0% to 73%, but none were statistically significant at the 5% level.
- 6.29 Comparisons between 15vPCV and 13vPCV were based on one trial (PNEU-DAY). For serotypes 3, 6B, 18C and 23F the lower bound of the 95% CI was  $> 1$  thus favouring 15vPCV, while for serotypes 4, 5, 7F and 9V the upper bound of the 95% CI was  $< 1$  thus favouring 13vPCV. For the additional two serotypes 22F and 33F not covered by the 13vPCV, the upper bounds of the 95% CI were  $> 1$ . The submission claimed that for these serotypes 15vPCV was superior to 13vPCV as the GMRs (95% CI) were 13.47 (10.14, 17.88) and 5.33 (4.41, 6.45), respectively. As above, claims for superiority should be interpreted with caution.

**Results from ITC comparing 20vPCV with 15vPCV**

- 6.30 Figure 1 shows the results of the indirect comparisons between 20vPCV and 15vPCV for the 13 shared serotypes for the  $\geq 50$  years age group. For serotypes 3, 6B and 23F, lower bounds of the 95% CI were  $< 0.5$ , thus did not meet the non-inferiority criteria.

Figure 1: Forest plot of IC1 – Indirect comparison of 20vPCV vs 15vPCV GMR at 1 month after vaccination (≥ 50 years) for 13-shared serotypes



Source: Figure 2.6.5, p422 of the submission

Abbreviations: 13vPCV, 13-valent pneumococcal conjugate vaccine; 20vpCV, 20-valent pneumococcal conjugate vaccine; CI, confidence interval; GMR, geometric mean ratio; GMT, geometric mean titre; GMR, geometric mean ratio

- 6.31 The results for the indirect comparisons between 20vPCV and 15vPCV for the 15 shared serotypes for the 18-49 years age group were similar to those for the ≥ 50 years age group. For serotypes 6B, 18C and 23F, lower bounds of the 95% CI were < 0.5, thus did not meet the non-inferiority criteria.
- 6.32 The results of the ITCs should be interpreted in the context of the differences across the trials. This includes differences in serotype specific OPA GMT in the common-comparator arm (13vPCV) across studies, geographical locations in which the studies were conducted, assay methods, statistical analytical methods used to calculate GMRs and characteristics of study populations. These differences affect transitivity in a variety of ways; thus the direction of impact is unclear.
- 6.33 Table 7 presents a summary of evidence presented in the submission indicating if non-inferiority criteria were met in the comparisons of 20vPCV against 13vPCV and 15vPCV. In the comparison between 20vPCV and 13vPCV, serotype 8 did not meet the non-inferiority criteria and the majority of the results for the matched serotypes favoured 13vPCV. In the indirect comparisons between 20vPCV and 15vPCV, three

serotypes (3, 6B and 23F in IC1 and 6B, 18C and 23F in IC2) did not meet the non-inferiority criteria.

**Table 7: Summary demonstrating if non-inferiority criteria were met across serotypes evaluated**

Source of results	20vPCV vs 13vPCV	20vPCV vs 15vPCV (indirect comparison)	
	B7471007 Cohort 1 ≥ 60 years (which vaccine is favoured)	IC1 ≥ 50 years (which vaccine is favoured)	IC2 18-49 years (which vaccine is favoured)
<b>13vPCV matched serotypes</b>			
1	Y (13v)	Y	Y (15v)
3	Y (13v)	N	Y (15v)
4	Y (13v)	Y	Y (20v)
5	Y (13v)	Y	Y
6A	Y (13v)	Y (15v)	Y
6B	Y (13v)	N	N
7F	Y (13v)	Y	Y
9V	Y	Y	Y
14	Y	Y	Y
18C	Y (13v)	Y (15v)	N
19A	Y (13v)	Y	Y
19F	Y (13v)	Y (15v)	Y (15v)
23F	Y (13v)	N	N
<b>Additional serotypes only included in 20vPCV</b>			
8	N	No comparative data	No comparative data
10A	Y (20v)		
11A	Y (20v)		
12F	Y (20v)		
15B	Y (20v)		
22F	Y (20v)		
33F	Y (20v)		

Source: Compiled during the evaluation from Section 2 of the submission

Abbreviations: 13vPCV, 13-valent pneumococcal conjugate vaccine; 20vPCV, 20-valent pneumococcal conjugate vaccine (13v) or (15v) Favours 13vPCV or 15vPCV as the upper bound of the 95% CI were <1

(20v) Favours 20vPCV as lower bound of the 95% CI were >1

Shaded cells indicate that non-inferiority was not met

### Comparative harms

6.34 Table 8 provides a summary of 20vPCV safety data from B7471007. Results were presented for each of the three cohorts separately.

Table 8: Summary of key adverse events reported in B7471007

	20vPCV n with event/N (%)	13vPCV n with event/N (%)	Difference in % Estimate (95% CI)
<b>Cohort 1 – age ≥ 60 years</b>	<b>N=1507</b>	<b>N=1490</b>	
Any local reactions <sup>a</sup>	864 (57.4)	830 (56.0)	1.4 (-2.1, 5.0)
Any systemic event <sup>b</sup>	831 (55.2)	822 (55.4)	-0.2 (-3.8, 3.4)
Adverse event <sup>c</sup>			
Upper respiratory tract infection	12 (0.8)	8 (0.5)	0.3 (-0.4, 0.9)
Arthralgia	6 (0.4)	1 (0.1)	0.3 (-0.0, 0.8)
Viral infection	5 (0.3)	0 (0)	<b>0.3 (0.1, 0.8)</b>
Fall	5 (0.3)	7 (0.5)	-0.1 (-0.7, 0.4)
<b>Cohort 2 – age 50-59 years</b>	<b>N=334</b>	<b>N=111</b>	
Any local reactions <sup>a</sup>	241 (72.8)	78 (70.3)	2.5 (-6.7, 12.7)
Any systemic event <sup>b</sup>	230 (69.5)	75 (67.6)	1.9 (-7.7, 12.3)
Adverse event <sup>c</sup>			
Upper respiratory tract infection	4 (1.2)	2 (2.7)	-1.5 (-6.5, 1.0)
Fall	4 (1.2)	0	1.2 (-2.2, 3.0)
<b>Cohort 3 – age 18-49 years</b>	<b>N=335</b>	<b>N=112</b>	
Any local reactions <sup>a</sup>	272 (81.2)	92 (82.1)	-0.9 (-8.5, 8.0)
Any systemic event <sup>b</sup>	266 (79.4)	93 (83.0)	-3.6 (-11.2, 5.3)
Adverse event <sup>c</sup>			
Influenza	7 (2.1)	1 (0.9)	1.2 (-2.9, 3.6)
Nasopharyngitis	6 (1.8)	2 (1.8)	0.0 (-4.6, 2.5)
Upper respiratory tract infection	7 (2.1)	1 (0.9)	1.2 (-2.9, 3.6)

Source: Compiled from data extracted from Section 2.5 of the submission and from B7471007 CSR

Abbreviations: 13vPCV, 13-valent pneumococcal conjugate vaccine; 20vPCV, 20-valent pneumococcal conjugate vaccine; CI, confidence interval; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk

Bold text indicates statistically significant differences.

a Any local reaction = any pain at injection site, any swelling > 2.0 cm, or any redness > 2.0 cm during Day 1 to Day 10 after vaccination

b Any systemic event = any fever ≥ 38.0°C, any fatigue, any headache, any joint pain, or any muscle pain during Day 1 to Day 7 after Vaccination 1.

c Selected (amongst most frequently reported) tier 2 adverse events reported during Day 1 to Day 10 after vaccination

d Related adverse events considered by investigator to be related to study vaccine at 1 month follow up

- 6.35 Across the 3 cohorts, the proportions of participants reporting any local reactions (redness, swelling, pain at injection site) or systemic events (fever, fatigue, headache, muscle pain, joint pain) were similar in both 20vPCV and 13vPCV groups.
- 6.36 The most frequent local reaction reported was pain at injection site (Cohort 1: 55.4%, Cohort 2: 72.5%, Cohort 3: 81.2%) which was mostly mild or moderate in severity. The most frequent systemic event reported was muscle pain (Cohort 1: 39.1%, Cohort 2: 49.8%, Cohort 3: 66.6%) which was mostly mild or moderate in severity.
- 6.37 With the exception of increased viral infections observed in participants in Cohort 1 (0.3% vs. 0%; RD 0.3% [95%CI, 0.1, 0.8]) and increased influenza and upper respiratory infection in Cohort 3 there were no notable differences in adverse events reported between 20vPCV and 13vPCV.
- 6.38 Safety outcomes in the supplementary trials (B7471008 and B7471006 where either 13vPCV or 23vPPV served as a safety control) were descriptive. The proportions of participants who reported any local reactions or systemic events were similar across 20vPCV and safety control groups. Most local reactions and systemic events were mild or moderate in severity.

## **Benefits/harms**

6.39 Given the non-inferiority claims for the shared serotypes, and the superiority claims for the additional serotypes were based on immunogenicity data, a benefits/harms table has not been presented.

## **Clinical claim**

6.40 For the existing NIP populations the efficacy claims were:

- 20vPCV has equivalent efficacy against IPD and PP to 13vPCV for the shared serotypes and superior efficacy against IPD and PP for the additional 7 serotypes.
- 20vPCV has equivalent efficacy against IPD and PP to 15vPCV for the shared serotypes and superior efficacy against IPD and PP for the additional 5 serotypes.

6.41 The efficacy claims made in the submission were based on a non-inferiority trial comparing immunogenicity between 20vPCV and 13vPCV for the '13 matched' serotypes and 23vPPV for the 7 additional serotypes (the B7471007 clinical trial).

6.42 The ESC noted that while correlation of immunogenicity with clinical protection has not been established for adults, the PBAC has previously considered the use of immunogenic response as a surrogate for disease prevention (Vaxneuvance PSD, November 2021 PBAC meeting) and this approach has been used previously for 13vPCV in Australia. The ESC also noted that ATAGI considered the bridge to efficacy reasonable, although noted there may be uncertainty as to whether the relationship to clinical outcomes will necessarily hold for the 7 unmatched serotypes (p30, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022). The WHO has also cautioned on using immunogenicity to predict efficacy stating that the interpretation of the immune responses to added or new subtypes in a vaccine is not straightforward as serotype specific correlates of protection may vary<sup>1</sup>.

