

## **5.13 PNEUMOCOCCAL CONJUGATE VACCINE, 20-VALENT, 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 National Immunisation Program (NIP) listing for 20-valent pneumococcal conjugate vaccine (20vPCV) for the prevention of pneumococcal disease in the following paediatric populations:
- Children aged 12 months or younger in NSW, VIC, ACT, and TAS and non-Indigenous children aged 12 months or younger in QLD, NT, WA and SA (2+1 schedule).
  - Aboriginal and Torres Strait Islander children aged 12 months or younger in QLD, NT, WA and SA (3+1 schedule).
  - Children aged 12 months or younger with currently NIP-funded risk conditions (3+1 schedule).
  - Children aged more than 12 months with currently NIP-funded risk conditions (single dose).
- 1.2 Listing was requested on the basis of a cost-minimisation approach versus 13-valent pneumococcal conjugate vaccine (13vPCV) and 15-valent pneumococcal conjugate vaccine (15vPCV).
- 1.3 Table 1 shows the key components addressed by the submission.

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

Component	Description
Population	<ul style="list-style-type: none"> <li>• Infants in ACT, NSW, TAS and VIC and non-Indigenous infants in QLD, NT, WA and SA (2+1 schedule)</li> <li>• Aboriginal and Torres Strait Islander infants in QLD, NT, WA and SA (3+1 schedule)</li> <li>• Children ≤12 months with currently NIP-funded risk conditions (3+1 schedule) <sup>a</sup></li> <li>• Children &gt; 12 months with currently NIP-funded risk conditions (1 dose at diagnosis) <sup>a</sup></li> </ul>
Intervention	20vPCV is a pneumococcal polysaccharide conjugate vaccine conjugated to CRM197 carrier protein which includes serotype-specific capsular polysaccharides 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F.
Comparator	13vPCV and 15vPCV
Outcomes	<ul style="list-style-type: none"> <li>• Efficacy: Cases of IPD, pneumonia and acute otitis media caused by <i>Streptococcus pneumoniae</i> serotypes 1, 3, 4, 5, 6A, 6B, 6C, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F; sequelae of IPD cases; hospitalisations; deaths</li> <li>• Immunogenicity including IgG concentrations and OPA titres.</li> <li>• Safety: local reactions, systemic reactions; serious adverse events; non-serious reactions; adverse events of special interest <sup>b</sup></li> </ul>
Clinical claim	In the paediatric populations who are currently eligible for funded 13vPCV under the NIP, 20vPCV has equivalent immunogenicity, and by extrapolation efficacy, against IPD, pneumococcal pneumonia and otitis media, to the shared serotypes with 13vPCV and 15vPCV but is superior for the additional serotypes contained in 20vPCV and not in 13vPCV or 15vPCV. 20vPCV provides clinical and economic benefits compared to 13vPCV and 15vPCV because of the additional serotypes covered <sup>c</sup>

Source: Table 1.1.1, pp5-7 of the submission.

13vPCV = 13 valent pneumococcal conjugate vaccine; 15vPCV = 15 valent pneumococcal conjugate vaccine; 20vPCV = 20 valent pneumococcal conjugate vaccine; ACT = Australian Capital Territory; IgG = immunoglobulin G; IPD = invasive pneumococcal disease; NIP = National Immunisation Program; NSW = New South Wales; NT = Northern Territory; OPA = Opsonophagocytic activity; QLD = Queensland; SA = South Australia; TAS = Tasmania; VIC = Victoria; WA = Western Australia.

<sup>a</sup> NIP-funded risk conditions for pneumococcal disease can be found in Table 3.

<sup>b</sup> The submission presented in Section 2 local reactions, systemic events, adverse events, serious adverse events, and newly diagnosed chronic medical conditions.

<sup>c</sup> The submission stated '20vPCV provides clinical and economic benefits compared to 13vPCV and 15vPCV'.

## 2 Background

### Registration status

2.1 The submission was made under the Therapeutic Goods Administration (TGA)/ Pharmaceutical Benefits Advisory Committee (PBAC) Parallel Process. 20vPCV was TGA registered for the prevention of pneumococcal disease caused by *Streptococcus 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 aged 18 years and over. A submission to the TGA was lodged on 20 December 2022, which proposed expanding the indication to individuals aged 6 weeks or older. At the time of PBAC consideration the TGA Delegate's overview was available.

2.2 On 27 April 2023, the United States Food and Drug Administration approved 20vPCV for paediatric use from 6 weeks of age and older.

### Previous PBAC consideration

2.3 The PBAC recommended in July 2010 that 13vPCV be listed on the NIP under the same circumstances of use as the existing NIP listed 7-valent pneumococcal conjugate

vaccine (7vPCV) (section 12, pneumococcal polysaccharide conjugate vaccine, 13-valent adsorbed, public summary document [PSD], July 2010 PBAC meeting).

2.4 The PBAC recommended in March 2023 that 15vPCV be a designated vaccine for the purposes of the *National Health Act 1953*, for the prevention of pneumococcal disease in the following paediatric populations (paragraph 7.1, pneumococcal conjugate vaccine, 15 valent adsorbed, PSD, March 2023 PBAC meeting):

- Non-indigenous infants and Aboriginal and Torres Strait Islander infants living in NSW, VIC, ACT, and TAS: three doses at ages 2, 4 and 12 months (2+1 doses).
- Infants with specified medical risk conditions and Aboriginal and Torres Strait Islander infants living in WA, NT, SA and Qld: four doses at ages 2, 4, 6 and 12 months (3+1 doses).
- Children and adolescents between 12 months and 18 years newly diagnosed with a specified medical risk condition (one dose).
- Haematopoietic stem cell transplant recipients aged 12 months to <18 years: three doses at 6, 8, and 12 months after haematopoietic stem cell transplant (three doses).

2.5 The PBAC recommended in November 2022 that 20vPCV be a designated vaccine for the purposes of the *National Health Act 1953*, for the prevention of pneumococcal disease in individuals with a NIP-funded risk condition aged  $\geq 18$  years, non-Indigenous adults aged  $\geq 70$  years and Aboriginal and Torres Strait Islander adults aged  $\geq 25$  years. The PBAC's recommendation 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, 13vPCV and 15vPCV (paragraph 7.1, pneumococcal conjugate vaccine, 20-valent adsorbed, PSD, November 2022 PBAC meeting).

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

### 3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Nationally Negotiated Price	Proprietary Name and Manufacturer
PNEUMOCOCCAL POLYSACCHARIDE CONJUGATE VACCINE, 20 VALENT ADSORBED		
Pneumococcal polysaccharide conjugate vaccine, 20 valent adsorbed 0.5 mL, Injection, Prefilled syringe	\$ [REDACTED]	Prevenar 20 Pfizer Australia Pty Ltd

#### Current NIP populations:

- Infants in NSW, VIC, ACT, TAS and non-Indigenous infants in QLD, NT, WA and SA: 2+1 schedule
- Indigenous infants in QLD, NT, WA and SA: 3+1 schedule
- Infants ≤12 months with risk conditions <sup>a</sup>: 3+1 schedule
- Children >12 months with risk conditions <sup>a</sup>: 1 dose on diagnosis

NIP = National Immunisation Program.

<sup>a</sup> NIP-funded risk conditions for pneumococcal disease (Table 3).

- 3.1 The proposed price for 20vPCV was the same as for 13vPCV and 15vPCV.
- 3.2 The proposed NIP listing differs from what was proposed in the request for ATAGI Advice to the PBAC. Proposals included in the ATAGI Advice to the PBAC not included in the proposed NIP listing were for the 20vPCV replacing the 23 valent pneumococcal polysaccharide vaccine (23vPPV), using 20vPCV to complete a dose series that initiated with 13vPCV, a catch-up dose with 20vPCV for children aged under 3 years who completed the primary vaccination schedule with 13vPCV, and an expanded list of risk conditions.
- 3.3 The requested listing was consistent with the proposed TGA indication, the evidence presented in the submission for healthy children, the cost-minimisation approach presented and the estimates of use in clinical practice. The evidence presented in the submission did not include use in Aboriginal and Torres Strait Islander population and children with risk conditions.

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

### 4 Population and disease

- 4.1 Pneumococcal disease caused by *Streptococcus pneumoniae* can cause severe invasive pneumococcal disease (IPD), including meningitis, sepsis, and pneumonia with bacteraemia. It can also lead to non-invasive diseases such as nonbacteremic pneumonia and otitis media. Pneumococcal disease caused by *Streptococcus pneumoniae* continues to be a source of significant morbidity and mortality, especially for older adults and those with underlying medical conditions.
- 4.2 The target disease and proposed population groups are those currently covered on the NIP by 13vPCV and are included in Table 2.

**Table 2: Population groups covered on the NIP by 13vPCV**

Vaccine Preventable Disease	Target Population Group	Australian Immunisation Handbook Recommendation(s)
Pneumococcal disease caused by the bacterium <i>Streptococcus pneumoniae</i>	Children aged 12 months or younger in NSW, VIC, ACT, and TAS and non-Indigenous children aged 12 months or younger in QLD, NT, WA and SA	All children are recommended to receive 13vPCV in a three-dose schedule at 2, 4 and 12 months of age. Children aged 12 months or younger can receive their first dose of pneumococcal conjugate vaccine as early as 6 weeks of age. If the first dose is given at the age of 6 weeks, children aged 12 months or younger should still receive their next scheduled dose at four months of age
	Aboriginal and Torres Strait Islander infants aged 12 months or younger in QLD, NT, WA and SA	In addition to the three doses for all children aged 12 months or younger, Aboriginal and Torres Strait Islander children aged 12 months or younger living in the following states and territories are recommended to receive an additional dose of 13vPCV at 6 months of age: QLD, NT, WA and SA These children are also recommended to receive two doses of 23vPPV: <ul style="list-style-type: none"> <li>• One dose at 4 years of age</li> <li>• Second dose at least 5 years later</li> </ul>
	Infants aged 12 months or younger with NIP risk conditions	In addition to the three doses of 13vPCV routinely recommended for healthy non-Indigenous children less than 12 months of age with risk conditions for pneumococcal disease are recommended to receive: <ul style="list-style-type: none"> <li>• An additional dose of 13vPCV at 6 months of age</li> <li>• A dose of 23vPPV at 4 years of age</li> <li>• A second dose of 23vPPV at least 5 years after the first dose of 23vPPV</li> </ul> Any child aged 6 to 11 months with a newly identified risk condition who has not received an additional dose of 13vPCV at 6 months of age should receive this dose at diagnosis. The exception is children who have received a haematopoietic stem cell transplant — these children are recommended to receive three doses of 13vPCV after transplantation, followed by two doses of 23vPPV
	Infants > 12 months with risk conditions	All children and adolescents with newly identified risk conditions are recommended to receive: <ul style="list-style-type: none"> <li>• One dose of 13vPCV at diagnosis (at least 2 months after any previous doses of 13vPCV)</li> <li>• One dose of 23vPPV 12 months after 13vPCV (2 to 12 months later is acceptable) or at four years of age whichever is later</li> <li>• A second dose of 23vPPV at least 5 years later</li> </ul>

Source: Table 1.1.3, pp9-10 of the submission.

13vPCV = 13 valent pneumococcal conjugate vaccine; 23vPPV = 23 valent pneumococcal polysaccharide vaccine; ACT = Australian Capital Territory; NIP = National Immunisation Program; NSW = New South Wales; NT = Northern Territory; QLD = Queensland; SA = South Australia; TAS = Tasmania; VIC = Victoria; WA = Western Australia.

