

6.08 PNEUMOCOCCAL POLYSACCHARIDE CONJUGATE VACCINE, 13-VALENT ADSORBED, Injection, 0.5 mL in pre-filled syringe, Prevenar 13[®], Pfizer Australia Pty Ltd

1 Purpose of Application

- 1.1 The submission requested listing on the National Immunisation Program (NIP) for 13-valent pneumococcal conjugate vaccine (13vPCV) for the prevention of pneumococcal disease (community acquired pneumonia [CAP] and invasive pneumococcal disease [IPD]) in individuals with an at-risk condition (aged ≥ 5 to < 65 years), and Indigenous adults (aged ≥ 25 years).
- 1.2 This is the first submission for 13vPCV for the proposed vaccination population. The PBAC recommended 13vPCV for use in non-Indigenous adults aged ≥ 65 years and Indigenous adults aged ≥ 50 years in July 2016.
- 1.3 The submission requested listing based on cost-effectiveness compared with 23-valent pneumococcal polysaccharide vaccine (23vPPV). The key components of the submission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	<ol style="list-style-type: none"> 1. Individuals (≥ 15 and < 65 years)/Indigenous adults (≥ 15 and $< 25^a$ years) at increased risk of pneumococcal disease; 2. Children aged ≥ 5 years and < 15 years at increased risk of pneumococcal disease; and 3. All Indigenous adults aged ≥ 25 years^b regardless of risk status.
Intervention	Single dose of 13vPCV.
Comparator	Single dose of 23vPPV.
Outcomes	Reduction in pneumococcal disease: IPD and VT-CAP.
Clinical claim	<p>Efficacy: 13vPCV is more effective than 23vPPV in terms of the reduction in pneumococcal disease (VT-IPD and VT-CAP).</p> <p>Safety: Equivalent to 23vPPV in terms of treatment emergent adverse events (TEAEs) and serious AEs (SAEs).</p>

Source: Table 1.1.1 p19 and p203 of the submission and p1 of the PSCR.

Abbreviations: 13vPCV=13-valent pneumococcal conjugate vaccine; 23vPPV=23-valent pneumococcal polysaccharide vaccine; AE=Adverse event; CAP=Community-acquired pneumonia; IPD=Invasive pneumococcal disease; SAE=Serious adverse event; TEAE=Treatment emergent adverse event; VT=Vaccine-type.

^a Noted in submission as at-risk Indigenous adults (≥ 15 and < 50 years), however, this has been amended to (≥ 15 and < 25 years) for consistency with the requested listing for all Indigenous adults aged ≥ 25 years to < 50 .

^b Change of age from the recommendation in July 2016 of ≥ 50 years.

2 Requested listing

2.1 The submission sought the following listing:

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	NIP price	Proprietary name and manufacturer
PNEUMOCOCCAL POLYSACCHARIDE CONJUGATE VACCINE, 13 VALENT ADSORBED Pre-filled syringe, 0.5 mL	1	1	0	\$█	Prevenar 13, Pfizer Australia Pty Ltd
National Immunisation Program <ul style="list-style-type: none"> ▪ A single 13vPCV dose for Indigenous adults aged 25 years and over ▪ A single 13vPCV dose in children aged ≥5 years and <15 years at increased risk of pneumococcal disease^a ▪ A single 13vPCV dose in individuals aged ≥15 years and < 65 years at increased risk of pneumococcal disease 					

Source: Table 1.4.1 p32 of the submission and p1 of the PSCR.

Abbreviations: 13vPCV=13-valent pneumococcal conjugate vaccine; mL=millilitres; NIP=National Immunisation Program

^a The proposed NIP listing in the submission (p32) specified this NIP population as: “A single 13vPCV dose in children aged ≥5 years and <15 years”. The addition of “at increased risk of pneumococcal disease” was included during the preparation of the ESC Advice (see paragraph 2.3).