6.43 The key potential issues regarding the efficacy claims were:

- In study B7471007 the OPA GMRs for 11 of the 13 matched serotypes had the upper bound of the 95% CI < 1, thus favouring 13vPCV. ATAGI considered the observed differences had a low likelihood of resulting in a loss in protection of clinical significance (p2, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022).
- In study B7471007 serotype 8 did not meet the non-inferiority criteria (noting this was against 23vPPV).
- In Study B7471007 6 of the 7 additional serotypes in 20vPCV were nominally superior to 23vPPV, however superiority for the 7 additional serotypes could not be formally tested as non-inferiority was not achieved for all 7 serotypes. ATAGI

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<sup>1</sup> World Health Organization (2016) Guidelines on clinical evaluation of vaccines: regulatory expectations Revision of WHO TRS 924, Annex 1, P49-50.  
[https://www.who.int/biologicals/expert\\_committee/Clinical\\_changes\\_IK\\_final.pdf](https://www.who.int/biologicals/expert_committee/Clinical_changes_IK_final.pdf)

noted the degree of difference in immunogenicity that translates into differences in protection against clinical disease is unknown (p4, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022).

6.44 For the indirect comparisons of 20vPCV and 15vPCV, the ESC noted the key potential issues were:

- In people aged  $\geq 50$  years, three serotypes (3, 6B, 23F) did not meet the non-inferiority criteria and 6 of 10 favoured 15vPCV.
- In people aged 18-49 years, three serotypes (6B, 18C, 23F) did not meet non-inferiority criteria and 6 of 10 favoured 15vPCV.
- There was no evidence presented to support the superiority claims for the additional 5 serotypes.

The PSCR considered that the differences in immunogenicity reflected in the indirect comparisons would not necessarily translate into a difference in vaccine effectiveness.

6.45 For the additional NIP population (Aboriginal and Torres Strait Islander adults aged 25-49 years) the efficacy claims was:

- 20vPCV has superior efficacy against IPD and PP to no vaccine.

6.46 The ESC considered the efficacy claim for superiority of 20vPCV against no vaccine for the expanded NIP population supported but considered the correlation between immunogenicity outcomes and efficacy in disease prevention uncertain.

6.47 For the existing NIP populations the submission claimed that 20vPCV has equivalent safety to 13vPCV and 15vPCV. For Aboriginal and Torres Strait Islander adults aged 25-49 the submission claimed that 20vPCV has inferior safety to no vaccine.

6.48 The ESC considered the submission's safety claim against 13vPCV appeared adequately supported, noting there was a lack of safety data on Indigenous populations and in those with current NIP-funded risk conditions. For Aboriginal and Torres Strait Islander people (with no risk factors) aged 25-49 years, the ESC considered the claim that 20vPCV has inferior safety to no vaccine was supported.

6.49 The ESC considered the submission's safety claim against 15vPCV not adequately supported because the submission did not conduct indirect comparisons on the safety outcomes between 20vPCV and 15vPCV. It was noted by the ESC that the PBAC has previously supported the claim of non-inferior safety of 15vPCV compared to 13vPCV but noted that ATAGI considered tolerability of 15vPCV may be considered inferior to 13vPCV (paragraph 7.8, Vaxneuvance, PSD, November 2021 PBAC meeting).

6.50 The PBAC considered the submission's claim of non-inferior effectiveness for 20vPCV versus 13vPCV (and 15vPCV) for the shared serotypes is 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 is uncertain. Overall,

the PBAC considered a claim of non-inferior comparative effectiveness of 20vPCV compared with 13vPCV (and 15vPCV) to be appropriate.

- 6.51 The PBAC considered the efficacy claim for superiority of 20vPCV against no vaccine for the expanded NIP population was reasonable, however considered the correlation between immunogenicity outcomes and efficacy in disease prevention uncertain.
- 6.52 The PBAC considered that the claim of non-inferior comparative safety versus 13vPCV was supported by the data. The PBAC considered the submission's safety claim of non-inferior safety against 15vPCV reasonable, noting the submission did not provide a comparison on the safety outcomes between 20vPCV and 15vPCV.
- 6.53 The PBAC considered that the claim of inferior comparative safety versus no vaccine was reasonable.

### ***Economic analysis***

- 6.54 The type of economic evaluation presented was a cost-utility analysis and a cost-effectiveness analysis. The ESC noted 15vPCV was listed on a cost minimisation basis versus 13vPCV and considered a similar approach would be appropriate for the current NIP populations if the available evidence does not adequately support superiority of 20vPCV over 13vPCV or 15vPCV. The pre-PBAC response acknowledged the potential for the PBAC to make a recommendation for listing 20vPCV on the basis of a cost minimisation approach to 13vPCV or 15vPCV, whilst claiming clinical and economic benefits had been demonstrated.
- 6.55 The key components of the economic evaluation comparing 20vPCV with 15vPCV and 13vPCV is presented in Table 9. Separate Markov models were developed for each of the four target populations. The ESC considered the model structure appropriate, although noted not all sensitivity analyses requested by ATAGI were able to be implemented (see paragraph 6.75).
- 6.56 The submission stated that the economic model was identical to the model presented in the 13vPCV submission and reviewed by the ATAGI and the PBAC for individuals aged  $\geq 15$  years with at-risk conditions (13vPCV PSD, November 2018 PBAC meeting).
- 6.57 The submission stated there was no epidemiological data available that reflected vaccination with 13vPCV and 15vPCV and the most recent data available was from 2019 (or earlier) when only 23vPPV was available. Therefore, the economic model used 23vPPV as a common comparator between 20vPCV and 13vPCV or 15vPCV for the existing NIP populations.

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

Component	Summary
Treatments	20vPCV vs 15vPCV vs 13vPCV via 23vPPV as the common comparator
Time horizon	i) Non-Indigenous adults aged ≥ 70 years: lifetime (100 years) ii) At-risk adults aged 18-69 years: until age 70 years iii) Indigenous adults aged ≥ 50 years: lifetime (100 years) iv) Indigenous adults aged 25-49 years: until age 50 years
Outcomes	Years of life lived Quality-adjusted life years (QALYs)
Methods used to generate results	Decision analysis Markov state-transition modelling Cohort expected value analysis
Health states	1. Alive, no (long-term) meningitis complications 2. Alive, (long-term) meningitis complications 3. Dead
Cycle length	1 year
Transition probabilities	Incidence of IPD: 2019 IPD incidence data (National Notifiable Diseases Surveillance System) and population data published by the ABS (2019). Case fatality rates for incident bacteraemia, meningitis, and PNE hospitalisation: Dirmesropian et al. (2018). Incidence of hospitalisations and GP visits for pneumococcal pneumonia: hospitalisation data for years 2018-2019 published by the AIHW.
Extrapolation method	The extrapolation of transition probabilities and other input variables across individual ages or age-groups, including how the marginal benefits of the PCVs over 23vPPV and placebo were estimated, were based on VE and waning effectiveness. To estimate CFRs for PNE hospitalisations (hospitalisations caused by pneumococcal pneumonia) for individuals aged < 45 years in the models for at-risk adults aged 18-69 years and Indigenous adults aged 25-49 years, extrapolation using exponential functions was applied to plots of age versus CFR values reported by Dirmesropian et al. (2018). This was likely reasonable; however, the submission did not apply other extrapolation functions in sensitivity analysis and did not provide any validation or model traces to justify their approach.
Health related quality of life	Alive (no meningitis complications) was associated with age-specific utilities and based on a study using Assessment of Quality of Life, 4 Dimensions (AqoL-4D) data from the 2007 National Survey of Mental Health and Wellbeing conducted by the ABS (Hawthorne, 2013). Alive (with meningitis complications) was assigned an additional disutility of 0.261, which was the value used in the 2018 13vPCV submission considered by the PBAC (Prevenar 13, PSD, November 2018 PBAC meeting).

Source: Adapted from Table 3.1.2, p455 of the submission and compiled during the evaluation from Section 3.4 of the submission  
Abbreviations: 13vPCV, 13 valent pneumococcal conjugate vaccine; 15vPCV, 15 valent pneumococcal conjugate vaccine; 20vPCV, 20 valent pneumococcal conjugate vaccine; 23vPPV, 23 valent pneumococcal polysaccharide vaccine; ABS, Australian Bureau of Statistics; ATAGI, Australian Technical Advisory Group on Immunisation; CFR, case fatality rate; GP, general practitioner; IPD, invasive pneumococcal disease; PBAC, Pharmaceutical Benefit Advisory Committee; PCV, pneumococcal conjugate vaccine; PNE, pneumococcal pneumonia; VE, vaccine effectiveness

6.58 The assumptions made for vaccine coverage in the economic model are detailed in Table 10 (also see Table 3). The ESC and PBAC noted the vaccine coverage varied widely across the different populations and were based on relatively small numbers of patients.

**Table 10: Serotype coverage of the four pneumococcal vaccines assumed in the economic model**

Vaccine	Non-Indigenous aged ≥ 70 years	Indigenous aged ≥ 50 years	At-risk aged 18-69 years	Indigenous aged 25-49 years
23vPPV	59%	70%	76%	80%
20vPCV	53%	64%	66%	72%
15vPCV	44%	45%	51%	38%
13vPCV	32%	34%	38%	32%

Source: Table 3.4.5 of the submission, based on NNDSS (2019). Compiled during ESC evaluation.

6.59 The assumptions made for vaccine effectiveness in the economic model are detailed in Table 11. It was unclear why the vaccine effectiveness (VE) estimates for at-risk adults aged 18-69 were different to that used for the other populations, but the differences were small, and this was in line with ATAGI advice (p62, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022).