#### 4.3 Table 3 describes the current paediatric NIP-funded risk conditions.

**Table 3: National Immunisation Program funded risk conditions**

<b>Risk condition</b>	<b>&lt; 5 years</b>	<b>≥ 5 years</b>
Previous episode of invasive pneumococcal disease	✓	✓
<b>Functional or anatomical asplenia including</b>		
Sickle cell disease or other haemoglobinopathies	✓	✓
Congenital or acquired asplenia (for example, splenectomy or hyposplenia)	✓	✓
<b>Immunocompromising conditions, including</b>		
Congenital or acquired immune deficiency, including symptomatic IgG subclass or isolated IgA deficiency	✓	✓
Haematological malignancies	✓	✓
Solid organ transplant	✓	✓
Haematopoietic stem cell transplant	✓	✓
HIV infection	✓	✓
<b>Proven or presumptive cerebrospinal fluid leak, including</b>		
Cochlear implants	✓	✓
Intracranial shunts	✓	✓
<b>Chronic respiratory disease, including</b>		
Suppurative lung disease, bronchiectasis and cystic fibrosis	✓	✓
Chronic lung disease in preterm infants	✓	✓
<b>Chronic renal disease</b>		
Relapsing or persistent nephrotic syndrome	✓	✓
Chronic renal impairment - eGFR <15 mL/min	✓ <sup>a</sup>	✓ <sup>a</sup>
<b>Cardiac disease, including</b>		
Congenital heart disease	✓	
Coronary artery disease	✓	
Heart failure	✓	
<b>Others</b>		
Children born less than 28 weeks gestation	✓	
Trisomy 21	✓	

Source: Table 1.1.1, pp5-7 of the submission; Table 1-1 of the ATAGI Advice to the PBAC.

eGFR = estimated glomerular filtration rate; HIV = human immunodeficiency virus; IgA = immunoglobulin A; IgG = immunoglobulin G.

<sup>a</sup> Funded under the NIP for eGFR < 15mL/min only (including patients on dialysis).

- 4.4 In 2019 there were 459 cases of IPD in children and adolescents aged 19 or less in Australia, of which 65 were in Aboriginal and Torres Strait Islander children and adolescents.<sup>1</sup> The ATAGI Advice to the PBAC noted a 1.3% case fatality rate for children aged 2 years or less, which might be 1.6 times higher for Aboriginal and Torres Strait Islander children (ATAGI Advice to the PBAC).
- 4.5 The submission also estimated that approximately 0.96% of children aged 1 to 17 years had a risk condition.
- 4.6 Table 4 summarises IPD cases per serotype distribution and population.

<sup>1</sup> <https://www.health.gov.au/resources/publications/national-notifiable-diseases-surveillance-system-nndss-public-dataset-pneumococcal-disease-invasive?language=en> [accessed 9 September 2023]

**Table 4: IPD serotype distribution in age groups and Indigenous status for paediatric NIP populations**

Vaccine	Children <2 years in NSW, ACT, and TAS and non-Indigenous children <2 years in NT, QLD, SA and WA <sup>a, b</sup>	Aboriginal and Torres Strait Islander children <2 years (NT, QLD, SA and WA)	Non-indigenous children <2 years with risk conditions	Non-indigenous children 5-<18 years with risk conditions	Children <12 months <sup>a, c</sup>	Children 1-17 years <sup>a, c</sup>
% of cases involving strains in 13vPCV <sup>d</sup>	29%	9%	28%	17%	36%	43%
% of cases involving strains in 15vPCV but not in 13vPCV	11%	0%	13%	25%	10%	5%
% of cases involving strains in 20vPCV but not in 15vPCV	8%	9%	9%	0%	9%	8%

Source: Table 1.1.7, p14 of the submission; Table 2.4-3, p42 of the ATAGI Advice to the PBAC.

13vPCV = 13 valent pneumococcal conjugate vaccine; 15vPCV = 15 valent pneumococcal conjugate vaccine; 20vPCV = 20 valent pneumococcal conjugate vaccine; ACT = Australian Capital Territory; IPD = invasive pneumococcal disease; NIP = National Immunisation Program; NSW = New South Wales; NT = Northern Territory; QLD = Queensland; SA = South Australia; TAS = Tasmania; VIC = Victoria; WA = Western Australia.

<sup>a</sup> Excludes Aboriginal and Torres Strait Islander children less than 2 years in NT, QLD, SA or WA.

<sup>b</sup> It is unclear from the submission or the ATAGI advice if Victoria was included.

<sup>c</sup> Sourced from ATAGI Advice to the PBAC.

<sup>d</sup> Serotype 3 represents 24% of all cases.

4.7 The ATAGI Advice to the PBAC noted that IPD had an appreciable incidence in Australia caused by serotypes included in 20vPCV but not included in 13vPCV, which caused 14% of IPD in all children but 30% in Aboriginal and Torres Strait Islander children (p7 of the ATAGI Advice to the PBAC). Additionally, serotypes included in 13vPCV caused 41% of IPD in all children younger than 18 years and 25% of IPD in Aboriginal and Torres Strait Islander children (p7 of the ATAGI Advice to the PBAC). Serotype 3 (covered by 13vPCV and 15vPCV, and although covered by 20vPCV the vaccine efficacy may be less than for 13vPCV and 15vPCV) caused 24% of IPD in all children (p7 of the ATAGI Advice to the PBAC).

4.8 The clinical management algorithm was based on the existing 13vPCV paediatric NIP listing. The evaluation considered that this was reasonable.

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

## 5 Comparator

- 5.1 The submission nominated 13vPCV and 15vPCV as the main comparators. 13vPCV is currently NIP-funded for the proposed target populations. 15vPCV was nominated as a near-market comparator as it received a positive recommendation for NIP listing for paediatric populations at the March 2023 PBAC meeting. The evaluation considered the comparators were reasonable.
- 5.2 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(4D) of the *National Health Act 1953*, when the proposed vaccine is substantially more costly than an alternative vaccine, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed vaccine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative vaccine. If the committee is so satisfied, it must make a statement to this effect. The alternative vaccines include 13vPCV, and if listed, 15vPCV.

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

## 6 Consideration of the evidence

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The representative discussed the unmet disease burden associated with pneumococcal disease in Australia caused by *Streptococcus pneumoniae*. The representative stated that 20vPCV has an increased serotype coverage compared with 13vPCV and 15vPCV, and emphasised that the additional serotypes included in 20vPCV are prevalent and medically significant. The representative discussed an example, stating that additional serotypes 10A, 11A, 15B, and 33F were significantly associated with the development of otitis media and considered it had significantly contributed to hearing loss in the Australian indigenous paediatric population. The representative further discussed the serotype distribution and associated IPD that are covered by 7vPCV, 13vPCV, 15vPCV, and 20vPCV for non-indigenous and indigenous children in Australia. The representative highlighted that there is evidence to suggest that 20vPCV provides an additional 21% protection against the IPD serotype distribution in Australia compared with 13vPCV and 12% more than 15vPCV in children aged 0–23 months. Furthermore, 20vPCV provides an additional 30% protection against the IPD serotype distribution in Australia compared with 13vPCV and 19% more than 15vPCV among indigenous children aged 0–23 months. A second representative discussed the immunogenicity of 20vPCV to serotype 3 and emphasised that overall 20vPCV is comparable to 13vPCV based on OPA titres and immune memory response, and therefore considered that effectiveness for all shared serotypes, including serotype 3, would be similar.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from 1 organisation via the Consumer Comments facility on the PBS website.
- 6.3 The Immunisation Foundation of Australia (IFA) expressed its strong support for the NIP listing of 20vPCV for the current NIP paediatric populations. The IFA noted that 20vPCV provided additional coverage to circulating pneumococcal serotypes in Australia. It considered the NIP listing of 20vPCV would likely lead to reduced case numbers and the burden of disease associated with pneumococcal experienced by the Australian healthcare system and Australian families. The IFA provided a statement from a parent advocate sharing the loss of a family member due to a serotype of pneumococcal not contained in currently available PCVs and expressed their strong support for increased coverage to pneumococcal serotypes for infants and toddlers in Australia.

### **Clinical studies/trials**

- 6.4 The submission was based on four head-to-head randomised controlled trials (RCTs) comparing 20vPCV to 13vPCV and one single-arm study, all in healthy children:
- One phase III RCT of 20vPCV vs 13vPCV using the 2+1 schedule (two infant doses at 2 and 4 months and a toddler dose at 12 months): B7471012 (N = 1,207).
  - One phase III RCT of 20vPCV vs 13vPCV using a 3+1 schedule (three infant doses at 2, 4, and 6 months and a toddler dose at 12 months): B7471011 (N=1,997).
  - One phase III safety RCT of 20vPCV vs 13vPCV using a 3+1 schedule: B7471013 (N = 1,511).
  - One phase II RCT of 20vPCV vs 13vPCV using a 3+1 schedule: B7471003 (N = 460).
  - One single-arm study assessing a single dose of 20vPCV for children 15 months to 17 years: B7471014 (N = 839).
- 6.5 The B7471012 trial was most relevant for the proposed population of children aged 12 months or younger in NSW, VIC, ACT, TAS and non-Indigenous children aged 12 months or younger in QLD, NT, WA and SA (2+1 schedule).
- 6.6 The B7471011, B7471013 and B7471003 trials were most relevant to the proposed population of Aboriginal and Torres Strait Island children aged 12 months or younger in QLD, NT, WA and SA and children aged 12 months or younger with risk conditions aged 12 months or less (3+1 schedule).
- 6.7 The B7471014 study was most relevant to the proposed population of children and adolescents with NIP-funded risk conditions aged 1-17 years (single dose).
- 6.8 The submission also presented three head-to-head RCTs comparing 15vPCV to 13vPCV:

- Two phase III RCTs of 15vPCV vs 13vPCV using a 2+1 schedule: PNEU-PED-EU-1 (N = 1,184) and PNEU-PED-EU-2 (N = 1,191).
- One phase III RCT of 15vPCV vs 13vPCV using a 3+1 schedule: PNEU-PED (N = 1,720).

6.9 A summary list of trials and vaccine schedules included in the submission and whether the PBAC has previously considered them is presented in Table 5.

**Table 5: Summary list of trials / study**

Trial / study	Vaccine schedule			Previously seen by the PBAC (context)
	2+1	3+1	Single dose	
<b>20vPCV</b>				
B7471012	✓			N
B7471011		✓		N
B7471013		✓		N
B7471003		✓		N
B7471014			✓	N
<b>15vPCV</b>				
PNEU-PED-EU-1	✓			Y (paragraph 6.7, pneumococcal conjugate vaccine, 15 valent adsorbed, PSD, March 2023 PBAC meeting)
PNEU-PED-EU-2	✓			
PNEU-PED		✓		

Source: Table 2.3.3, pp53 & 251-252 of the submission.

15vPCV = 15 valent pneumococcal conjugate vaccine; 20vPCV = 20 valent pneumococcal conjugate vaccine; N = no; PBAC = Pharmaceutical Benefits Advisory Committee; Y = yes.