2.2 The proposed price (\$█) is higher than that proposed in the July 2016 submission (\$█) for non-Indigenous adults aged ≥65 years and Indigenous adults aged ≥50 years which was recommended by the PBAC. The pre-PBAC response proposed a reduced price of \$█.

2.3 The ESC noted that the submission was unclear and contradictory regarding the requested listing on the NIP schedule for children aged ≥5 years and <15 years. The descriptions of this requested population used in the submission included:

- children ≥5 to <15 years at increased risk regardless of previous doses of 13vPCV (p17 and Table 1.1.1 on p19),
- children ≥5 to <15 years who have not previously been vaccinated through the universal infant or catch-up program, regardless of at-risk condition status (p19 and Summary of proposed NIP listing sub-section on p17-18) and
- all children ≥5 to <15 years (Table 1.4.1 on p32).

The evaluation noted that the economic evaluation in Section 3 and the financial implications in Section 4 of the submission were restricted to the at-risk populations. The Pre-Sub-Committee Response (PSCR, p1) stated that “ATAGI’s advice with regard to use in children has differed across correspondence. For the purposes of the PBAC submission it was assumed that the restriction was for children ≥5 years and <15 years at increased risk of pneumococcal disease, regardless of the number of 13vPCV doses that they had previously received”. The ATAGI recommended that a dose of 13vPCV be given to children ≥5 years newly diagnosed with an at-risk condition regardless of the number of 13vPCV doses received previously through routine infant vaccination (pre-PBAC submission advice, p19 and re-affirmed in its post-submission advice, p1). For the purposes of PBAC consideration, the requested population was considered to be children ≥5 years and <15 years at increased risk of pneumococcal disease.

- 2.4 The Australian Immunisation Handbook recommends that individuals who have undergone a haematopoietic stem cell transplant (HSCT) require three doses of 13vPCV within three to six months post-transplant. The need for repeat dosing in this patient group was not considered in the requested listing, the economic evaluation or the financial implications estimates in the submission. The PSCR acknowledged that repeat dosing was not considered in the submission, noting that the size of the population undergoing HSCT is likely to be small relative to the overall population at increased risk of pneumococcal disease. Accordingly, the PSCR claimed that repeat dosing for this subpopulation is likely to have minimal impact on the results.
- 2.5 ATAGI considers that the variability in the source of funding (NIP or PBS) for existing additional doses of 23vPPV offered to at-risk individuals adds further complexity, where currently the criteria for funding are not fully aligned with existing clinical recommendations (ATAGI pre-PBAC submission advice, June 2018, p1). Accordingly, ATAGI proposed (p1) that all pneumococcal vaccines recommended for individuals at-risk are funded on the NIP (i.e. 23vPPV and 13vPCV). Given the complexity of funding mechanisms, ATAGI suggested that the PBAC may wish to consider revisions to the current restrictions on PBS and NIP funded vaccinations, noting that supply of 23vPPV is provided by a different sponsor than that of 13vPCV (ATAGI pre-PBAC submission advice, June 2018, p1).

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

3 Background

Registration status

- 3.1 13vPCV was registered by the Therapeutic Goods Administration (TGA) on 16 March 2010 for infants and children from 6 weeks up to 5 years of age. Registration was extended on 28 October 2011 for adults aged 50 years and older; on 30 of August 2013 for infants and children aged from 6 weeks to 17 years; and on 27 May 2014 for adults aged 18 to 49 years. These approvals were based on immunogenicity studies.

Previous PBAC considerations

- 3.2 Vaccination using 23vPPV (the comparator in this submission) was introduced in 1999 for all Indigenous adults aged ≥ 50 years and younger Indigenous adults with risk factors. Since January 2005, 23vPPV has also been funded on the NIP for non-Indigenous adults aged ≥ 65 years. Implementation of these 23vPPV programs pre-dated the requirement for a PBAC recommendation for vaccines to be funded on the NIP. Accordingly, the PBAC has not previously considered the clinical and cost-effectiveness of 23vPPV for these cohorts. Persons aged < 65 years with a condition(s) associated with an increased risk of IPD can access 23vPPV through the PBS.
- 3.3 13vPCV has been listed on the NIP since 1 July 2011 for children (currently provided at 2, 4 and 12 months). A summary of the prior PBAC considerations pertaining to the listing of 13vPCV on the NIP for use children is presented in paragraphs 3.3 and 3.4 of the March 2015 13vPCV Public Summary Document (PSD).