**Table 11: Vaccine effectiveness of the four pneumococcal vaccines assumed in the economic model**

Vaccine	Non-Indigenous aged ≥ 70 years	Indigenous aged ≥ 50 years	At-risk aged 18-69 years	Indigenous aged 25-49 years
Invasive pneumococcal disease				
23vPPV	61.1%	61.1%	61.1%	61.1%
20vPCV, 15vPCV and 13vPCV	74.5%	74.5%	74.4%	74.5%
Pneumococcal pneumonia hospitalisations				
23vPPV	5.6%	5.6%	5.6%	5.6%
20vPCV, 15vPCV and 13vPCV	45.6%	45.6%	45.2%	45.6%
Pneumococcal pneumonia GP visits				
23vPPV	5.6%	5.6%	5.6%	5.6%
20vPCV, 15vPCV and 13vPCV	21.8%	21.8%	21.6%	21.8%

Source: Table 3.4.6 of the submission, based on the CAPiTA trial (20vPCV, 15vPCV and 13vPCV) and ATAGI advice (23PPV), compiled during ESC evaluation.

Abbreviations: GP, general practitioner

6.60 The assumptions made for vaccine waning in the economic model are detailed in Table 12. The ESC noted it was assumed that the waning of efficacy following 23vPPV was much faster than for the PCVs.

**Table 12: Waning efficacy of the four pneumococcal vaccines assumed in the economic model**

Vaccine	All populations
23vPPV	
Years 1-2	0%
Years 3-5	Linear decline to 0% vaccine effectiveness at Year 5
20vPCV, 15vPCV and 13vPCV	
Years 1-5	0%
Years 6-10	5%
Years 11-15	10%
Years 16+	15%

Source: Table 3.4.7 of the submission, based on assumptions made for 13vPCV in the 2018 submission. Compiled during ESC evaluation.

6.61 The baseline data on the burden of pneumococcal disease was based on IPD data drawn from 2019 when 13vPCV and 15vPCV were not yet available, therefore the baseline data reflected background vaccination with 23vPPV only. As such, the

modelled economic evaluation was based on an indirect approach. The indirect approach used by the submission does not reflect the comparative evidence presented in clinical effectiveness section of the submission which was based on direct comparisons of immunogenicity evidence for the new serotypes between 20vPCV and 13vPCV or 15vPCV. The PSCR stated that it was not possible for the economic model to be based on comparisons of 20vPCV and 13vPCV or 15vPCV, as there was no epidemiological data available reflecting vaccination with 13vPCV and 15vPCV. The PBAC noted the incidence of IPD in the proposed expanded population (34 per year per 100,000 persons), although less than in the Indigenous population aged  $\geq 50$  years (72 per year per 100,000 persons), was higher than in the non-Indigenous population aged  $\geq 70$  years (22 per year per 100,000 persons).

6.62 While it may be appropriate to use the same overall model structure as used in the 13vPCV submission (Prevenar 13, PSD, November 2018 PBAC meeting) to reflect the progression of each of the proposed NIP populations, the following key issues identified were:

- The common comparator via 23vPPV may obscure the accurate isolation of the additional serotypes in 20vPCV. The effect size associated with 23vPPV is relatively large and may reduce the ability to accurately differentiate smaller incremental effects for the additional serotypes. Ideally, the structure of the economic model would allow the vaccine effectiveness of the additional serotypes in 20vPCV to be isolated and varied in sensitivity analysis in order to assess their uncertainty and effect. The PSCR disagreed with the evaluation, stating that the estimation of the incremental effects of 20vPCV, 13vPCV and 15vPCV is not dependent on the effect size of 23vPPV vaccine effectiveness.
- The economic model assumed that the populations considered have a background vaccination with 23vPPV, which may not be fully representative of the proposed NIP populations. It is possible that many of those in the proposed populations are vaccine naïve.
- Serotype replacement was not considered in the economic evaluation. The ESC has previously considered that the exclusion of serotype replacement in the economic model could bias the results in favour of 13vPCV (compared to 23vPPV) given the uncertainty in the potential changes in patterns and distribution of pneumococci serotypes and expected waning of antibody levels over time (paragraph 6.24, Prevenar 13, PSD, November 2018 PBAC meeting). This issue may be relevant to the economic evaluation of 20vPCV. While the use of 20vPCV in the proposed populations is not likely to drive serotype replacement over the short-term (p6, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022), the ESC considered it remained an uncertainty in the economic model, especially given the relatively long time horizons. In order to address uncertainty related to potential serotype replacement additional sensitivity analyses were provided in

the PSCR that reduced the overall vaccine effectiveness by up to 15%; these analyses are shown in Table 20.

- Time horizon: ATAGI stated that there are difficulties projecting over the long-term because of the uncertainty of impacts beyond a decade of implementation of the program and it is highly uncertain of serotype distribution beyond 5-10 years. ATAGI considered making extrapolations beyond 5-10 years especially tenuous (p70, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022). The ESC agreed with ATAGI that long-term projections are likely to be uncertain due to potential changes in the pattern and distribution of serotypes and the uncertain rate of decline in vaccine efficacy over time, and noted the economic model was sensitive to changes in time horizon, as documented in Table 18 and Table 19.
- Incidence of IPD: The submission applied incidence data from the National Notifiable Diseases Surveillance System (NNDSS 2019). These data do not include the Australian Capital Territory (ACT). As the incidence of IPD fluctuates over time data over a longer time period (e.g. 2016-2019) would have provided more reliable estimates of IPD incidence. The incidence is divided by the total population in Australia (including ACT) and is therefore likely to be slightly underestimated. The PSCR argued that there was likely very few cases of disease from the ACT and therefore the impact of the missing data would likely be small.
- Incidence of general practitioner (GP) visits for pneumococcal pneumonia: The submission assumed that the incidence of GP visits for PP was equal to the incidence of hospitalisation for subjects of the same age from 2018-2019 data published by the Australian Institute of Health and Welfare (AIHW). This differs from the ATAGI advice that recommended estimates of incidence of pneumonia in primary care be sourced from the BEACH study (p15, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022). Previous submissions for pneumococcal vaccines have used the BEACH study.
- Extrapolation of case fatality rates (CFRs) for pneumococcal pneumonia hospitalisations: the exponential function used was not tested in the sensitivity analyses. When the CFRs were varied in the sensitivity analysis, the ICERs were sensitive to these values.
- Vaccine efficacy: The submission assumed that the VE of both 20vPCV and 15vPCV was equivalent to the VE of 13vPCV. ATAGI agreed that it was reasonable to assume VE of 20vPCV and 15vPCV was equivalent to 13vPCV for shared serotypes but noted there may be some uncertainty as to whether the same relationship between immunogenicity and efficacy will necessarily hold for the 7 additional serotypes (p42, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022). The model did not provide an option to modify the effectiveness for the additional serotypes. The ESC agreed with ATAGI that the relationship between immunogenicity and efficacy for the additional serotypes was uncertain and considered it would have been appropriate for the unmatched serotypes to be

isolated and varied separately in the model. The ESC noted that additional sensitivity analyses were provided in the PSCR that reduced the overall vaccine effectiveness by up to 15% (Table 20) and considered these may be informative.

- 6.63 For the population of at-risk adults aged 18-69 years the economic model was incorrectly populated with data from the Indigenous population (incorrect cells were selected). When these values were corrected the ICER remained dominant for the comparison with 13vPCV, and from \$0 to < \$5,000 per QALY gained to dominant for the comparison with 15vPCV.
- 6.64 The cost of 23vPPV administration in years 2 and 5 of the model were not discounted when included in the model for Indigenous adults aged > 50 years. Therefore, the cost of 23vPPV administration may be slightly overestimated.
- 6.65 Table 13 and Table 14 show the extent to which the costs of vaccination were offset by treating clinical disease. The ESC noted the key offsets were reduced costs associated with treating bacteraemia events and PNE (pneumococcal pneumonia) hospitalisations.

**Table 13: Health care resource items: disaggregated summary of cost impacts (undiscounted) for non-Indigenous adults aged ≥ 70 years, Indigenous adults aged ≥ 50 years, and at-risk adults aged 18-69 years, per 1,000 individuals**

Resource item	20vPCV	13vPCV	Incremental cost	% of total incremental cost	15vPCV	Incremental cost	% of total incremental cost
<b>Non-Indigenous adults &gt; 70 years followed until age of 100 years</b>							
Vaccination	\$█	\$█	\$█	17%	\$█	\$█	51%
Bacteraemia events	\$26,059	\$30,235	-\$4,176	-14.2%	\$27,930	-\$1,872	-19%
Meningitis wo cx events	\$241	\$279	-\$38	-0.13%	\$258	-\$17	-0.17%
Meningitis w cx events	\$214	\$251	-\$37	-0.13%	\$231	-\$17	-0.17%
PNE hospitalisation events	\$376,510	\$496,365	-\$29,855	-102%	\$389,307	-\$12,797	-130%
PNE GP visits	\$8,645	\$8,940	-\$295	-1%	\$8,772	\$126	1%
Total	\$█	\$█	-\$█	100%	\$█	-\$█	100%
<b>Indigenous Australians &gt; 50 years followed until age of 100 years<sup>a</sup></b>							
Vaccination	\$█	\$█	\$█	7.9%	\$█	\$█	13%
Bacteraemia events	\$134,216	\$158,447	-\$24,231	-38%	\$149,565	-\$15,348	-40%
Meningitis wo cx events	\$2,538	\$2,988	-\$450	-1%	\$2,823	-\$285	-1%
Meningitis w cx events	\$2,665	\$3,184	-\$519	-1%	\$3,184	-\$328	-1%
PNE hospitalisation events	\$504,805	\$547,280	-\$42,475	-67%	\$531,713	-\$26,907	-71%
PNE GP visits	\$8,858	\$9,167	-309	-0.5%	\$9,054	-\$196	-1%
Total	\$█	\$█	-\$█	100%	\$█	-\$█	-100%
<b>At-risk Australians aged 18-69 years followed until age of 70 years</b>							
Vaccination	\$█	\$█	\$█	29%	\$█	\$█	29%
Bacteraemia events	\$82,404	\$93,955	-\$11,552	-65%	\$88,592	-\$6,188	-87%
Meningitis wo cx events	\$1,869	\$2,131	-\$262	-1%	\$2,009	-\$140	-2%
Meningitis with cx events	\$2,597	\$2,961	-\$364	-2%	\$2,792	-\$195	-3%
PNE hospitalisation events	\$133,128	\$143,984	-\$10,856	-61%	\$138,944	-\$5,861	-82%
PNE GP visits	\$2,351	\$2,430	-\$79	-0.4%	\$2,293	-\$42	-1%
Total	\$█	\$█	-\$█	100%	\$█	-\$█	100%

Source: Generated from the Excel sheets 'Prevenar 70', 'Prevenar AtRisk 18-69' and 'Prevenar Indig 50' during the evaluation.