6.10 Details of the trials/study presented in the submission are provided in Table 6.

**Table 6: Trials/study and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>20vPCV</b>		
B7471012 NCT04546425	A phase 3, randomised, double-blind trial to evaluate the safety and immunogenicity of a 20-valent pneumococcal conjugate vaccine given as a series of 2 infant doses and 1 toddler dose in healthy infants	October 2022
B7471011 NCT04382326	A phase 3, randomised, double-blind trial to evaluate the safety and immunogenicity of a 20-valent pneumococcal conjugate vaccine in healthy infants	October 2022
B7471013 NCT04379713	A phase 3, randomised, double-blind trial to evaluate the safety of a 20-valent pneumococcal conjugate vaccine in healthy infants	October 2022
B7471014 NCT04642079	A phase 3, single-arm study to evaluate the safety and immunogenicity of a 20-valent pneumococcal conjugate vaccine in healthy children 15 months through 17 years of age.	July 2022
B7471003 NCT03512288	A phase 2, randomised, double-blind trial to evaluate the safety and immunogenicity of a multivalent pneumococcal conjugate vaccine in healthy infants Senders S, Klein NP, et al. Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Infants in the United States	July 2020 <i>The Pediatric Infectious Disease Journal</i> , 2021, 40: 944-951
<b>15vPCV</b>		
PNEU-PED-EU-1 NCT04031846	A phase 3, multicentre, randomised, double-blind, active-comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of V114 in healthy infants (PNEU-PED-EU-1)	January 2022
PNEU-PED-EU-2 NCT04016714	A phase 3, multicentre, randomised, double-blind, active-comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of V114 in healthy infants (PNEU-PED-EU-2) Benfield T, Rämets M, et al. Safety, tolerability, and immunogenicity of V114 pneumococcal vaccine compared with PCV13 in a 2+1 regimen in healthy infants: A phase III study (PNEU-PED-EU-2).	May 2022 <i>Vaccine</i> , 2023, 41: 2456-2465
PNEU-PED NCT03893448	Safety, tolerability and immunogenicity of V114 in health infants (V114-029) (PNEU-PED) Lupinacci R, Rupp R, et al. A phase 3, multicenter, randomised, double-blind, active-comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of a 4-dose regimen of V114, a 15-valent pneumococcal conjugate vaccine, in healthy infants (PNEU-PED).	Not reported <i>Vaccine</i> , 2023; 41:1142-1152

Source: Table 2.2.1, p46 of the submission and sourced during the evaluation.

15vPCV = 15 valent pneumococcal conjugate vaccine; 20vPCV = 20 valent pneumococcal conjugate vaccine; PCV = pneumococcal conjugate vaccine.

6.11 The key features of the RCTs and study are summarised in Table 7.

**Table 7: Key features of the included evidence - indirect comparison**

Trial	N	Design/ median duration of follow-up	Risk of bias	Patient population	Primary pneumococcal outcomes
<b>20vPCV vs 13vPCV <sup>a</sup></b>					
B7471012	20vPCV: 603 13vPCV: 604	R, DB, MC, 2+1	Low	Healthy children, aged 42-112 days	GMR (infant and toddler doses), response rate <sup>b</sup> (infant dose)
B7471011	20vPCV: 1004 13vPCV: 993	R, DB, MC, 3+1	Low	Healthy children, aged 42-98 days	GMR (infant and toddler doses), response rate <sup>b</sup> (infant dose)
B7471013	20vPCV: 1006 13vPCV: 505	R, DB, MC, Safety 3+1	Low	Healthy children, aged 42-98 days	Not applicable <sup>c</sup>
B7471003	20vPCV: 232 13vPCV: 228	R (phase II), DB, MC, 3+1	Low	Healthy children, aged 42-98 days	Not applicable <sup>d</sup>
B7471014	Cohort 1 (≥15–<24 m): 210 Cohort 2 (≥2–<5 y): 219 Cohort 3 (≥5–<10 y): 203 Cohort 4 (≥10–<18 y): 207	Single-arm, OL, MC 1 dose	Low <sup>e</sup>	Children aged ≥1 5 months to < 5 years of age with at least 3 prior doses of 13vPCV and children ≥ 5 to <1 8 years of age	IgG GMFR (Cohorts 1 and 2), OPA GMFR (Cohorts 3 and 4)
<b>15vPCV vs 13vPCV <sup>a</sup></b>					
PNEU-PED- EU-1	15vPCV: 591 13vPCV: 593	R, DB, MC, 2+1, 3+1 (preterm)	Low	Healthy children, aged 42-90 days	GMR and response rate <sup>b</sup> (toddler dose)
PNEU-PED- EU-2	15vPCV: 595 13vPCV: 596	R, DB, MC, 2+1	Low	Healthy children: aged 42 (72) -111 days	GMR and response rate <sup>b</sup> (toddler dose)
PNEU-PED	15vPCV: 860 13vPCV: 860	R, DB, MC, 3+1	Low	Healthy children, aged 42-90 days	GMR (infant and toddler doses), response rate <sup>b</sup> (infant dose)
Meta- analysis	15vPCV: 1,186 13vPCV: 1,189	Included PNEU-PED-EU-1 and PNEU-PED-EU-2; assessed GMR toddler dose.			

Source: Compiled from Section 2 of the submission.

13vPCV = 13 valent pneumococcal conjugate vaccine; 15vPCV = 15 valent pneumococcal conjugate vaccine; 20vPCV= 20 valent pneumococcal conjugate vaccine; DB = double blind; IgG = Immunoglobulin G; GMFR = geometric mean fold rise; GMR = geometric mean ratio; MC = multi centre; OL = open label; OPA = opsonophagocytic activity; R = randomised.

Text in italics was sourced in the evaluation.

<sup>a</sup> Common comparator.

<sup>b</sup> Defined in the submission as a percentage of participants with predefined pneumococcal serotype-specific IgG concentrations.

<sup>c</sup> The B7471013 trial was a safety trial. No immunogenicity outcomes were evaluated.

<sup>d</sup> The B7471003 trial was a phase II trial not powered to assess non-inferiority for immunogenicity outcomes. Therefore, immunogenicity outcomes were deemed as secondary.

<sup>e</sup> Assessed with Risk Of Bias In Non-randomised Studies - of Interventions tool (ROBINS-I).

- 6.12 The submission conducted a meta-analysis of two RCTs comparing 15vPCV and 13vPCV, 2+1 schedule: PNEU-PED-EU-1, PNEU-PED-EU-2.
- 6.13 The submission presented two indirect comparisons of 20vPCV and 15vPCV using 13vPCV as the common comparator:
- Indirect comparison 1 (2+1 schedule): trial B7471012 compared with a meta-analysis of trials PNEU-PED-EU-1 and PNEU-PED-EU-2.
  - Indirect comparison 2 (3+1 schedule): trial B7471011 vs PNEU-PED.
- 6.14 It was unclear why trial B7471003 was not considered for indirect comparison 2 given it was also an RCT studying the 3+1 schedule.
- 6.15 The trials were not analysed on an intent-to-treat basis, rather they were analysed based on the evaluable immunogenicity populations, defined as:
- All eligible randomised participants.
  - Within the protocol-defined window for dose 1 (not B7471014).
  - Received the randomised vaccine.
  - One valid immunogenicity result one month after evaluation dose.
  - Blood collection appropriate window for a visit.
  - No major protocol deviations.
- 6.16 The percentage of participants analysed was similar between trial arms but differed between trials. The B7471012 trial analysed between 82.4% and 83.4% of participants after the toddler dose. Whereas the B7471011 trial analysed between 75.0% and 75.2%, and the B7471003 trial analysed between 72.4% and 72.8%.
- 6.17 Overall, the risk of bias was considered low for all 20vPCV randomised trials (B7471012, B7471011, B7471013, and B7471003) and the single arm study B7471014. The 15vPCV trials (PNEU-PED-EU-1, PNEU-PED-EU-2, and PNEU-PED) were previously considered by the PBAC and were reported to have a low risk of bias (Table 3, pneumococcal conjugate vaccine, 15 valent adsorbed, PSD, March 2023 PBAC meeting). The ESC considered the trial evidence presented in the submission was reliable and had a low risk of bias, however noted that the evidence did not include the Aboriginal and Torres Strait Islander population or children with risk conditions.
- 6.18 The trials were similar in terms of trial design. The submission identified several sources of heterogeneity across the trials, such as countries included in the trials, assay methods, statistical methods, ethnicity, and concomitant vaccines. Additionally, minor differences were observed in recruitment age, inclusion of preterm infants, and age at administration of infant and toddler doses.
- 6.19 Key efficacy outcomes in the trials were immunological responses and included:

- Serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMC) and geometric mean ratios (GMRs) one month after the infant and toddler doses.
  - Percentages of participants with predefined pneumococcal IgG levels (response rate) one month after the infant and toddler doses, where the 20vPCV trials used  $\geq 0.35 \mu\text{g/ml}$  for all serotypes except serotype 5  $\geq 0.23 \mu\text{g/ml}$ , serotype 6B  $\geq 0.1 \mu\text{g/ml}$  and serotype 19A  $\geq 0.12 \mu\text{g/ml}$ ; and the 15vPCV trials used  $\geq 0.35 \mu\text{g/ml}$  for all serotypes.
  - Opsonophagocytic activity (OPA) geometric mean titre (GMT) in a subset of patients one month after the infant and toddler doses. OPA was not a primary outcome in the key 20vPCV trials (B7471012 and B7471011), it was only collected for a subset of patients (approximately between 10% to 20%) and was not used in the indirect comparisons.
- 6.20 Non-inferiority margins from the B7471012, B7471011, PNEU-PED-EU-1, PNEU-PED-EU-2, and PNEU-PED trials are presented in Table 8.

**Table 8: Non-inferiority margins proposed in the submission**

	Outcome		
	GMR one month after infant dose	GMR one month after toddler dose	Response rate one month after infant dose
Non-inferiority margin	The lower bound of the 2-sided 95% CI for the IgG GMR of 20vPCV to 13vPCV was greater than 0.5 (2-fold non-inferiority margin)		The lower bound of the 2-sided 95% CI for the difference (20vPCV – 13vPCV) in percentages, computed using the Miettinen and Nurminen method, was greater than -10%
Method of comparing non-13vPCV serotypes	B7471012, B7471011, and PNEU-PED: compared non-13vPCV serotypes of the 20vPCV arm to the lowest GMR or response rate of 13vPCV serotypes from the 13vPCV arm, except for serotype 3. PNEU-PED-EU-1, and PNEU PED-EU-2: compared non-13vPCV serotypes of the 20vPCV arm GMR or response rate to matched serotypes from the 13vPCV arm		
ATAGI Advice to the PBAC	<ul style="list-style-type: none"> <li>WHO guidelines suggest a lower bound of 0.67, and authorities may consider 0.5 (p46 of the ATAGI Advice to the PBAC).</li> <li>Comparisons at a margin of 0.5 make interpretation of the clinical relevance of immunological measures increasingly difficult, i.e., 'by approving vaccines based on non-inferiority to a prior vaccine, which itself was justified based on non-inferiority, it is possible that subsequent vaccines could be accepted despite having inferior immunogenicity to an originally licensed vaccine' (p46 of the ATAGI Advice to the PBAC).</li> <li>The WHO guidelines raise the concern of potential downward drift for sequential non-inferiority evaluations (p46 of the ATAGI Advice to the PBAC).</li> <li>For listing 13vPCV 'serotype 3 did not meet non-inferiority for IgG Responders or IgG GMCs, and OPA GMTs', showing the potential of downward drift' (p47 of the ATAGI Advice to the PBAC).</li> </ul>		'WHO documents indicate that there are concerns regarding uncertain applicability across all serotypes (correlates of protection for children vary by serotype), and in different populations, and that this level should not be taken alone as the sole consideration for licensure' (p46 of the ATAGI Advice to the PBAC).