- 3.4 The clinical evidence in this submission was similar to that presented in prior submissions of 13vPCV in non-Indigenous adults aged ≥ 65 years and Indigenous adults aged ≥ 50 years (considered by the PBAC in March 2015, July 2015, and July 2016).
- In July 2015, the PBAC recommended that a single dose of 13vPCV be made available to pneumococcal vaccine naïve non-Indigenous adults aged 65 years and over, and to pneumococcal vaccine naïve Indigenous adults aged 50 years and over, on the basis of cost-minimisation to 23vPPV. The PBAC recommended that this dose of 13vPCV should replace the single dose (or the first dose for those adults with risk factors) of 23vPPV that is currently provided to these populations. The PBAC noted that if 13vPCV was included on the NIP for adults, then individuals in specified at-risk groups would continue to receive 23vPPV five years following the primary dose of 13vPCV. (July 2015 PSD, 13vPCV, paragraphs 7.1-2)
 - In making the July 2015 recommendation, the PBAC noted that the evidence for 13vPCV over no vaccination was of higher quality than that for 23vPPV over no vaccination. In the absence of directly comparative evidence between 13vPCV and 23vPPV, the PBAC accepted that the effectiveness of 13vPCV against pneumococcal 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. Although the PBAC considered that 13vPCV was likely to be superior to 23vPPV in terms of prevention of VT-CAP, the submission had not provided sufficient evidence to allow the PBAC to be confident that recommending 13vPCV at the requested price would be cost-effective. The PBAC also recalled that a 13vPCV infant program was only introduced in Australia in 2011, and considered that further reductions in the prevalence of the 13 serotypes in age groups other than those vaccinated (including the ≥ 65 year old population) would be likely to occur. (July 2015 PSD, 13vPCV, paragraphs 7.6-8)
 - In July 2016, the PBAC changed the basis of the July 2015 recommendation for 13vPCV to cost-effectiveness compared with 23vPPV. In making this recommendation, the PBAC noted that the cost-effectiveness of 23vPPV had not been previously reviewed and that the information provided in the 13vPCV submission suggested that 23vPPV is unlikely to prevent pneumococcal CAP. The PBAC requested advice from ATAGI on the clinical place and effectiveness of 23vPPV on the NIP with a view to potentially informing a review of the cost-effectiveness of 23vPPV compared with no vaccine. The PBAC requested that the review include the use of 23vPPV as currently specified in the NIP schedule (i.e. in children and Aboriginal and Torres Strait Islander adolescents medically at risk, and in adults with and without risk factors). The PBAC noted that any outcomes of the review of 23vPPV may have implications for the 13vPCV listing. (July 2016 PSD, 13vPCV, paragraphs 7.1-2)
- 3.5 In July 2017, the PBAC considered the outcome of the ATAGI's review of the clinical place and effectiveness of 23vPPV on the NIP (July 2017 PBAC). The ATAGI maintained

its previous advice to the PBAC that there is unlikely to be significant benefit of 23vPPV in preventing pneumococcal CAP in elderly adults, particularly when given in addition to 13vPCV and given to adults without medical comorbidities. The primary benefit of vaccination with 23vPPV following 13vPCV is the broadening of vaccine protection to include disease caused by 23v-non13v serotypes for adults with medical comorbidities at risk of IPD. The PBAC considered that there is likely to be a large opportunity cost associated with vaccinating non-Indigenous adults without risk factors against IPD, given that the incidence of IPD in this group is low. The PBAC therefore recommended a review of the cost-effectiveness of 23vPPV compared with no vaccination for the currently NIP-funded indications for non-Indigenous adults aged ≥ 65 years, with and without risk factors; and Aboriginal and Torres Strait Islander adults aged ≥ 50 years, with and without risk factors. The PBAC noted that this review may have implications for the cost-effective price for 13vPCV. Given the high and disproportionate burden of IPD in Aboriginal and Torres Strait Islander adults, the PBAC also recommended a review of a stepped economic analysis and financial impact of providing 13vPCV, with or without 1 or 2 doses of 23vPPV, to all Aboriginal and Torres Strait Islander people not previously vaccinated with 7vPCV or 13vPCV.