Abbreviations: 13vPCV, 13 valent pneumococcal conjugate vaccine; 15vPCV, 15 valent pneumococcal conjugate vaccine; 20vPCV, 20 valent pneumococcal conjugate vaccine; cx, complications; GP, general practitioner; PNE, pneumococcal pneumonia; wo, without.

a The economic model uses discounted vaccination costs, so these results should be interpreted carefully.

**Table 14: Health care resource items: disaggregated summary of cost impacts (undiscounted) for Indigenous Australians aged 25-49 years followed until age of 50 years, per 1,000 individuals**

Resource item	20vPCV	No vaccination	Incremental cost	% of total incremental cost
Vaccination	\$	\$0	\$	395%
Bacteraemia events	\$42,502	\$68,583	-\$26,081	-219%
Meningitis without cx events	\$0	\$0	\$0	0%
Meningitis with cx events	\$0	\$0	\$0	0%
PNE hospitalisation events	\$32,022	\$40,972	-\$8,951	-75%
PNE GP visits	\$586	\$655	-\$68	-1%
Total	\$	\$110,210	\$	100%

Source: Generated from the Excel sheet 'Prevenar Indig 25-49' during the evaluation.

Abbreviations: 20vPCV, 20-valent pneumococcal conjugate vaccine; cx, complications; GP, general practitioner; PNE, Pneumococcal pneumonia.

6.66 The PBAC noted the key drivers of the economic model shown in Table 15.

**Table 15: Key drivers of the model**

Description	Method/Value	Impact on base case ICERs
Case fatality rate for pneumococcal hospitalisations	Base case analysis sourced age-adjusted rates from Dirmesropian (2018) that ranged from 0.71% to 16.75%. Sensitivity analysis in the submission changed these to 3.8% and 20.5% as recommended by ATAGI for CAP CFRs (p68, ATAGI advice February 2016).	Remains dominant with CFRs tested in sensitivity analyses for the existing populations.  Medium impact for the expanded population.
Comparative effectiveness of 20vPCV	The CEA results rely on the relationship between serotype coverage and the vaccine effectiveness for those serotypes.	Likely high. As a result of the information provided, model structure, and presentation of results, there was limited ability to feasibly conduct additional sensitivity analyses to robustly test the impact of the efficacy of the additional serotypes.
Waning efficacy for 13vPCV, 15vPCV and 20vPCV	Base case used an annual reduction in vaccine efficacy: 0% for years 0-5, 5% for years 6-10, 10% for years 11-15, and 15% for years 16+. Sensitivity analysis conducted: <ul style="list-style-type: none"> <li>• 0% for years 0-5</li> <li>• 50% for years 6-10</li> <li>• 100% for years 10+</li> </ul>	Remains dominant with waning testing in sensitivity analysis for at-risk adults aged 18-69 years.  High impact for expanded population.
Serotype coverage for 20vPCV – Indigenous adults (aged 25-49 years)	Base case = 72%. Sensitivity analysis conducted during the evaluation reduced this value by 15% to 61%.	Medium impact for expanded population.
Time horizon	The time horizons varied depending on the population considered. As such, the periods of extrapolations varied substantially across populations. <ul style="list-style-type: none"> <li>• Non-Indigenous population aged ≥70 years with follow-up until age 100 years</li> <li>• At-risk population with follow-up until age 70 years</li> <li>• Indigenous population aged ≥50 years with follow-up until age 100 years</li> <li>• Indigenous population aged 25-49 years with follow-up until age 50 years</li> </ul> Sensitivity analysis conducted during the evaluation reduced the follow up time to 5 years.	Remains dominant with a 5 year time horizon for the comparisons with 13vPCV and 15vPCV for non-Indigenous Australians ≥ 70 years and Indigenous Australians aged ≥ 50 years.  High impact for at-risk Australians aged 18-69 years and for Indigenous Australians aged 25-49 years.

Source: Tables 3.9.1, 3.9.2 and 3.9.4, p498-9 of the submission and compiled during the evaluation from the Excel sheets 'Prevenar 70', 'Prevenar AtRisk 18-69', 'Prevenar Indig 25-49' and 'Prevenar Indig 50'.

Abbreviations: 13vPCV, 13-valent pneumococcal conjugate vaccine; 15vPCV 15-valent pneumococcal conjugate vaccine; 20vPCV, 20-valent pneumococcal conjugate vaccine; 23vPPV 23-valent pneumococcal polysaccharide vaccine; CAP, community acquired pneumonia; CEA cost-effectiveness analysis; CFR, case fatality rates

6.67 The time period for extrapolation for each population is different, and this could have an impact on the interpretation of the results. In a policy landscape where changes can have a large impact in a short time period, a shorter time horizon would be more appropriate. The ESC noted that sensitivity analyses conducted during the evaluation showed that the ICER was highly sensitive to the time horizon (results presented in Table 18 and Table 19).

- 6.68 ATAGI considered the assumption of constant serotype distribution beyond 5-10 years is highly uncertain. ATAGI noted if changes were made to the paediatric PCV schedule in the near future, for example the move to extended valency PCVs, this would highly likely impact serotype distributions (e.g., ST3 has been increasing proportionally as a cause of pneumococcal disease in Australia in recent years in the absence of an effective vaccine against this serotype), making extrapolations beyond 5-10 years especially tenuous. ATAGI acknowledged that a 20-year waning profile has been used in previous models, however considered it may be appropriate that either apply (i) a short-term time horizon assuming no change in coverage or (ii) a medium-term time horizon that predicts some degree of coverage reduction (or both), at least as a sensitivity analysis. (p70, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022).
- 6.69 Table 16 presents the results from the economic evaluation for the existing NIP populations.
- 6.70 For non-Indigenous adults aged  $\geq 70$  years the model assumed that the additional 7 (5) serotypes would increase vaccine coverage by 21% (9%) (Table 10) and this results in:
- A reduction in bacteraemia events of 0.30 (0.13) per 1,000 people vaccinated;
  - A reduction in meningitis events of 0.01 (0.00) per 1,000 people vaccinated;
  - A reduction in PNE GP visits or hospital admissions of 6.53 (2.80) per 1,000 people vaccinated; and
  - The cost saving associated with avoiding the above events is \$| (\$|). This exceeds the additional cost for the 20vPCV vaccine of \$| per 1,000 people (Table 13).
- 6.71 For Indigenous adults aged  $\geq 50$  years the model assumed that the additional 7 (5) serotypes would increase vaccine coverage by 30% (19%) (Table 10) and this results in:
- A reduction in bacteraemia events of 1.80 (1.14) per 1,000 people vaccinated;
  - A reduction in meningitis events of 0.11 (0.07) per 1,000 people vaccinated;
  - A reduction in PNE GP visits or hospital admissions of 8.50 (5.38) per 1,000 people vaccinated; and
  - The cost saving associated with avoiding the above events is \$| (\$|). This exceeds the additional cost for the 20vPCV vaccine of \$| (\$|) per 1,000 people (Table 13).
- 6.72 For at-risk adults aged 18-69 years the model assumed that the additional 7 (5) serotypes would increase vaccine coverage by 28% (15%) (Table 10) and this results in:
- A reduction in bacteraemia events of 0.86 (0.46) per 1,000 people vaccinated;
  - A reduction in meningitis events of 0.07 (0.04) per 1,000 people vaccinated;

- A reduction in PNE GP visits or hospital admissions of 2.17 (1.16) per 1,000 people vaccinated; and
- The cost saving associated with avoiding the above events is \$| (\$|). This exceeds the additional cost for the 20vPCV vaccine of \$| per 1,000 people (Table 13).

**Table 16: Results of the economic evaluation for non-Indigenous adults aged ≥ 70 years, Indigenous adults aged ≥ 50 years, and at-risk adults aged 18-69 years, per 1,000 individuals**

Component	20vPCV	13vPCV	Increment (20vPCV vs 13vPCV)	15vPCV	Increment (20vPCV vs 15vPCV) <sup>a</sup>
<b>Non-Indigenous adults aged ≥ 70 years</b>					
Costs	\$	\$	-\$	\$	-\$
Years of life lived	8,165	8,162	2.45	8,164	1.05
Incremental cost/extra year of life lived			Dominant		Dominant
QALY	6,534	6,532	1.91	6,533	0.82
Incremental cost/extra QALY gained			Dominant		Dominant
<b>Indigenous adults aged ≥ 50 years</b>					
Costs	\$	\$	-\$	\$	-\$
Years of life lived	12,391	12,387	3.89	12,389	2.46
Incremental cost/extra year of life lived			Dominant		Dominant
QALY	10,636	10,633	3.18	10,634	2.02
Incremental cost/extra QALY gained			Dominant		Dominant
<b>At-risk adults aged 18-69 years<sup>b</sup></b>					
Costs	\$	\$	-\$	\$	-\$
Years of life lived	14,122	14,122	0.60	14,122	0.32
Incremental cost/extra year of life lived			Dominant		Dominant
QALY	12,663	12,663	0.56	12,663	0.30
Incremental cost/extra QALY gained			Dominant		Dominant

Source: Table 3.8.1 p492, Table 3.8.2 p492, Table 3.8.5 p494, and Table 3.8.6 p495 of the submission.