Source: Compiled from Section 2.4 of the submission; PNEU-PED-EU-1, PNEU-PED-EU-2, & PNEU-PED study protocols.

13vPCV = 13 valent pneumococcal conjugate vaccine; 20vPCV = 20 valent pneumococcal conjugate vaccine; ATAGI = Australian Technical Advisory Group on Immunisation; CI = confidence interval; GMC = geometric mean concentration; GMR = geometric mean ratio; GMT = geometric mean titre; IgG = immunoglobulin G; OPA = opsonophagocytic activity; PBAC = Pharmaceutical Benefits Advisory Committee; Public Summary Document = PSD.

### **Comparative effectiveness**

6.21 Table 9 shows GMRs one month after the toddler dose for the evaluable immunogenicity population in the 20vPCV and 15vPCV trials presented by the submission. GMR after the toddler dose was used for the indirect comparisons.

Table 9: Pneumococcal IgG GMRs (95%CI) – 1 month after toddler dose –evaluable immunogenicity population<sup>a</sup>

Serotype	20vPCV/13vPCV		15vPCV/13vPCV		
	B7471012 (2+1)	B7471011 (3+1)	PNEU-PED-EU-1 (2+1)	PNEU-PED-EU-2 (2+1)	PNEU-PED (3+1)
<b>13vPCV</b>					
1	0.67 (0.60, 0.75)	0.69 (0.63, 0.76)	0.62 (0.57, 0.68)	0.58 (0.54, 0.63)	0.66 (0.62, 0.72)
3	0.66 (0.59, 0.73)	0.66 (0.61, 0.73)	1.28 (1.17, 1.39)	1.31 (1.2, 1.43)	1.35 (1.25, 1.46)
4	0.77 (0.68, 0.87)	0.78 (0.70, 0.86)	0.75 (0.68, 0.82)	0.7 (0.63, 0.78)	0.77 (0.71, 0.84)
5	0.72 (0.64, 0.81)	0.74 (0.67, 0.82)	0.64 (0.59, 0.7)	0.62 (0.56, 0.68)	0.63 (0.58, 0.69)
6A	0.66 (0.57, 0.75)	0.77 (0.70, 0.85)	0.68 (0.61, 0.76)	0.6 (0.54, 0.67)	0.6 (0.54, 0.65)
6B	0.57 (0.48, 0.67)	0.7 (0.62, 0.79)	0.95 (0.85, 1.07)	0.89 (0.79, 1)	0.74 (0.67, 0.81)
7F	0.73 (0.67, 0.80)	0.76 (0.70, 0.82)	0.79 (0.72, 0.85)	0.74 (0.69, 0.81)	0.7 (0.65, 0.77)
9V	0.73 (0.66, 0.81)	0.8 (0.73, 0.88)	0.72 (0.66, 0.76)	0.7 (0.64, 0.76)	0.73 (0.67, 0.80)
14	0.8 (0.69, 0.92)	0.9 (0.81, 1.00)	0.75 (0.67, 0.83)	0.78 (0.7, 0.87)	0.81 (0.73, 0.89)
18C	0.75 (0.67, 0.84)	0.74 (0.67, 0.82)	0.88 (0.8, 0.95)	0.85 (0.77, 0.92)	0.85 (0.78, 0.93)
19A	0.82 (0.72, 0.93)	0.85 (0.77, 0.94)	0.83 (0.75, 0.91)	0.74 (0.68, 0.82)	0.74 (0.68, 0.80)
19F	0.77 (0.68, 0.87)	0.86 (0.78, 0.96)	0.88 (0.8, 0.97)	0.79 (0.72, 0.87)	0.79 (0.74, 0.86)
23F	0.6 (0.52, 0.69)	0.64 (0.57, 0.72)	0.87 (0.79, 0.97)	0.9 (0.81, 1)	0.61 (0.56, 0.68)
<b>Additional</b>					
8	1.48 (1.32, 1.66)	1.87 (1.71, 2.06)	Not applicable		
10A	2.02 (1.77, 2.30)	2.94 (2.64, 3.26)			
11A	1.55 (1.37, 1.75)	1.67 (1.51, 1.84)			
12F	0.77 (0.68, 0.87)	0.88 (0.79, 0.97)			
15B	5.42 (4.82, 6.10)	5.95 (5.39, 6.55)			
22F <sup>b</sup>	3.84 (3.40, 4.34)	5.01 (4.54, 5.52)	71.79 (65.16, 79.1)	68.34 (61.73, 75.65)	4.69 (4.30, 5.11)
33F <sup>b</sup>	2.64 (2.33, 2.99)	4.4 (3.99, 4.85)	46.58 (42.19, 51.42)	48.99 (44.45, 54.01)	2.59 (2.36, 2.83)

Source: Compiled from Section 2.5 of the submission.

13vPCV = 13 valent pneumococcal conjugate vaccine; 15vPCV = 15 valent pneumococcal conjugate vaccine; 20vPCV = 20 valent pneumococcal conjugate vaccine; CI = confidence interval; GMR = geometric mean ratio; IgG = immunoglobulin G.

Red indicates that non-inferiority criteria was not met (<0.5), green indicates superiority with a lower CI limit >2. Blue indicates already seen by the PBAC.

<sup>a</sup> Trials B7471013 and B7471003 are not presented as the trials did not present GMRs or evaluate non-inferiority.

<sup>b</sup> Trials PNEU-PED-EU-1 and PNEU-PED-EU-2 made 20vPCV comparisons against matched 13vPCV serotypes. Other trials made the comparison against the lowest GMC of shared 13vPCV serotype, except for serotype 3.

6.22 The ESC noted that in the B7471012 trial (2+1 schedule) serotype 6B (included in 13vPCV) did not meet the non-inferiority criteria after the toddler dose for the GMR. The additional serotypes 15B, 22F and 33F had a confidence interval (CI) lower bound greater than two, indicating superiority. In addition, in the B7471012 trial serotypes 6A, 6B, 9V and 23F (included in 13vPCV) did not meet the non-inferiority criteria after the infant doses for the GMR and response rate (results not shown). Serotypes 1, 3, 4, and 5 did not meet the non-inferiority criteria after the infant dose for the response rate (results not shown). Serotypes 8, 10A, 11A, 12F, and 33F did not meet the superiority criteria in a primary outcome. Serotypes 10A (2+1 schedule) and 12F (2+1 and 3+1 schedules) (unique to 20vPCV) also did not meet the non-inferiority criteria for the response rate (results not shown). The ESC considered the differences in response rates were minor for most serotypes, except serotype 3, with a difference of -10.6% (95%CI -14.7%, -6.7%).

- 6.23 In the B7471011 trial (3+1 schedule) all serotypes met the non-inferiority criteria after the toddler and infant doses for the GMR. However, serotypes 1, 3, 4, 9V, and 23F (included in 13vPCV) and serotype 12F (unique to 20vPCV) did not meet the non-inferiority criteria for the response rate after the infant doses (results not shown). The ESC noted that serotype 3 had the largest difference in the response rate for the toddler dose with -12.1% (95%CI -16.2%, -8.1%).
- 6.24 The submission provided supporting evidence for serotypes that did not meet the non-inferiority criteria. The submission noted that based on the supportive data, the immune responses of 20vPCV were expected to be similarly protective as serotypes that met non-inferiority using the totality of data. The ATAGI Advice to the PBAC noted that there may be a risk window relative to 13vPCV between infant and toddler doses (p66 of the ATAGI Advice to the PBAC). Although real-world evidence exists for 13vPCV indicating protection between the infant and toddler doses, it was uncertain if this evidence would apply to 20vPCV (p66 of the ATAGI Advice to the PBAC).
- 6.25 The Pre-Sub-Committee Response (PSCR) acknowledged that several serotypes did not meet the non-inferiority criteria after the second infant dose in the B7471012 pivotal trial for both primary parameters. However, the PSCR argued that following the toddler booster dose, the difference between treatment groups decreased and non-inferiority was met for most of the serotypes. The PSCR emphasised the importance of the toddler dose, in addition to the infant series, for the overall suppression of pneumococcal disease in children of all ages. However, the PSCR acknowledged the concerns that lower immunogenicity after dose 2 could result in lower vaccine efficacy in the window between the last infant dose and the toddler dose.
- 6.26 In response to these concerns, the sponsor conducted trade-off analyses. The analyses sought to determine the minimum vaccine effectiveness (VE) for the 7 additional 20vPCV serotypes that would be required to offset any potential increase in breakthrough cases that could occur for the shared serotypes that did not meet the non-inferiority criteria on one or more endpoints after dose 2. The analysis assumed 50-75% less vaccine efficacy for the serotypes that did not meet a non-inferiority endpoint. The base case analysis estimated that a minimum vaccine efficacy of 10-22% would be required for the 7 additional serotypes to offset potential breakthrough cases due to a reduction of 50-75% in vaccine efficacy for the serotypes that did not meet a non-inferiority endpoint. The PSCR concluded that even with conservative assumptions of low vaccine efficacy and increased probability of breakthrough disease, the number of cases predicted to be averted by 20vPCV is still likely to exceed the number of cases that could re-emerge due to lowered vaccine efficacy associated with the serotypes that did not meet a non-inferiority endpoint.
- 6.27 The ESC considered the trade-off analysis presented in the PSCR appeared clinically and mathematically reasonable. However, considered that based on the clinical trial evidence there remained a risk window of lower vaccine efficacy relative to 13vPCV between the last infant dose and the toddler booster dose. The ESC considered the

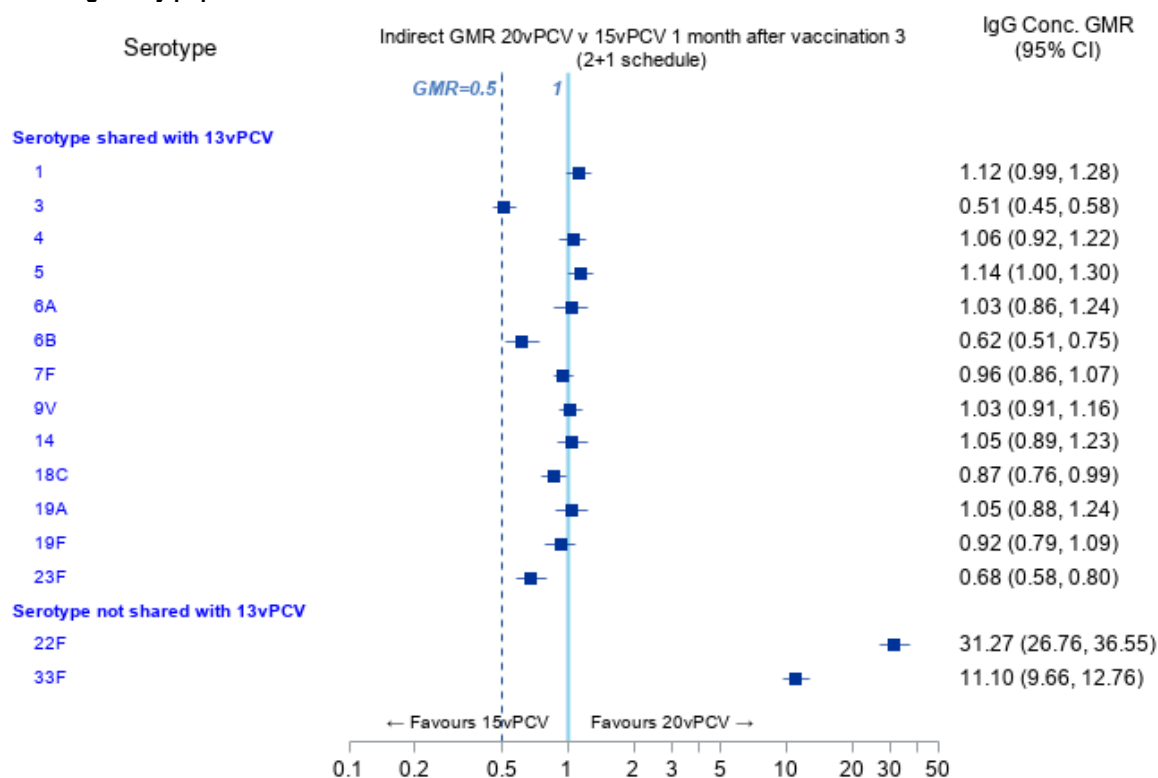
data provided in the PSCR for the observed cases of IPD in Australia suggested that the potential clinical impact associated with serotype 3 was meaningful. The ESC considered the number of additional serotype 3 infections that could emerge in children as a result of lower vaccine efficacy was uncertain but had the potential to be important.

- 6.28 The single-arm study B7471014 showed that 20vPCV improved primary outcomes in all cohorts compared to baseline (prior vaccination with 13vPCV).

**Indirect comparisons**

- 6.29 The submission conducted a meta-analysis of GMRs in the 15vPCV (2+1 schedule) trials: PNEU-PED-EU-1 and PNEU-PED-EU-2. The meta-analysis showed all shared serotypes had GMRs less than one, favouring 13vPCV, except for serotypes 3 and 6B. Serotype 6B had an upper CI bound of one, meaning no vaccine was favoured. Serotype 3 had a GMR and a lower bound CI greater than one, favouring 15vPCV, but clinical significance was not supported (lower CI bound greater than two). Substantial heterogeneity was observed for serotypes 6A and 19A with  $I^2$  of 61% and 64% and chi-square p-values of 0.11 and 0.09, respectively. Moderate heterogeneity was observed for serotype 19F, with an  $I^2$  of 59% and a chi-square p-value of 0.12.
- 6.30 The submission presented two indirect comparisons between 20vPCV and 15vPCV using 13vPCV as the common comparator using the Bucher method.
- 6.31 Indirect comparison results for the 2+1 schedule with the B7471012 20vPCV trial and the PNEU-PED-EU-1 and PNEU-PED-EU-2 15vPCV trials using GMR after the toddler dose for evaluable immunogenicity populations are presented in Figure 1.

Figure 1: Indirect comparison results of GMR one month after the toddler dose for 2+1 schedule – evaluable immunogenicity population

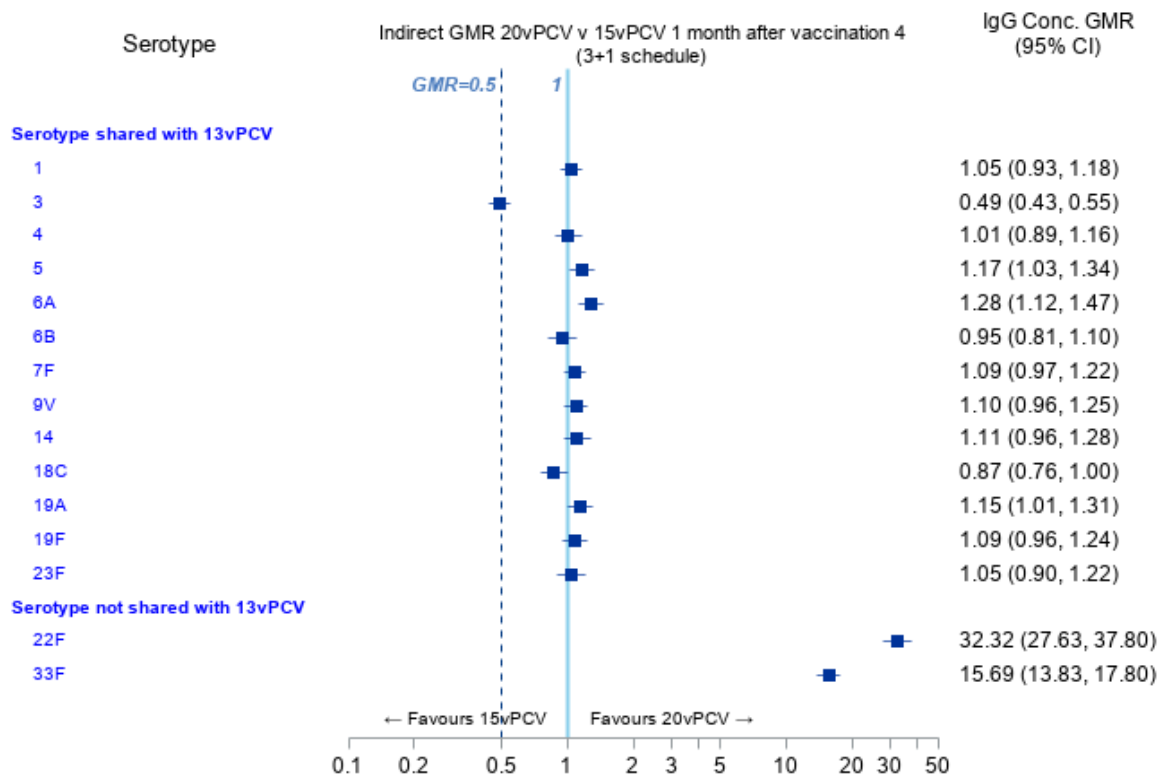


Source: Figure 2.6.5, p309 of the submission.

13vPCV = 13 valent pneumococcal conjugate vaccine; 15vPCV = 15 valent pneumococcal conjugate vaccine; 20vPCV = 20 valent pneumococcal conjugate vaccine; CI = confidence interval; GMR = geometric mean ratio; SE = standard error.

6.32 Indirect comparison results for the 3+1 schedule with the B7471011 20vPCV trial and the PNEU-PED 15vPCV trial using GMR after the toddler dose for evaluable immunogenicity populations are presented Figure 2.

Figure 2: Indirect comparison results of GMR one month after the toddler dose for 3+1 schedule – evaluable immunogenicity population



Source: Figure 2.6.6, p311 of the submission.

13vPCV = 13 valent pneumococcal conjugate vaccine; 15vPCV = 15 valent pneumococcal conjugate vaccine; 20vPCV = 20 valent pneumococcal conjugate vaccine; CI = confidence interval; GMR = geometric mean ratio; SE = standard error.

- 6.33 The submission claimed that both indirect comparisons showed non-inferiority of 20vPCV to 15vPCV for every 13vPCV serotype, except serotype 3. The ESC considered that this was reasonable.
- 6.34 The submission claimed that 20vPCV was superior to 15vPCV in the additional 5 serotypes as well as the 2 serotypes contained in 15vPCV but not 13vPCV (22F and 33F). The ESC considered that this was reasonable.
- 6.35 The submission acknowledged that not meeting the non-inferiority criteria in the indirect comparisons for serotype 3 or the observed superiority for serotypes 22F and 33F might be due to transitivity issues.
- 6.36 Table 10 presents a summary of evidence in the submission regarding GMR one month after the toddler dose indicating if the non-inferiority criteria were met comparing 20vPCV against 13vPCV or 15vPCV.

Table 10: Summary demonstrating if non-inferiority criteria were met across serotypes evaluated for GMR one month after the toddler dose

Serotype	20vPCV vs 13vPCV		20vPCV vs 15vPCV (indirect comparison)	
	B7471012 (2+1 schedule)	B7471011 (3+1 schedule)	2+1 schedule	3+1 schedule
<b>13vPCV</b>				
1	Y (13v)	Y (13v)	Y	Y
3	Y (13v)	Y (13v)	N	N
4	Y (13v)	Y (13v)	Y	Y
5	Y (13v)	Y (13v)	Y (20v)	Y (20v)
6A	Y (13v)	Y (13v)	Y	Y (20v)
6B	N	Y (13v)	Y (15v)	Y
7F	Y (13v)	Y (13v)	Y	Y
9V	Y (13v)	Y (13v)	Y	Y
14	Y (13v)	Y	Y	Y
18C	Y (13v)	Y (13v)	Y (15v)	Y
19A	Y (13v)	Y (13v)	Y	Y (20v)
19F	Y (13v)	Y (13v)	Y	Y
23F	Y (13v)	Y (13v)	Y (15v)	Y
<b>Additional</b>				
8	Y (20v)	Y (20v)	Not applicable	
10A	Y (20v)	Y (20v)		
11A	Y (20v)	Y (20v)		
12F	Y (13v)	Y (13v)		
15B	Y (20v)	Y (20v)		
22F	Y (20v)	Y (20v)	Y (20v)	Y (20v)
33F	Y (20v)	Y (20v)	Y (20v)	Y (20v)

Source: Compiled from Section 2.5 of the submission.

13vPCV = 13 valent pneumococcal conjugate vaccine; 15vPCV = 15 valent pneumococcal conjugate vaccine; 20vPCV = 20 valent pneumococcal conjugate vaccine; vs = versus.

Red indicates that non-inferiority criteria was not met (<0.5), green indicates superiority with a lower CI limit >2.

(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.

### Comparative harms

6.37 A summary of adverse events is presented in Table 11.

Table 11: Summary of key adverse events in the trials

Trial	Dose	20vPCV or 15vPCV, n/N (%)	13vPCV, n/N (%)	Difference (95% CI)
<b>Any AE, Dose 1 to one month after dose 2</b>				
B7471012	Any	83/601 (13.8)	87/603 (14.4)	NR
<b>Any AE, Dose 3 to one month after dose 3</b>				
B7471012	Any	91/588 (15.5)	98/594 (16.5)	NR
<b>Any AE, Dose 1 to one month after dose 3</b>				
B7471011	Any	366/1001 (36.6)	389/988 (39.4)	NR
B7471013	Any	296/1,000 (29.6)	139/503 (27.6)	NR
<b>Any AE, Dose 4 to one month after dose 4</b>				
B7471011	Any	129/853 (15.1)	126/841 (15.0)	NR
B7471013	Any	139/923 (15.1)	73/461 (15.8)	NR
<b>Any AE</b>				
B7471003	Any	154/231 (66.7)	153/227 (67.4)	NR
PNEU-PED-EU-1	Any	138/587 (28.5)	81/591 (13.8)	14.7 (NR)
PNEU-PED-EU-2	Any	236/595 (39.7)	187/594 (31.5)	8.2 (NR)
PNEU-PED	Any	234/858 (27.3)	214/855 (25.0)	2.3 (NR)
<b>Any SAE</b>				
B7471012	Any	34/601 (5.7)	40/603 (6.6)	NR
B7471011	Any	45/1001 (4.5)	31/988 (3.1)	NR
B7471013	Any	44/1000 (4.4)	28/503 (5.6)	NR
B7471003	Any	12/231 (5.2)	5/227 (2.2)	NR
PNEU-PED-EU-1	Any	57/587 (9.7%)	70/591 (11.8%)	- 2.1 (-5.7, 1.4)
PNEU-PED-EU-2	Any	30/595 (5.0%)	28/594 (4.7%)	0.3 (-2.2, 2.8)
PNEU-PED	Any	88/858 (10.3%)	81/855 (9.5%)	0.8 (NR)
<b>NDCMC</b>				
B7471012	Any	6/601 (1.0)	6/603 (1.0)	NR
B7471011	Any	50/1001 (5.0)	58/988 (5.9)	NR
B7471013	Any	28/1000 (2.8)	14/503 (2.8)	NR
B7471003	Any	12/231 (5.2)	8/227 (3.5)	NR
PNEU-PED-EU-1	Any	NR	NR	NR
PNEU-PED-EU-2	Any	NR	NR	NR
PNEU-PED	Any	NR	NR	NR

Source: Compiled from Section 2.5 of the submission; trials B7471011, B7471012, B7471013, & B7471003 clinical study reports; Table 6, paragraph 6.20, pneumococcal conjugate vaccine, 15 valent adsorbed, PSD, March 2023 PBAC meeting.