Abbreviations: 13vPCV, 13 valent pneumococcal conjugate vaccine; 15vPCV, 15 valent pneumococcal conjugate vaccine; 20vPCV, 20 valent pneumococcal conjugate vaccine; 23vPPV, 23 valent pneumococcal polysaccharide vaccine; QALY, Quality-adjusted life-year

a Dominant ICER indicates that 20vPCV dominates comparator through being more effective and less costly.

b Compiled during the evaluation based on information sourced from the Excel sheet 'Prevenar At Risk 18-69'

6.73 Table 17 presents the results from the economic evaluation for the expanded population. For Indigenous adults aged 25-49 years the model assumed that the 20 serotypes would cover 72% of pneumococcal cases (Table 10) and this results in:

- A reduction in bacteraemia events of 1.93 per 1,000 people vaccinated;
- A reduction in meningitis events of 0.00 per 1,000 people vaccinated;
- A reduction in PNE GP visits or hospital admissions of 1.82 per 1,000 people vaccinated; and
- The cost saving associated with avoiding the above events is \$|. The additional cost for the 20vPCV vaccine is \$| per 1,000 people (Table 13).

**Table 17: Results of the economic evaluation for Indigenous adults aged 25-49 years, per 1,000 individuals**

Component	20vPCV	Placebo	Increment (20vPCV vs Placebo)
Costs	\$	\$74,120	\$
Years of life lived	10,205	10,204	0.60

Component	20vPCV	Placebo	Increment (20vPCV vs Placebo)
Incremental cost/extra year of life lived			\$ <sup>1</sup>
QALY	9,191	9,190	0.53
Incremental cost/extra QALY gained			\$ <sup>1</sup>

Source: Table 3.8.4, p493 and Table 3.8.8, p495 of the submission

Abbreviations: 20PCV, 20-valent pneumococcal conjugate vaccine; QALY, Quality-adjusted life-year; YoLS, Years of life saved

The redacted values correspond to the following ranges:

<sup>1</sup> \$25,000 to < \$35,000

<sup>2</sup> \$35,000 to < \$45,000

6.74 The results of key univariate sensitivity analyses are summarised in Table 18 and Table 19. The ICER for the sensitivity analyses remained ‘dominant’ (20vPCV more effective and less costly) for the comparison to 13vPCV and 15vPCV for the existing NIP populations, with the exception of the scenario of a 5 year time horizon for the at-risk adults aged 18-69 years population (\$35,000 to < \$45,000/QALY for the comparison with 13vPCV and \$155,000 to < \$255,000/QALY for the comparison with 15vPCV). The PBAC noted that the ICER for the expanded population was sensitive to the model time horizon and assumptions regarding efficacy waning. The ICER increased from \$35,000 to < \$45,000 to \$355,000 to < \$455,000/QALY if the time horizon was reduced to 5 years and to \$75,000 to < \$95,000/QALY if the vaccine was assumed to have no effect from year 10.

6.75 The ESC noted that ATAGI suggested a number of sensitivity analyses that were not addressed in the submission, these included:

- Removal of 23vPPV doses from the schedule: ‘ATAGI recommend thorough exploration of the proposal to remove the doses of 23vPPV from the schedule’ (p66, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022);
- Variation to the proportion of CAP due to pneumococcal: ‘As a sensitivity analysis, apply the incidence rate ratio seen for IPD for Aboriginal and Torres Strait Islander people and non-Indigenous people to pneumococcal CAP rates for each age group to calculate rates for Indigenous people.’ (p68, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022);
- Variation to the proportion of GP CAP due to pneumococcal: ‘Note the percentage of GP CAP caused by pneumococcus may be less than that in hospitalised cases (20.6%). The lower (13.8%) calculated CI should be used as a sensitivity analyses’ (p68, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022);
- Variation to vaccine efficacy for unmatched serotypes: ‘Overall CAPITA estimates should be used as the base case, with the lower and upper CIs of the estimates for VT IPD and VT non-invasive CAP from CAPITA for a sensitivity analysis. The same VE estimates should be applied to all non-PCV13 serotypes contained in PCV15 and PCV20. Suggest exploring reduced efficacy for ST8, e.g. 50%\*75% for IPD and 50%\*45% for CAP’ (p69, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022);

- Reduced vaccine efficacy for serotype 3: ‘For ST3: For all PCV a VE of 26% (based on Pilshvili 2018) should be used as the base case for IPD, with a range from 0% to 75% (from CAPiTA). This was recommended in the V114 (15vPCV) advice, with a base case of  $26\% \times 0.45/0.75$  (15.6%) for CAP, with a range from 0% to 45% for sensitivity analyses.’ (p69, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022); and
- Variation to vaccine uptake: ‘Among non-Indigenous adults  $\geq 65$  years, the assumed uptake of 53% is applied to the forecasted number of persons turning 65 each year. This uptake rate is obtained from the advice provided by ATAGI in June 2018. No sensitivity analysis was proposed in the Request, but the October 2014 ATAGI advice, where a number of these estimates were first provided, suggests 35% to 75%.’ (p71-72, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022).

**Table 18: Sensitivity analyses for non-Indigenous adults aged ≥ 70 years, Indigenous Australians aged ≥ 50 years, and at-risk adults aged 18-69**

Variation to input variable	20vPCV vs 13vPCV			20vPCV vs 15vPCV		
	Incremental		ICER	Incremental		ICER
	Cost (\$)	QALY	\$/QALY <sup>a</sup>	Cost (\$)	QALY	\$/QALY <sup>a</sup>
<b>Base case for non-Indigenous adults aged ≥ 70 years<sup>b</sup></b>	-	1.91	Dominant	-	0.82	Dominant
CFR for pneumococcal hospitalisations: 3.8% <sup>c</sup>	-	0.75	Dominant	-	0.32	Dominant
CFR for pneumococcal hospitalisations: 20.5% <sup>c</sup>	-	3.24	Dominant	-	1.39	Dominant
Discount rate: 0% <sup>d</sup>	-	3.18	Dominant	-	1.36	Dominant
Discount rate: 3.5% <sup>d</sup>	-	2.20	Dominant	-	0.94	Dominant
Time horizon: 5 years <sup>d,e</sup>	-	0.35	Dominant	-	0.15	Dominant
<b>Base case for Indigenous Australians aged ≥ 50 years<sup>f</sup></b>	-	3.18	Dominant	-	2.02	Dominant
CFR for pneumococcal hospitalisations: 3.8% <sup>c</sup>	-	2.02	Dominant	-	1.28	Dominant
CFR for pneumococcal hospitalisations: 20.5% <sup>c</sup>	-	6.43	Dominant	-	4.07	Dominant
Discount rate: 0% <sup>d</sup>	-	7.76	Dominant	-	4.91	Dominant
Discount rate: 3.5% <sup>d</sup>	-	4.06	Dominant	-	2.57	Dominant
Time horizon: 5 years <sup>d,e</sup>	-	0.18	Dominant	-	0.11	Dominant
<b>Base case for at-risk adults aged 18-69<sup>g,h</sup></b>	-	0.56	Dominant	-	0.30	Dominant
CFR for pneumococcal hospitalisations: 3.8% <sup>c,h</sup>	-	0.55	Dominant	-	0.29	Dominant
CFR for pneumococcal hospitalisations: 20.5% <sup>c,h</sup>	-	1.90	Dominant	-	1.02	Dominant
Discount rate: 0% <sup>d</sup>	-	1.46	Dominant	-	0.78	Dominant
Discount rate: 3.5% <sup>d</sup>	-	0.72	Dominant	-	0.39	Dominant
Waning efficacy for PCV: 0% for years 0-5, 50% for years 6-10, 100% for years >10 <sup>d</sup>	-	0.36	Dominant	-	0.19	Dominant
Relative vaccine efficacy: 100% <sup>d,i</sup>	-	0.44	Dominant	-	0.23	Dominant
Relative vaccine efficacy: 140% <sup>d,i</sup>	-	0.65	Dominant	-	0.35	Dominant
Time horizon: 5 years <sup>d,e</sup>	-	0.04	\$ <sup>1</sup>	-	0.02	\$ <sup>2</sup>

Source: Tables 3.9.1 and 3.9.2, p498 of the submission and compiled during the evaluation from the Excel sheets 'Prevenar 70', 'Prevenar AtRisk 18-69' and 'Prevenar Indig 50' during the evaluation. Incremental costs and QALYs calculated during ESC evaluation.

Abbreviations: 13vPCV, 13-valent pneumococcal conjugate vaccine; 15vPCV, 15-valent pneumococcal conjugate vaccine; 20vPCV, 20-valent pneumococcal conjugate vaccine; CFR, case fatality rate; NIP, National Immunisation Programme; PCV, pneumococcal conjugate vaccine; VE, vaccine effectiveness; QALY=Quality-adjusted life-year

a Dominant ICER indicates that 20vPCV dominates comparator through being more effective and less costly.

b Base case used CRF varied by age (6.22% for ages 70-74, 9.09% for ages 75 to 84, and 16.35% for ages >85); discount rate 5%; lifetime horizon to 100 years.

c Variation to input as per ATAGI's recommendations (ATAGI advice, February 2016).

d Conducted during the evaluation.

e Variation to input as per ATAGI's recommendations (p70, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022).

f Base case used CRF varied by age (4.96% for ages 50-64, 6.64% for ages 65-74, 9.53% for ages 75-84, and 16.75% for ages >85); discount rate 5%; lifetime horizon to 100 years.

g Base case used CRF varied by age (1.15% for ages 15-24, 1.62% for ages 25-34, 2.28% for ages 35-44, 4.96% for ages 45-64, and 6.64% for ages 65-69); discount rate 5%; waning efficacy for PCV (0% for years 0-5, 5.35% for years 6-10, 10% for years 11-15, and 15% for years >16), relative vaccine efficacy of 120%, up to 52 year time horizon to 70 years.

h Corrected during the evaluation so that population distribution was taken from 'Pop' instead of 'IndigPop' in Excel book 'Prevenar ATRisk

18-69<sup>1</sup>.

<sup>1</sup> Variation to input as per ATAGI's recommendations (p66, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022).