Blue indicates previously seen by the PBAC.

13vPCV = 13 valent pneumococcal conjugate vaccine; 15vPCV = 15 valent pneumococcal conjugate vaccine; 20vPCV = 20 valent pneumococcal conjugate vaccine; AE = adverse event; CI = confidence interval; NDCMC = newly diagnosed chronic medical conditions; NR = not reported; SAE = serious adverse event.

6.38 A summary of local and systemic reactions is presented in Table 12.

**Table 12: Summary of local and systemic reactions in the trials**

Trial	Dose	20vPCV or 15vPCV, n/N (%)	13vPCV, n/N (%)	Difference (95% CI)
<b>Local Reaction</b>				
B7471012	Dose 1	284/598 (47.5)	284/603 (47.1)	0.4 (-5.2, 6.0)
	Dose 2	260/592 (43.9)	255/594 (42.9)	1.0 (-4.6, 6.6)
	Dose 3	347/580 (59.8)	334/586 (57.0)	2.8 (-2.8, 8.5)
	Dose 4	NA	NA	NA
B7471011	Dose 1	594/993 (59.8)	550/974 (56.5)	3.4 (-1.0, 7.7)
	Dose 2	499/940 (53.1)	487/924 (52.7)	0.4 (-4.1, 4.9)
	Dose 3	464/914 (50.8)	442/901 (49.1)	1.7 (-2.9, 6.3)
	Dose 4	370/826 (44.8)	374/815 (45.9)	-1.1 (-5.9, 3.7)
B7471013	Dose 1	512/992 (51.6)	267/498 (53.6)	-2.0 (-7.3, 3.4)
	Dose 2	436/952 (45.8)	238/485 (49.1)	-3.3 (-8.7, 2.2)
	Dose 3	363/940 (38.6)	191/477 (40.0)	-1.4 (-6.8, 3.9)
	Dose 4	362/892 (40.6)	192/454 (42.3)	-1.7 (-7.3, 3.8)
B7471003	Dose 1	139/229 (60.7)	140/224 (62.5)	NR
	Dose 2	109/215 (50.7)	121/204 (59.3)	NR
	Dose 3	110/201 (54.7)	121/204 (59.3)	NR
	Dose 4	91/186 (48.9)	88/185 (47.6)	NR
PNEU-PED-EU-1	Any	427/587 (72.7%)	398/591 (67.3%)	5.4 (NR)
PNEU-PED-EU-2	Any	525/595 (88.2%)	531/594 (89.4%)	-1.2 (NR)
PNEU-PED	Any	598/858 (69.7%)	595/855 (69.6%)	0.1 (NR)
<b>Systemic reactions</b>				
B7471012	Dose 1	516/598 (86.3)	522/603 (86.6)	-0.3 (-4.2, 3.6)
	Dose 2	494/592 (83.4)	488/594 (82.2)	1.3 (-3.0, 5.6)
	Dose 3	482/580 (83.1)	477/586 (81.4)	1.7 (-2.7, 6.1)
	Dose 4	NA	NA	NA
B7471011	Dose 1	853/993 (85.9)	823/974 (84.5)	1.4 (-2.8, 5.6)
	Dose 2	771/940 (82.0)	744/924 (80.5)	1.5 (-2.0, 5.1)
	Dose 3	676/914 (74.0)	654/901 (72.6)	1.4 (-2.7, 5.4)
	Dose 4	585/826 (70.8)	580/815 (71.2)	-0.3 (-4.7, 4.1)
B7471013	Dose 1	837/992 (84.4)	414/498 (83.1)	1.2 (-2.6, 5.4)
	Dose 2	748/952 (78.6)	385/485 (79.4)	-0.8 (-5.1, 3.8)
	Dose 3	645/940 (68.6)	321/477 (67.3)	1.3 (-3.8, 6.5)
	Dose 4	590/892 (66.1)	309/454 (68.1)	-1.9 (-7.1, 3.4)
B7471003	Dose 1	200/229 (87.3)	204/224 (91.1)	NR
	Dose 2	175/215 (81.4)	183/204 (89.7)	NR
	Dose 3	156/201 (77.6)	166/204 (81.4)	NR
	Dose 4	130/186 (69.9)	136/185 (73.5)	NR
PNEU-PED-EU-1	Any	536/587 (91.3%)	526/591 (89.0%)	2.3 (NR)
PNEU-PED-EU-2	Any	588/595 (98.8%)	587/594 (98.8%)	0
PNEU-PED	Any	785/858 (91.5%)	766/855 (89.6%)	1.9 (NR)

Source: Compiled from Section 2.5 of the submission; trials B7471011, B7471012, B7471013, & B7471003 clinical study reports; Table 6, paragraph 6.20, pneumococcal conjugate vaccine, 15 valent adsorbed, PSD, March 2023 PBAC meeting.

Blue indicates previously seen by the PBAC.

13vPCV = 13 valent pneumococcal conjugate vaccine; 15vPCV = 15 valent pneumococcal conjugate vaccine; 20vPCV = 20 valent pneumococcal conjugate vaccine; CI = confidence interval; NR = not reported.

6.39 The submission stated that local reactions, systemic events, adverse events, serious adverse events, and newly diagnosed chronic medical conditions were generally similar between groups of 20vPCV trials.

6.40 The submission noted that 20vPCV in study B7471014 (single dose) was well tolerated.

- 6.41 The ESC considered that overall, the safety profiles of 20vPVC and 13vPVC appear similar, however the ESC noted that no specific safety data are available for those considered at risk as per the NIP or for Aboriginal and Torres Strait Islander people.

### **Benefits/harms**

- 6.42 A benefits and harms table is not presented as the submission made a claim of non-inferiority for the shared serotypes, and the superiority claims for additional serotypes were based on immunogenicity data.

### **Clinical claim**

- 6.43 The submission claimed that in the paediatric populations who are currently eligible for funded 13vPCV under the NIP, 20vPCV has equivalent immunogenicity, and by extrapolation efficacy, against IPD, pneumococcal pneumonia and otitis media, for the shared serotypes with 13vPCV and 15vPCV but is superior for the additional serotypes contained in 20vPCV and not in 13vPCV or 15vPCV.
- 6.44 The claim of non-inferior effectiveness was based on comparative immunogenicity data, where non-inferiority was not proven for all serotypes. The ATAGI Advice to the PBAC stated ‘that the clinical significance of missing some non-inferiority criteria is unknown. However, the use of a bridge to a bridge also raises concerns regarding the potential for downward drift, and whether the immunological/clinical relationship will still hold for 20vPCV. It is also unknown whether the lower immunological responses seen with 20vPCV will impact duration of protection’ (ATAGI Advice to the PBAC). The PSCR argued that real-world effectiveness studies and data from surveillance systems globally following the introduction of 13vPCV demonstrated that missing non-inferiority comparisons in the 13vPCV clinical development program for serotypes 6B, 9V or 23F vs 7vPCV did not translate into lower effectiveness or breakthrough disease<sup>2</sup>. The PSCR also argued that similar evidence has been reported for 10vPCV, despite lower immunogenicity compared to 13vPCV and 7vPCV<sup>3,4</sup>.
- 6.45 The ATAGI Advice to the PBAC discussed that serotype 3 missed the non-inferiority criteria for the difference in IgG response rates after the final infant dose in both the B7471011 and B7471012 trials, and although response rate was not assessed for non-inferiority after the final toddler dose in either trial, a larger difference between 20vPCV and 13vPCV was observed in these trials for serotype 3 than other matched

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<sup>2</sup> Savulescu C, Krizova P, Valentiner-Branth P, et al. Effectiveness of 10 and 13-valent pneumococcal conjugate vaccines against invasive pneumococcal disease in European children: SplDnet observational multicentre study. *Vaccine*. 2022;40(29):3963-74.

<sup>3</sup> Savulescu C, Krizova P, Valentiner-Branth P, et al. Effectiveness of 10 and 13-valent pneumococcal conjugate vaccines against invasive pneumococcal disease in European children: SplDnet observational multicentre study. *Vaccine*. 2022;40(29):3963-74.

<sup>4</sup> Hanquet G, Krizova P, Dalby T, Ladhani SN, Nuorti JP, Danis K, et al. Serotype replacement after introduction of 10-valent and 13-valent pneumococcal conjugate vaccines in 10 countries, Europe. *Emerg Infect Dis*. 2022;28(1):137-8.

serotypes (2+1 trial: -10.6% (95%CI -14.7%, -6.7%); 3+1 trial: -12.1% (-16.2%, -8.1%)). RDCs displayed a similar distribution of IgG concentrations in both vaccine groups, although the distribution of concentrations for serotype 3 in the 20vPCV group was shifted to the left, indicating an overall lower response. The ATAGI advice stated that overall 'if these data were to correlate with reduced (or even similar) levels of clinical protection as 13vPCV, particularly following the infant series, then 20vPCV would be unlikely to have any additional impact on IPD attributed to serotype 3' (ATAGI Advice to the PBAC).

- 6.46 The Pre-PBAC response acknowledged that 20vPCV provides lower immunogenicity for serotype 3. However, it argued that it is unlikely that other PCVs would offer additional benefit for serotype 3 compared with 20vPCV. The Pre-PBAC response emphasised that serotype 3 has unique biological properties that make it different and more challenging compared to other serotypes. The Response stated that there is evidence to suggest that serotype 3 has a thick polysaccharide rich capsule which it is able to release (shed) contributing to its increased virulence and ability to escape immune responses, limiting protection offered by anti-serotype 3 antibodies.<sup>5,6</sup> The Response stated that evidence also suggests that a distinct immunological mechanism involving memory B cells may also reduce antibody persistence. The response stated that substantially higher immune responses (up to 8x higher), that are rarely attained from vaccination, are likely to be needed for clinical protection against serotype 3, as noted in the ATAGI advice to the PBAC. The Response argued that as a consequence, the higher valency PCVs are unlikely to have a significant impact on serotype 3 and a different approach is likely needed to address this issue, such as new vaccine development and different vaccination strategies.
- 6.47 The Pre-PBAC response stated that while serotype 3 did not meet non-inferiority for the percent responders to the pre-defined criteria of IgG concentrations over  $\geq 0.35$   $\mu\text{g/ml}$ , functional antibody response for serotype 3 did exceed non-inferiority post-toddler dose in both the B7471012 and B7471011 trials. The Response emphasised that the percent IgG responders  $\geq 0.35$   $\mu\text{g/ml}$  was not a pre-defined estimate and / or endpoint in either the B7471012 or B7471011 trials for the post-toddler dosages. For both pivotal studies, the primary pneumococcal outcomes were the GMR, between 20vPCV and 13vPCV, following the infant and toddler doses, and the response rate following the infant doses. The Response stated that the totality of evidence includes a functional antibody response, as measured by OPA GMTs, induction of adequate priming after 2 infant doses resulting in boosting after the toddler dose, and clear differentiation of 20vPCV RDCs from 13vPCV at all timepoints for serotype 3. The Pre-PBAC Response emphasised that based on these data that 20vPCV is comparable to

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<sup>5</sup> Choi EH, Zhang F, Lu YJ, Malley R. Capsular Polysaccharide (CPS) Release by Serotype 3 Pneumococcal Strains Reduces the Protective Effect of Anti-Type 3 CPS Antibodies. *Clin Vaccine Immunol.* 2015 Dec 16;23(2):162-7.