The redacted values correspond to the following ranges:

<sup>1</sup> \$35,000 to < \$45,000

<sup>2</sup> \$155,000 to < \$255,000

**Table 19: Sensitivity analysis for Indigenous Australians aged 25-49 years for 20vPCV as compared to placebo.**

Variation to input variable	Incremental cost (\$)	Incremental QALY	\$/QALY
<b>Base case<sup>a</sup></b>		<b>0.53</b>	<b>1</b>
Incidence of IPD: - 20% <sup>b</sup>		0.46	2
Incidence of IPD: + 20% <sup>b</sup>		0.61	3
CFR for pneumococcal hospitalisations: 3.8% <sup>c</sup>		0.62	3
CFR for pneumococcal hospitalisations: 20.5% <sup>c</sup>		1.67	4
Discount rate: 0% <sup>d</sup>		0.92	4
Discount rate: 3.5% <sup>d</sup>		0.62	3
Waning efficacy for PCV: 0% for years 0-5, 50% for years 6-10, 100% for years >10 <sup>d</sup>		0.35	5
Serotype coverage for 20vPCV: 61% <sup>d</sup>		0.45	2
Time horizon: 5 years <sup>d,e</sup>		0.09	6
23vPPV booster x2 <sup>f</sup>		0.73	7
Multivariate analysis: 23vPPV booster x2 + 20vPCV price = \$ <span style="background-color: black; color: black;">[REDACTED]</span> <sup>f</sup>		0.73	2

Source: Table 3.9.4, p499 of the submission and compiled during the evaluation from the Excel sheet 'Prevenar Indig 25-49'. Incremental costs and QALYs calculated during ESC evaluation.

Abbreviations: 20vPCV, 20 valent pneumococcal conjugate vaccine; CFR, case fatality rate; PCV, pneumococcal conjugate vaccine; QALY, Quality-adjusted life-year

a Base case used Incidence of IPD of 34.0, CRF varied by age (1.62% for ages 25-34, 2.28% for ages 35-44, and 4.96% for ages 45-49); discount rate 5%; waning efficacy for PCV (0% for years 0-5, 5.35% for years 6-10, 10% for years 11-15, and 15% for years ≥ 16), serotype coverage for 20vPCV of 72%, up to 23 year time horizon to 50 years.

b Variation to input as per ATAGI's recommendations (p67, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022).

c Variation to input as per ATAGI's recommendations (ATAGI advice, February 2016).

d Conducted during the evaluation.

e Variation to input as per ATAGI's recommendations (p70, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022).

f Provided in the pre-PBAC response. Incremental cost calculated as \$[REDACTED] - \$[REDACTED] (the difference in the cost of the vaccine).

The redacted values correspond to the following ranges:

<sup>1</sup> \$35,000 to < \$45,000

<sup>2</sup> \$45,000 to < \$55,000

<sup>3</sup> \$25,000 to < \$35,000

<sup>4</sup> \$5,000 to < \$15,000

<sup>5</sup> \$75,000 to < \$95,000

<sup>6</sup> \$355,000 to < \$455,000

<sup>7</sup> \$55,000 to < \$75,000

6.76 In order to address uncertainty related to differential vaccine effectiveness across additional serotypes and the potential impact of serotype replacement additional sensitivity analyses that reduced the overall vaccine effectiveness by up to 15% were provided in the PSCR. These analyses are shown in Table 20. For the comparisons with 13vPCV the ICER remained dominant. For the comparison with 15vPCV the ICER remained dominant for Indigenous adults aged ≥ 50 years, increased to \$35,000 to < \$45,000/QALY for non-Indigenous adults aged ≥ 70 years and to \$155,000 to < \$255,000/QALY in at-risk adults aged 18-69 years. For the expanded population the ICER increased to \$45,000 to < \$55,000/QALY. The ESC considered

these analyses, while not precise, may be informative when considering the uncertainty related to the effectiveness for the additional serotypes.

Table 20: Additional sensitivity analyses provided in the PSCR

Overall vaccine effectiveness	20vPCV vs 13vPCV			20vPCV vs 15vPCV		
	Incremental		ICER	Incremental		ICER
	Cost (\$)	QALY	\$/QALY <sup>b</sup>	Cost (\$)	QALY	\$/QALY <sup>b</sup>
<b>Base case for non-Indigenous adults ≥ 70 years</b>	█	1.91	Dominant	█	0.82	Dominant
Reduced by 5%	█	1.66	Dominant	█	0.58	Dominant
Reduced by 10%	█	1.42	Dominant	█	0.34	█ <sup>3</sup>
Reduced by 15%	█	1.18	Dominant	█	0.10	█ <sup>1</sup>
<b>Base case for Indigenous Australians ≥ 50 years</b>	█	3.18	Dominant	█	2.02	Dominant
Reduced by 5%	█	2.75	Dominant	█	1.58	Dominant
Reduced by 10%	█	2.32	Dominant	█	1.15	Dominant
Reduced by 15%	█	1.89	Dominant	█	0.72	Dominant
<b>Base case for at-risk adults 18-69 years<sup>a</sup></b>	█	0.56	Dominant	█	0.30	Dominant
Reduced by 5%	█	0.47	Dominant	█	0.21	█ <sup>3</sup>
Reduced by 10%	█	0.38	Dominant	█	0.12	█ <sup>4</sup>
Reduced by 15%	█	0.29	Dominant	█	0.03	█ <sup>5</sup>
	<b>20vPCV vs no vaccination</b>					
<b>Base case for Indigenous Australians 25-49 years</b>	█	0.53	█ <sup>1</sup>			
Reduced by 5%	█	0.51	█ <sup>1</sup>			
Reduced by 10%	█	0.48	█ <sup>2</sup>			
Reduced by 15%	█	0.45	█ <sup>2</sup>			

Source: PSCR and developed during ESC evaluation

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year

<sup>a</sup> Using corrected model

<sup>b</sup> Dominant ICER indicates that 20vPCV dominates comparator through being more effective and less costly.

The redacted values correspond to the following ranges:

<sup>1</sup> \$35,000 to < \$45,000

<sup>2</sup> \$45,000 to < \$55,000

<sup>3</sup> \$0 to < \$5,000

<sup>4</sup> \$15,000 to < \$25,000

<sup>5</sup> \$135,000 to < \$155,000

6.77 The pre-PBAC response provided additional cost-effectiveness analyses for the expanded NIP population of Indigenous Australians aged 25-49 years that assumed two booster doses of 23vPPV administered at one and five years following the initial dose of 20vPCV. The pre-PBAC response stated that when compared with the results from the submission, the addition of the two booster doses of 23vPPV resulted in an additional 0.22 discounted years of life gained (0.82 versus 0.60), 0.20 discounted QALYs gained (0.73 versus 0.53), and \$█ discounted costs (\$█ versus \$█). The ICER was reported as \$45,000 to < \$55,000 per year of life gained (versus \$25,000 to < \$35,000) and \$55,000 to < \$75,000 per QALY gained (versus \$35,000 to < \$45,000) (see Table

19). The pre-PBAC response noted that if the price of 20vPCV was reduced from \$1 to \$0.5, the ICER would be \$45,000 to < \$55,000 per QALY gained.

### Vaccine cost/patient/course

Table 21: Vaccine unit costs included in the economic evaluation

Type of resource item	Natural unit of measurement	Unit cost for general population and Indigenous Australians	Unit cost for at-risk populations <sup>a</sup>	Source of unit cost	Usage of various resources
20vPCV	0.5 mL injection	\$1	\$1	Proposed NIP price	1 dose
13vPCV	0.5 mL injection	\$1	\$1	Nationally Negotiated Price provided by sponsor	1 dose
15vPCV	0.5 mL injection	\$1	\$1	Nationally Negotiated Price provided by sponsor	1 dose
23vPPV	0.5 mL injection	\$1	\$1	Nationally Negotiated Price assumed by sponsor	1 dose

Source: p488 and p513 of the submission

Abbreviations: 13vPCV, 13-valent pneumococcal conjugate vaccine; 15vPCV, 15-valent pneumococcal conjugate vaccine; 20vPCV, 20-valent pneumococcal conjugate vaccine; 23vPPV, 23-valent pneumococcal polysaccharide vaccine; NIP, National Immunisation Program

<sup>a</sup> It is not clear why the submission proposed a higher price for at-risk populations. No justification was provided in the submission.

6.78 As noted in paragraph 3.1, the pre-PBAC response acknowledged that the PBAC may make a recommendation using a cost minimisation approach versus 13vPCV and 15vPCV and this would result in the same price per dose for 20vPCV, 15vPCV and 13vPCV.

### Estimated PBS usage & financial implications

6.79 This submission was not considered by DUSC.

6.80 The submission used an epidemiological approach to estimate the utilisation and financial impact of the proposed NIP listing of 20vPCV for non-Indigenous adults ≥ 70 years of age, Aboriginal and Torres Strait Islander adults ≥ 50 years of age and adults (> 18 years of age) with identified risk conditions for pneumococcal disease. For healthy indigenous adults aged ≥ 25 years and healthy non-indigenous adults aged ≥ 70 years the entire population is considered. This approach is consistent with previous submissions of 13vPCV to the NIP. The ESC noted during the evaluation it was considered that a market share approach based on current uptake of 13vPCV and 23vPPV would likely be more accurate. The pre-PBAC response stated that there was insufficient utilisation data available to inform a robust market share approach, noting that 13vPCV had only been available on the NIP for adults from July 2020.