<sup>6</sup> Luck JN, Tettelin H, Orihuela CJ. Sugar-Coated Killer: Serotype 3 Pneumococcal Disease. *Front Cell Infect Microbiol.* 2020 Dec 23;10:613287.

13vPCV, and that a different impact for the shared serotypes, including serotype 3, is unlikely. Importantly, vaccine effectiveness for the unique serotypes will offer additional benefit versus 13vPCV and 15vPCV ensuring an overall positive risk benefit profile.

- 6.48 The claim of superior effectiveness was based on comparative immunogenicity data, where superiority was not demonstrated for all the additional serotypes of 20vPCV not available in 13vPCV in the RCTs. The PBAC previously noted for 15vPCV that superiority is complex to assess due to difficulties translating immunogenicity to improved clinical protection (paragraph 7.5, pneumococcal conjugate vaccine, 15 valent adsorbed, PSD, March 2023 PBAC meeting). The PSCR noted that the ATAGI Advice to the PBAC stated ‘The claim of superiority to 13vPCV for the additional serotypes appears broadly reasonable’.
- 6.49 Table 13 presents the serotypes that did not meet the non-inferiority criteria of different outcomes or had upper limit of CI greater than two in the B7471012, B7471011 trials or indirect comparisons noting the number of IPD cases.

**Table 13: Serotypes that did not meet a non-inferiority criteria or that indicated superiority in the B7471012, B7471011 trials or indirect comparisons**

Serotype	20vPCV vs 13vPCV				20vPCV vs 15vPCV
	GMR toddler dose	GMR infant dose	Response rate infant dose	Response rate toddler dose <sup>a</sup>	Indirect comparison GMR toddler dose
<b>13vPCV (36%<sup>b</sup> to 43%<sup>c</sup> of cases)</b>					
1					
3 (24% of all cases <sup>d</sup> )					
4					
5					
6A					
6B					
7F					
9V					
14					
18C					
19A					
19F					
23F					
<b>15vPCV additional (to 5%<sup>c</sup> to 10%<sup>b</sup> of cases) <sup>e</sup></b>					
22F					
33F					
<b>20vPCV additional (8%<sup>c</sup> to 9%<sup>b</sup> of cases) <sup>e</sup></b>					
8					
10A					
11A					
12F					
15B					

Source: Compiled from Section 2.5 of the submission; pp71-72 of the ATAGI Advice to the PBAC

13vPCV = 13 valent pneumococcal conjugate vaccine; 15vPCV = 13 valent pneumococcal conjugate vaccine; 20vPCV = 20 valent pneumococcal conjugate vaccine; ATAGI = Australian Technical Advisory Group on Immunisation; GMR = geometric mean ratio; IPD = invasive pneumococcal disease; NNDSS = National Notifiable Diseases Surveillance System; PBAC = Pharmaceutical Benefits Advisory Committee.

Red indicates that non-inferiority criteria was not met.

<sup>a</sup> Not a non-inferiority criteria at this dose, green indicates superiority with a lower CI limit >2.

<sup>b</sup> NNDSS data presented in the ATAGI advice to the PBAC for children under 12 months of age.

<sup>c</sup> NNDSS data presented in the ATAGI advice to the PBAC for children over 12 months to 17 years of age.

<sup>d</sup> Incidence has steadily increased since 2015, despite the inclusion of serotype 3 in 13vPCV. The ATAGI Advice to the PBAC also noted that 20vPCV would unlikely have any additional impact on serotype 3 IPD (p71 of the ATAGI Advice to the PBAC).

<sup>e</sup> Additional serotypes of 20vPCV in the 20vPCV arm were compared to the lowest GMR or response rate of 13vPCV serotypes from the 13vPCV arm, except for serotype 3.

6.50 The submission did not present data for individuals with NIP-funded risk conditions or Aboriginal and Torres Strait Islander children. However, the ATAGI Advice to the PBAC stated that the non-inferiority immunogenicity data versus 13vPCV would reasonably translate to 20vPCV for individuals with NIP-funded risk conditions (ATAGI Advice to the PBAC).

6.51 Overall, consistent with its conclusion for 20vPCV for adults, 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.

6.52 The PBAC considered that, for the population outlined in the proposed listing, the claim of non-inferior comparative safety to 13vPCV and 15vPCV was reasonable.

### **Economic analysis**

6.53 The submission presented a cost-minimisation approach (CMA) based on the claim of equivalent effectiveness and safety compared with 13vPCV and 15vPCV. A CMA was consistent with the clinical claim of non-inferior effectiveness compared to 13vPCV and 15vPCV for shared serotypes and similar safety to 13vPCV.

6.54 The submission presented the CMA based on the nationally negotiated price for 13vPCV of \$1 per dose. Table 14 presents the results of the cost-minimisation approach presented in the submission.

**Table 14: Results of the cost-minimisation approach**

Schedule	2+1			3+1			Single dose		
Population	Children aged 12 months or younger in NSW, VIC, ACT, and TAS, and non-Indigenous children aged 12 months or younger in QLD, NT, WA, and SA <2 years			<ul style="list-style-type: none"> <li>Indigenous children aged 12 months or younger in QLD, NT, WA, and SA &lt; 2 years</li> <li>Children aged 12 months or younger with risk condition</li> </ul>			Infants, children, and adolescents 1-17 years with risk factors		
Vaccine	20vPCV	13vPCV	15vPCV	20vPCV	13vPCV	15vPCV	20vPCV	13vPCV	15vPCV
NNP/Dose (\$)									
Doses administered	3			4			1		
Total vaccine cost/course (\$)	■	■	■	■	■	■	■	■	■
Difference in cost/course (\$)	\$0	-	-	\$0	-	-	\$0	-	-

Source: Table 3.4.1, p336 of the submission.

13vPCV = 13 valent pneumococcal conjugate vaccine; 15vPCV = 15 valent pneumococcal conjugate vaccine; 20vPCV = 20 valent pneumococcal conjugate vaccine; ACT = Australian Capital Territory; NNP = Nationally Negotiated Price; NSW = New South Wales; NT = Northern Territory; QLD = Queensland; SA = South Australia; TAS = Tasmania; VIC = Victoria; WA = Western Australia.

### **Vaccine cost/patient/course**

6.55 The submission applied a cost of \$1 per dose for 20vPCV, 13vPCV and 15vPCV in the economic model and financial estimates. The total cost applied for a 2 + 1 schedule was \$3 and the total cost applied for the 3 + 1 schedule was \$4.

### **Estimated NIP usage & financial implications**

6.56 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impacts associated with the inclusion of 20vPCV on the NIP for paediatric populations. Given that 20vPCV was

expected to replace 13vPCV and 15vPCV a market share approach may have been simpler and therefore more appropriate.

- 6.57 The submission defined four patient populations and applied different uptake rates to each population:
- Population 1: 2+1 schedule in children aged 12 months or younger in NSW, VIC, ACT, and TAS, and non-Indigenous children aged 12 months or younger QLD, NT, WA, and SA.
  - Population 2: 3+1 schedule in Aboriginal and Torres Strait Islander children aged 12 months or younger in QLD, NT, WA, and SA.
  - Population 3: 3+1 schedule in children aged 12 months or younger with NIP-funded risk conditions (existing) i.e., 2+1 schedule plus an additional dose of 20vPCV.
  - Population 4: Single dose in children and adolescents more than 12 months newly diagnosed with NIP-funded risk conditions.
- 6.58 For Population 1, the submission:
- Estimated the population of children aged 12 months or younger in NSW, VIC, ACT, and TAS, and non-Indigenous children aged 12 months or younger in QLD, NT, WA, and SA receiving the first two doses by subtracting the Aboriginal and Torres Strait Islander population in QLD, NT, WA, and SA aged less than 12 months from the total population aged less than 12 months (Population 1A).
  - Estimated the population of toddlers in NSW, VIC, ACT, and TAS, and non-Indigenous toddlers in QLD, NT, WA, and SA receiving the third dose by subtracting the Aboriginal and Torres Strait Islander population in QLD, NT, WA, and SA aged 12 months from the total population aged 12 months (Population 1B).
- 6.59 The same methodology was applied for Population 2. The submission estimated the Aboriginal and Torres Strait Islander children aged 12 months or younger population in QLD, NT, WA, and SA for the first three doses (Population 2A); and the Aboriginal and Torres Strait Islander Indigenous population aged 12 months in QLD, NT, WA, and SA for the fourth dose (Population 2B).
- 6.60 The key inputs used in the financial estimates are presented in Table 15.

**Table 15: Key inputs for financial estimates**

Parameter	Value applied and source	Comment
Eligibility	100%	Eligibility for the NIP is linked to eligibility for Medicare benefits. Assuming all persons identified in ABS data are eligible for Medicare benefits may overestimate the eligible population.
Prevalence of NIP-funded risk conditions	Prevalence of 0.96% based on estimates of prevalence of individual at-risk conditions for pneumococcal disease based on ABS National Health Survey (NHS) 2014/15 data and published data from the UK (for conditions not available in the NHS)	The evaluation considered the sources were reasonable and consistent with the ATAGI Advice to the PBAC. The ATAGI Advice to the PBAC stated that this was not unreasonable, noting the limitations of prevalence data not being available that exactly matches the recommended groups on the NIP (p103 of the ATAGI Advice to the PBAC).
Uptake rate	Population 1: 94.6% for 2 infant doses (<12 months), 92.6% for third (toddler) dose (12 months) based on AIHW. Population 2: 92.4% for 3 infant doses (<12 months), 91.4% for fourth (toddler) dose (12 months) based on AIHW. Population 3: 93.1% based on Kabir 2021 Population 4: 8.9% based on Kabir 2021	The sources used in the PBAC submission were consistent with the ATAGI submission (p103 of the ATAGI Advice to the PBAC). The ATAGI Advice to the PBAC noted the impact of COVID on treatment-seeking behaviour and recommended 2019 NDSS data and 2019-20 AIHW hospitalisation data be used (pp14-16 of the ATAGI Advice to the PBAC). COVID may have also affected vaccination uptake rates. Consistent with the ATAGI Advice for other data sources, 2019 vaccination uptake data may be more appropriate.

Source: Tables 4.1.1 & 4.2.1-4.2.3, pp339-341 of the submission.

ABS = Australian Bureau of Statistics; AIHW = Australian Institute of Health and Welfare; ATAGI = Australian Technical Advisory Group on Immunisation; NHS = National Health Survey; NIP = National Immunisation Program; PBAC = Pharmaceutical Benefits Advisory Committee; UK = United Kingdom.

- 6.61 The submission assumed that 20vPCV would replace 13vPCV for the proposed NIP populations and that a dose of 20vPCV would substitute for a dose of 13vPCV in these populations at the specific time points. The submission also noted that 20vPCV may replace 15vPCV in practice and since 15vPCV was recommended on a cost-minimisation basis to 13vPCV, 15vPCV can be expected to have the same Nationally Negotiated Price as 13vPCV.
- 6.62 The submission assumed that 100% of incident toddlers (Population 1B) in Year 1 would receive their third dose of pneumococcal vaccine as 20vPCV, which would mean interchanging 20vPCV and 13vPCV in the 2+1 schedule.
- 6.63 Table 16 presents the estimated financial implications for including 20vPCV on the NIP.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use – Population 1A (two infant doses of 2+1 schedule)</b>						
Number of patients treated	6	6	6	6	6	6
Number of scripts dispensed <sup>a</sup>	7	7	7	7	7	7
<b>Estimated extent of use – Population 1B (one toddler dose of 2+1 schedule)</b>						
Number of patients treated	6	6	6	6	6	6
Number of scripts dispensed <sup>b</sup>	6	6	6	6	6	6
<b>Estimated extent of use – Population 2A (three infant doses of 3+1 schedule)</b>						
Number of patients treated	2	3	3	3	3	3
Number of scripts dispensed <sup>c</sup>	4	5	5	5	5	5
<b>Estimated extent of use – Population 2B (one toddler dose of 3+1 schedule)</b>						
Number of patients treated	2	2	3	3	3	3
Number of scripts dispensed <sup>b</sup>	2	2	3	3	3	3
<b>Estimated extent of use – Population 3 (additional dose for children aged 12 months or younger with existing NIP-funded risk conditions)</b>						
Number of patients treated	1	1	1	1	1	1
Number of scripts dispensed <sup>d</sup>	1	1	1	1	1	1
<b>Estimated extent of use – Population 4 (additional dose for children and adolescents newly diagnosed with NIP-funded risk conditions)</b>						
Number of patients treated	1	2	2	2	2	2
Number of scripts dispensed <sup>d</sup>	1	2	2	2	2	2
<b>Total script numbers – 20vPCV</b>						
Total script numbers – 20vPCV	8	8	8	8	8	8
<b>Estimated financial implications 20vPCV</b>						
Cost to NIP	9	9	9	9	9	9
<b>Estimated financial implications for 13vPCV (and 15vPCV)</b>						
Cost to NIP	-10	-10	-10	-10	-10	-10
<b>Net financial implications</b>						
Net cost to NIP	11	11	11	11	11	11
Net cost to MBS	11	11	11	11	11	11
Net cost to Government	11	11	11	11	11	11

Source: Tables 4.2.4, 4.2.5, 4.3.3 & 4.4.1, pp341-342, 344 & 346-347 of the submission; Sheets '3a. Scripts – proposed and 4a. Scripts – affected' of the Section 4 workbook.

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.

<sup>a</sup> Assuming two infant vaccines per patient as estimated by the submission.

<sup>b</sup> Assuming one toddler vaccine per patient as estimated by the submission.

<sup>c</sup> Assuming three infant vaccine per patient as estimated by the submission.

<sup>d</sup> Assuming one additional vaccine for patients with an NIP-funded risk condition.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> 5,000 to < 10,000

<sup>3</sup> 10,000 to < 20,000

<sup>4</sup> 20,000 to < 30,000

<sup>5</sup> 30,000 to < 40,000

<sup>6</sup> 300,000 to < 400,000

<sup>7</sup> 600,000 to < 700,000

<sup>8</sup> 1,000,000 to < 2,000,000

<sup>9</sup> \$80 million to < \$90 million

<sup>10</sup> net cost saving

<sup>11</sup> \$0 to < \$10 million

6.64 Populations 1A and 1B represent the same patient population (2+1 schedule in children aged 12 months or younger in NSW, VIC, ACT, and TAS, and non-Indigenous children aged 12 months or younger QLD, NT, WA, and SA). However, Population 1B

had more patients during Year 2 and beyond than existed in Population 1A during Year 1 and beyond. This was due to the way patient cohorts were estimated (see Paragraphs 6.58 and 6.59 for further detail).

- 6.65 The number of persons estimated on sheet '8. ABS population' of the financial estimates workbook did not match the source provided (ABS 3222.0 – Series B, years 2012 to 2030). The number of patients in Populations 1 and 3 were overestimated and the number of patients in Population 4 were underestimated. As a result, the number of 20vPCV vaccines dispensed, the total cost of 20vPCV to the NIP and the total cost offsets for 13vPCV and 15vPCV to the NIP were all overestimated.
- 6.66 The ATAGI Advice to the PBAC stated that 'It is expected that the programmatic requirements for 20vPCV would be the same as for 13vPCV (or 15vPCV) and the vaccination would be delivered primarily in a GP setting. There are no substantial changes to administration costs, training, or storage requirements' (ATAGI Advice to the PBAC). Overall, the evaluation considered that it was reasonable to expect that no changes to the Medicare Benefits Schedule (MBS) would occur due to including 20vPCV on the NIP.
- 6.67 The submission expected the program to be cost-neutral to the NIP, the MBS, and the Australian Government health budget in the first 6 years of listing. The program remained cost-neutral when the ABS population data were updated to match the source provided.
- 6.68 The submission identified the prevalence of NIP-funded risk conditions and uptake rates as potential sources of uncertainty. Including 20vPCV on the NIP remained cost-neutral to the NIP, MBS, and Australian Government health budget in all sensitivity analyses conducted in the submission.

### ***Quality Use of Medicines***

- 6.69 The submission presented ATAGI advice that 'the vaccine will not require any additional measures for implementation to manage vaccine safety' (ATAGI Advice to the PBAC).
- 6.70 The submission stated that education, resources, and training on 20vPCV would be provided to healthcare professionals and that trained field personnel, a Medical Information hotline and an online portal would be available to address queries in a timely manner). The evaluation considered the proposed quality use of medicines activities were adequate.
- 6.71 The ESC noted the implementation issue raised by the ATAGI, that all three pneumococcal conjugate vaccines (13v, 15v, 20v) and 23vPPV may be available at the next request for tender for NIP pneumococcal vaccines (ATAGI Advice to the PBAC).

### ***Financial Management – Risk Sharing Arrangements***

- 6.72 The submission did not propose a risk-sharing arrangement.

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 the following paediatric populations:

- Children aged 12 months or younger in NSW, VIC, ACT, and TAS and non Indigenous children aged 12 months or younger in QLD, NT, WA and SA (2+1 schedule).
- Aboriginal and Torres Strait Islander children aged 12 months or younger in QLD, NT, WA and SA (3+1 schedule).
- Children aged 12 months or younger with currently NIP-funded risk conditions (3+1 schedule).
- Children aged more than 12 months with currently NIP-funded risk conditions (single dose).

These populations match those recommended for 13-valent pneumococcal conjugate vaccine (13vPCV) and 15-valent pneumococcal conjugate vaccine (15vPCV). The PBAC's recommendation for listing 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, 13vPCV and 15vPCV.

7.2 The PBAC welcomed the input from the Immunisation Foundation of Australia that described a range of benefits that the listing of 20vPCV for paediatric populations on the NIP will have for the Australian population.

7.3 The PBAC noted the ATAGI advice to the PBAC stating there is currently an appreciable incidence of pneumococcal disease in Australia driven by serotypes not included in 13vPCV, and serotype 3 against which the current vaccine has limited efficacy and considered that there remained a need for further pneumococcal vaccines in Australia.

7.4 The PBAC considered the nomination of 13vPCV and 15vPCV as main comparators was appropriate.

7.5 The PBAC advised that the equi-effective doses were 1 x 0.5 mL 20vPCV, 1 x 0.5 mL 15vPCV and 1 x 0.5 mL 13vPCV.

7.6 The submission was based on four head-to-head randomised controlled trials (RCTs) comparing 20vPCV to 13vPCV, one single-arm 20vPCV study, and three head-to-head RCTs comparing 15vPCV to 13vPCV. The PBAC noted that the assessment of comparative effectiveness was based on an immunological 'bridge to a bridge' approach. The PBAC considered this approach reasonable, noting 20vPCV is based on

the same technology and platform as 7vPCV and 13vPCV, and other advisory bodies such as the ATAGI and the TGA had previously accepted this approach.

- 7.7 The PBAC noted that serotype 3 missed the non-inferiority criteria for the difference in IgG response rates after the final infant dose in both the 2+1 and 3+1 pivotal clinical trials. The PBAC also noted that there was evidence to suggest that a higher immune response may be needed for serotype 3 compared with other serotypes for clinical protection (ATAGI advice to the PBAC)<sup>7</sup>. The PBAC noted the trade-off analysis presented in the PSCR assessing the potential risk of breakthrough cases due to the serotypes that did not meet the non-inferiority criteria (including serotype 3) exceeding the benefits of protection against the additional serotypes covered in 20vPCV for infants aged less than 12 months of age (pre-toddler dose).
- 7.8 Overall, consistent with its conclusion for 20vPCV for adults, 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.
- 7.9 The PBAC noted that the ATAGI advice to the PBAC stated that the 'Phase 3 safety data indicated that 20vPCV has a similar safety profile to 13vPCV'. While noting that the availability of comparative safety data were limited and no data were available for Aboriginal or Torres Strait Islander children, or medically at-risk infants and children, the PBAC considered the claim of non-inferior comparative safety to 13vPCV and 15vPCV was reasonable.
- 7.10 The PBAC noted that 20vPCV doses will replace 13vPCV and 15vPCV doses and, as the submission stated it would accept a cost-minimisation to the nationally negotiated price of 13vPCV and 15vPCV for children and infants, there would be no net cost to government.
- 7.11 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

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<sup>7</sup> Andrews NJ, Waight PA, Burbidge P, Pearce E, Roalfe L, Zancolli M, et al. Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: A postlicensure indirect cohort study. *Lancet Infect Dis.* 2014;14(9):839–46.

## 8 Recommended listing

### 8.1 Add new item to the Determination:

Vaccine and the circumstances in which vaccine may be provided	Brand	Formulation	Active ingredient and strength	Number and timing of doses
Pneumococcal (conjugate, 20-valent)	Prevenar 20	Injection (0.5mL)	Polysaccharides of the capsular antigens of <i>S. pneumoniae</i> serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F individually conjugated to CRM197.	2 or 3 doses of a primary course plus a booster dose or a single supplementary dose
<p>Circumstances Vaccine may be provided:</p> <ul style="list-style-type: none"> <li>(a) to a child who is: <ul style="list-style-type: none"> <li>(i) about 2 months old, and</li> <li>(ii) about 4 months old;</li> <li>(iii) in their second year of life; and</li> </ul> </li> <li>(b) the vaccine may be provided in the circumstances set out in subsection 7 (1)</li> </ul>				

***The wording of the item may be subject to further review. Should there be any changes made to the item 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 paediatric populations. 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 the Australian **paediatric population** vaccinated with 20vPCV.