6.81 Table 22 outlines the key inputs for the financial estimates.

**Table 22: Key inputs for financial estimates**

Parameter	Value applied and source	Comment
Incident population	Incident population based on ABS data sources for all population groups including ABS population (series 3222.0) and ABS population (series 3238.0)	The evaluation considered the data source appropriate and the approach used reasonable. In estimating the NIP incident population the submission assumed that each at risk condition was mutually exclusive, potentially overestimating the proportion of people with an at-risk condition.
Prevalent population	Prevalent population based on ABS data sources for all population groups including ABS population (series 3222.0) and ABS population (series 3238.0)	The evaluation considered the data source appropriate and approach used reasonable. However, for the NIP prevalent population, the submission assumed that each risk condition was mutually exclusive. This could potentially overestimate the proportion of people with an at-risk condition. Additionally, the proportion of the non-Indigenous population aged > 70 years may be an underestimate.
Uptake rate	Vaccination uptake rates of 20vPCV based upon ATAGI's advice for 13vPCV in adults (paragraph 6.28, pneumococcal conjugate vaccine; 13-valent, PSD, July 2015 PBAC meeting) and summarised in Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022 (p72-74).	The evaluation considered this approach reasonable. The PBAC noted for the expanded NIP population the uptake was assumed to be 20% for persons aged 25 years (incident population), and to reach 20% of persons aged 26-49 years by year 3 of listing (prevalent population).
Cost	20vPCV: \$ [REDACTED] – Non-indigenous adults >70 years and Aboriginal and Torres Strait Islander adults >25 years \$ [REDACTED] – Adults with identified risk conditions Source: Proposed ex-manufacturer price per vaccine dose.  13vPCV (or 15vPCV): \$ [REDACTED] – Non-indigenous adults (>70 years) and Aboriginal and Torres Strait Islander adults (>50 years) \$ [REDACTED] Adults (< 18 years) at risk Source: Nationally Negotiated Price provided by sponsor	
MBS item	Level A Consultation cost = \$17.90	

Source: Table 4.1.1, p514-515 of the submission, Table 4.2.1, p516 of the submission, Table 4.2.2 p517/518 of the submission, Table 4.2.3, p507 of the submission, Table 4.2.4, p519/520 of the submission, Table 4.2.5, p520/521 of the submission, Table 4.3.1 p522 of the submission, Table 4.3.2, p524 of the submission, Dose estimation, Budget Impact Model Excel

Abbreviations: 13vPCV 13-valent pneumococcal conjugate vaccine; 15vPCV 15-valent pneumococcal conjugate vaccine; 20vPCV, 20-valent pneumococcal conjugate vaccine; ABS, Australian Bureau of Statistics; MBS Medicare Benefits Schedule

6.82 Table 23 presents the estimated use and financial implications of 20vPCV as described in the submission. These estimates assume the PCV and PPV prices summarised in Table 21.

**Table 23: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of persons vaccinated	1	1	1	2	1	1
Non-Indigenous = 70 years	2	2	2	2	2	2
Non-Indigenous > 70 years	3	3	3	3	3	3
Aboriginal and Torres Strait Islanders = 25 years	4	4	4	4	4	4
Aboriginal and Torres Strait Islanders 26-50 years	5	5	5	4	4	4
Persons with NIP-funded risk conditions: age 18-69 years	5	5	5	5	3	3
Persons with NIP-funded risk conditions: age 18-69 years (prevalent)	6	6	6	6	6	6
Aboriginal and Torres Strait Islander persons age >50 years	4	4	4	4	4	4
Number of doses	1	1	1	1	1	1
Changes in doses of 13vPCV (or 15vPCV)	-2	-2	-2	-2	-2	-2
<b>Estimated financial implications of 20vPCV<sup>a</sup></b>						
Cost to NIP <sup>b</sup> (\$)	7	7	7	7	7	7
<b>Estimated financial implications for 13vPCV (or 15vPCV)<sup>a</sup></b>						
Cost to NIP <sup>b</sup> (\$)	8	8	8	8	8	8
<b>Net financial implications</b>						
Net cost to MBS (\$)	7	7	7	7	7	7
Net cost to NIP (\$)	7	7	7	7	7	7

Source: Table 4.2.5 p509/510 of the submission, Table 4.2.6 p511 of the submission, Table 4.3.1 p512/513 of the submission, Table 4.3.3 p513/514 of the submission, Table 4.4.1 p515 of the submission, Table 4.5.1 p516 of the submission, Table 4.5.2 p517 of the submission and calculated during the evaluation

Abbreviations: 13vPCV 13-valent pneumococcal conjugate vaccine; 15vPCV 15-valent pneumococcal conjugate vaccine; 20vPCV, 20-valent pneumococcal conjugate vaccine; MBS, Medicare Benefits Schedule; NIP, National Immunisation Program

a Assuming a single dose of vaccination as estimated by the submission.

b No co-payments were required for any of the financial estimates

The redacted values correspond to the following ranges:

<sup>1</sup> 200,000 to < 300,000

<sup>2</sup> 100,000 to < 200,000

<sup>3</sup> 20,000 to < 30,000

<sup>4</sup> 500 to < 5,000

<sup>5</sup> 10,000 to < 20,000

<sup>6</sup> 5,000 to < 10,000

<sup>7</sup> \$0 to < \$10 million

<sup>8</sup> net cost saving

6.83 The estimate of the cost to the NIP of listing 20vPCV was estimated in the submission to be \$0 to < \$10 million in year 1 and \$0 to < \$10 million in year 6, and a total of \$50 million to < \$60 million in the first 6 years of listing. The financial impact of reduced use of 13vPCV (or 15vPCV) over the first 6 years of the proposed listing of 20vPCV is \$0 to < \$10 million in year 1 increasing to \$0 to < \$10 million in year 6. Thus the net cost to the NIP was \$0 to < \$10 million in year 1 and \$0 to < \$10 million in year 6.

6.84 The net cost to MBS comprises the costs of vaccination administration for the proposed expanded NIP listing to include Aboriginal and Torres Strait Islanders aged

25-49 years (who were not eligible for vaccination in years prior). The additional vaccine administration cost was estimated to be \$0 to < \$10 million in year 1, decreasing to \$0 to < \$10 million in year 6 and a total of \$0 to < \$10 million in the first 6 years of listing.

- 6.85 The submission assumed that subsequent 23vPPV usage will not be changed by the availability of 20vPCV and therefore a subsequent dose of 23vPPV for the proposed expanded Aboriginal and Torres Strait Islander 25-49 year old population was not considered. ATAGI noted it is unclear if the expanded population of Aboriginal and Torres Strait Islander adults aged 25-49 years would require another dose of pneumococcal vaccine in their lifetime (p11, Prevenar 20, ATAGI pre-submission advice to PBAC, April 2022). The evaluation considered that the exclusion of subsequent 23vPPV usage in this population may have led to underestimated financial costs. The PSCR presented financial estimates including the cost of one subsequent dose of 23vPPV for the expanded population. The revised financial estimates provided in the PSCR are provided in Table 24. For these estimates, the PSCR stated that compliance to the first dose of 23vPPV is assumed to be 80%. The PSCR also stated that a second dose of 23vPPV was not considered in the financial estimates, as it was assumed that it would not be received within the financial forecasted period. This is consistent with current NIP recommendations<sup>2</sup>.

**Table 24: Estimated use and financial implications of one subsequent dose of 23vPPV for Aboriginal and Torres Strait Islander persons aged 25-49 years**

	2024	2025	2026	2027	2028	2029
Cost of additional 23vPPV doses <sup>a</sup> (\$)	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Cost of administration of additional 23vPPV doses (\$)	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Total cost of additional 23vPPV doses (\$)	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>

Source: PSCR

<sup>a</sup> Cost per dose of 23vPPV is assumed to be \$20 (consistent with the economic evaluation).

The redacted values correspond to the following ranges:

<sup>1</sup> \$0 to < \$10 million

- 6.86 The submission identified uptake rates as the key sources of uncertainty. For the non-Indigenous adults aged 70-years, there would be a 17% increase to the net cost to the NIP if the upper uptake rate (75%) was used, and a 14% decrease if the lower uptake rate (35%) was used. For the Aboriginal and Torres Strait Islanders aged 25-49 years old, using the upper limit of uptake rate (60% in 2024-26 and 2% in 2028-29) there would be an 18% increase and using the lower limit (10%/0.5%) there would be a 20% decrease in net cost to the NIP. Finally, for the non-indigenous population aged > 70 years there would be a 12% increase and 5% decrease to the net NIP costs if using upper (4.6%) and lower (0.6%) sensitivity uptake rates, respectively.
- 6.87 The ESC considered the key inputs of the financial estimates reasonable. However, the ESC considered the financial estimates may be underestimated for Aboriginal and Torres Strait Islander people, noting that population estimates for Aboriginal and

<sup>2</sup> <https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/pneumococcal-disease>

Torres Strait Islander people have recently increased following the 2021 Census<sup>3</sup>. The pre-PBAC response agreed with the ESC that the financial estimates for the Aboriginal and Torres Strait Islander population are likely to be underestimated. The pre-PBAC response noted that the latest census data, published on 21 September 2022, indicates that the number of Aboriginal and Torres Strait Islander persons (≥ 20 years) reported for the year to June 2021, is approximately 10% higher than the projection for the 2021 year in the Australian Bureau of Statistics (ABS) projections 2006-2031 (3238.0, Series B) which informed the submission estimates.

- 6.88 The pre-PBAC response acknowledged that ESC considered the cost to the MBS may be slightly underestimated, noting that the MBS item cost for a general practitioner Level A consultation has increased from \$17.90 to \$18.20 (as of 1 July 2022) and bulk-billing incentives were not considered. The ESC also noted that the total cost for general practitioner consultations was based on an 80% benefit. However, the cost to the MBS for a Level A consultation is 100% of the benefit.
- 6.89 The ESC also considered a proportion of the expanded population may receive vaccines through the Aboriginal Community Controlled Health (ACCHO), not a general practitioner.
- 6.90 The PBAC noted for the existing NIP populations, with the cost per dose for 20vPCV being the same as for 13vPCV and 15vPCV, there will be no additional cost to the NIP associated with the listing of 20vPCV.
- 6.91 The PBAC noted for the expanded NIP population, applying the reduced cost per dose for 20vPCV as per the pre-PBAC response (\$~~1~~ as compared with \$~~1~~), will reduce the associated cost to the NIP by approximately 10% (\$~~1~~/~~\$1~~).

### **Quality Use of Medicines**

- 6.92 The submission indicated that the use of 20vPCV involved a replacement of 20vPCV for 13vPCV, without removal of 23PPV doses, therefore, the implementation of 20vPCV on the NIP is expected to be straightforward. The submission did not propose a post-marketing surveillance study but indicated that a pharmacovigilance system is in place for collection and notification of any adverse reactions.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended that 20-valent pneumococcal conjugate vaccine (20vPCV, Prevenar 20) 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 ≥ 70 years and Aboriginal and Torres Strait Islander adults aged ≥ 25 years. The PBAC's recommendation for listing

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<sup>3</sup> <https://www.abs.gov.au/statistics/people/aboriginal-and-torres-strait-islander-peoples/estimates-aboriginal-and-torres-strait-islander-australians/jun-2021>

for the existing NIP populations (individuals with an at-risk condition aged  $\geq 18$  years, non-Indigenous adults aged  $\geq 70$  years and Aboriginal and Torres Strait Islander adults aged  $\geq 50$  years) was based on, among other matters, its assessment that the cost-effectiveness of 20vPCV would be acceptable if it were cost-minimised against the nominated comparators, 13-valent pneumococcal conjugate vaccine (13vPCV) and 15-valent pneumococcal conjugate vaccine (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 a cost per dose of \$ $\downarrow$  as proposed in the sponsor's pre-PBAC response.

- 7.2 The PBAC considered that nomination of 13vPCV as the main comparator for the existing NIP populations was appropriate. The PBAC accepted 15vPCV as a near market comparator, which was recommended for NIP-listing by the PBAC at the November 2021 meeting but was not listed on the NIP at the time of the 20vPCV consideration. For the expanded population, the PBAC accepted 'no vaccine' as the appropriate comparator.
- 7.3 The PBAC noted the clinical claims presented in the submission were based on serotype specific opsonophagocytic activity (OPA) from immunogenicity trials and extrapolation to 13vPCV effectiveness studies.
- 7.4 Study B7471007 was a phase 3, randomised, double-blind immunogenicity trial in pneumococcal vaccine-naïve adults aged  $\geq 18$  years comparing 20vPCV and 13vPCV for the 13 shared serotypes and 20vPCV and 23vPPV for the additional 7 serotypes. The PBAC noted in Cohort 1 of Study B7471007 (adults aged  $\geq 60$  years) the lower bounds of the 95% confidence interval (CI) for the OPA geometric mean ratios (GMRs) for 20vPCV versus 13vPCV were above 0.5 for the 13 shared serotypes and therefore the nominated non-inferiority criteria were met. However, the PBAC noted that the OPA GMRs for 11 of the 13 matched serotypes had upper bound 95% CIs  $< 1$ , thus favouring 13vPCV. The PBAC noted there is no specific threshold of OPA titre that correlates with disease prevention and therefore the impact of these differences is unknown.
- 7.5 The PBAC noted indirect treatment comparisons (ITCs) were presented in the submission comparing serotype specific OPA GMRs between 20vPCV and 15vPCV, using 13vPCV as a common comparator, across nominated age groups: indirect comparison 1 (IC1) age  $\geq 50$  years, and indirect comparison 2 (IC2) age 18-49 years. Data used for IC1 were obtained from B7471007 Cohorts 1 and 2 for 20vPCV and PNEU-AGE, PNEU-PATH and PNEU-TRUE for 15vPCV. For IC2, data were from B7471007 Cohort 3 and B7471008 for 20vPCV and PNEU-DAY for 15vPCV. The PBAC noted in IC1, of the 13 shared serotypes, serotypes 3, 6B, 23F did not meet the non-inferiority criteria of an OPA GMR  $\geq 0.5$  and favoured 15vPCV. In IC2 serotypes 6B, 18C, 23F did not meet the non-inferiority criteria and favoured 15vPCV.

- 7.6 The PBAC noted the vaccine effectiveness estimates for 20vPCV in the economic model, for both the 13 shared serotypes with 13vPCV and the 7 additional serotypes, were sourced from the CAPiTA trial. The CAPiTA trial was a randomised, placebo-controlled clinical trial of 13vPCV in 84,496 adults aged  $\geq 65$  years that assessed vaccine effectiveness in the prevention of vaccine-serotype pneumococcal community-acquired pneumonia and invasive pneumococcal disease (IPD). Although the PBAC considered 20vPCV is likely superior in effectiveness to 13vPCV for the additional 7 serotypes, the Committee noted the benefit in terms of disease prevention was uncertain 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 will not necessarily hold for the 7 unmatched serotypes.
- 7.7 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 is uncertain. On the basis of the available evidence, the PBAC considered a claim of non-inferior comparative effectiveness of 20vPCV compared with 13vPCV (and 15vPCV) to be appropriate.
- 7.8 For the existing NIP populations the submission claimed that 20vPCV has equivalent safety to 13vPCV and 15vPCV. For Aboriginal and Torres Strait Islander adults aged 25-49 years the submission claimed that 20vPCV has inferior safety to no vaccine. The PBAC considered the submission's safety claims were reasonable, while noting that the submission did not conduct indirect comparisons on the safety outcomes between 20vPCV and 15vPCV.
- 7.9 For the existing NIP populations, the PBAC considered 20vPCV would be cost-effective if it were cost-minimised against 13vPCV and 15vPCV. The PBAC advised that the equi-effective doses are 1 x 0.5 mL 20vPCV and either 1 x 0.5 mL 13vPCV or 1 x 0.5 mL 15vPCV, and noted that a cost minimisation approach would result in the same price per dose for 20vPCV as for 15vPCV and 13vPCV.
- 7.10 The PBAC noted a cost-utility analysis was presented for 20vPCV versus no vaccine for Aboriginal and Torres Strait Islander adults aged 25-49 years using an economic model with the same structure as for the model previously considered by the PBAC for the listing of 13vPCV. The PBAC noted the incidence of IPD in the proposed expanded population (34 per year per 100,000 persons), although less than in the Indigenous population aged  $\geq 50$  years (72 per year per 100,000 persons), was higher than in the non-Indigenous population aged  $\geq 70$  years (22 per year per 100,000 persons). The PBAC further noted the serotype coverage with 20vPCV was potentially higher in the Indigenous population aged 25-49 years compared with the non-Indigenous populations (Table 10), although the estimates of coverage were based on relatively small sample sizes.

- 7.11 The PBAC noted for the expanded population the submission proposed a single dose of 20vPCV (with no subsequent doses of 23vPPV) and a cost per dose of \$~~1~~. The PBAC noted a substantial proportion of the vaccination costs were offset by a reduction in hospitalisation for the treatment of pneumococcal disease (Table 14), and the incremental cost effectiveness ratio (ICER) for the submission scenario was \$35,000 to < \$45,000 per QALY gained. The PBAC noted the pre-PBAC response provided additional cost-effectiveness analyses for the expanded population that assumed two booster doses of 23vPPV administered at one and five years following the initial dose of 20vPCV. The pre-PBAC response stated that when compared with the results from the submission, the addition of the two booster doses of 23vPPV resulted in an additional 0.20 discounted QALYs gained (0.73 versus 0.53), and the ICER was reported as \$55,000 to < \$75,000 per QALY gained (versus \$35,000 to < \$45,000). The pre-PBAC response stated that if the price of 20vPCV was reduced from \$~~1~~ to \$~~1~~, the ICER would reduce to \$45,000 to < \$55,000 per QALY gained. Noting the disproportionately high burden of disease in the proposed expanded population, the PBAC considered 20vPCV, with or without one or two subsequent doses of 23vPPV, would be cost-effective at a cost per dose of \$~~1~~ as proposed in the pre-PBAC response.
- 7.12 The PBAC noted the financial estimates were sensitive to the assumed uptake rates. However, for the existing NIP populations the listing of 20vPCV is not expected to impact on the current uptake rates, and hence with the cost per dose for 20vPCV being the same as for 13vPCV and 15vPCV, there should be no additional cost to the NIP associated with the listing of 20vPCV for individuals with an at-risk condition aged ≥ 18 years, non-Indigenous adults aged ≥ 70 years and Aboriginal and Torres Strait Islander adults aged ≥ 50 years. The PBAC noted the uptake rate of 20% for the expanded population was based on ATAGI advice in which it was considered that the uptake amongst those aged 25-49 years may be lower than for those aged ≥50 years. The PBAC noted the financial estimates for the Aboriginal and Torres Strait Islander population aged 25-49 years should be revised to account for (i) the population size in the submission being underestimated (paragraph 6.87), and (ii) the reduced cost per dose (\$~~1~~) as proposed in the pre-PBAC response.
- 7.13 The following risk factors have not been included in the suggested wording for the 20vPCV determination. The PBAC advised the following risk factors should be removed from the recommended listing for Vaxneuvance from the November 2021 PBAC recommendation for the prevention of pneumococcal disease in non-Indigenous adults aged ≥ 70 years, Indigenous adults aged ≥50 years, and individuals at increased risk of pneumococcal disease aged ≥ 18 years.
- (I) born less than 28 weeks gestation; or
  - (J) trisomy 21; or
  - (K) chronic heart disease including cyanotic heart disease and heart failure;
  - (ii) who is at least 18 years of age and has been newly diagnosed with one or more of the medical risk conditions contained in subparagraph (a)(i);

7.14 The PBAC noted that this submission is not eligible for an independent review as independent review is only relevant to requests for PBS listing.

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Add new item to the Determination:

<b>Vaccine and the circumstances in which vaccine may be provided</b>	<b>Brand</b>	<b>Formulation</b>	<b>Number and timing of doses</b>
<i>Pneumococcal (conjugate, 20-valent)</i>	<i>Prevenar 20</i>	<i>Injection (0.5mL)</i>	<i>1 dose</i>

*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.*

8.2 Remove the following risk factors from the recommended listing for Vaxneuvance from the November 2021 PBAC recommendation for the prevention of pneumococcal disease in non-Indigenous adults aged ≥70 years, Indigenous adults aged ≥50 years, and individuals at increased risk of pneumococcal disease aged ≥18 years.

- (I) born less than 28 weeks gestation; or*
- (J) trisomy 21; or*
- (K) chronic heart disease including cyanotic heart disease and heart failure;*
- (ii) who is at least 18 years of age and has been newly diagnosed with one or more of the medical risk conditions contained in subparagraph (a)(i);*

***This restriction 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**

Pfizer welcomes the PBAC recommendation for 20vPCV for NIP-listing for the prevention of pneumococcal disease in adults. Additionally, the recommendation for expansion of NIP-listing to Aboriginal and Torres Strait Islander adults 25 years and older means that this population who have increased burden of disease will receive additional protection.

While the PBAC recommended NIP-listing on the basis of a cost minimisation approach to 13vPCV or 15vPCV, Pfizer considers the clinical and economic benefits of the additional serotype coverage will have value for Australian adults vaccinated with PCV20.