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

4 Population and disease

- 4.1 Infections with *Streptococcus pneumoniae* can cause IPD such as meningitis, septicaemia and bacteraemic pneumonia, and other forms of disease such as non-bacteraemic pneumonia. 13vPCV is a 13-valent pneumococcal conjugate vaccine. The pneumococcal vaccine currently listed on the PBS for individuals with an at-risk condition is a 23-valent capsular polysaccharide vaccine (23vPPV). 13vPCV covers 12 of the 23 serotypes covered by 23vPPV and one additional serotype. The claimed benefit for 13vPCV over 23vPPV is in the reduction of non-bacteraemic CAP (referred to here as CAP) and IPD.
- 4.2 ATAGI considers that all individuals with the conditions it listed as relevant risk factors (pre-PBAC submission advice, p14) are likely to benefit from a dose of 13vPCV irrespective of whether any doses of 23vPPV have been received previously (ATAGI pre-PBAC submission advice, June 2018, p19).
- 4.3 The submission proposed that in adults (≥ 15 to < 65 years), 13vPCV will replace:
 - the first single dose of 23vPPV in adults newly diagnosed with an at-risk condition or a subsequent dose of 23vPPV in adults with a pre-existing condition, noting that a dose of 23vPPV would still be required 12 months later (minimum interval of 6 months); and
 - the first single dose of 23vPPV in Indigenous adults (≥ 25 years), noting that a dose of 23vPPV would still be required 5 years later.

- 4.4 In children aged ≥ 5 to < 15 years, the submission (with clarification in the PSCR) proposed a single dose be given to those newly diagnosed with an at-risk condition. The submission proposed 13vPCV would:
- be given in addition to 23vPPV in children aged ≥ 5 to < 6 years; and
 - replace a dose of 23vPPV in children aged ≥ 6 to < 15 years.
- 4.5 In situations where 13vPCV is expected to replace 23vPPV, e.g. in children (≥ 6 to < 15 years) and adults (≥ 15 to < 64 years) with newly diagnosed at-risk conditions, the submission's proposal is reasonable. However, for some individuals (e.g. at-risk individuals who have already commenced a course of immunisation with 23vPPV), it is possible that they will receive a "catch-up" dose of 13vPCV that will not replace a dose of 23vPPV. In children (aged ≥ 5 and < 6 years), the dose of 13vPCV is given as an additional dose as part of the schedule with 23vPPV.
- 4.6 There is no empirical evidence to support the use of repeat doses of 13vPCV in adults with at-risk conditions, except for HSCT recipients (ATAGI pre-PBAC submission advice, June 2018, p19).

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

5 Comparator

- 5.1 The submission nominated 23vPPV as the main comparator. The submission identified the following comparisons of interest:
- 5- < 6 years: 13vPCV plus 23vPPV vs NIP funded 23vPPV
 - 6-14 years: 13vPCV vs first dose of PBS funded 23vPPV
 - 15-64 years: 13vPCV vs first dose of NIP-funded 23vPPV for Indigenous persons and PBS-funded 23vPPV for non-Indigenous persons.
- 5.2 The PBAC previously accepted 23vPPV as the appropriate comparator in the setting where a single dose of 13vPCV was to replace a single dose of 23vPPV (13vPCV PSD March 2015 paragraph 4.2 and 7.4).

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 input from one organisation, Seqirus (the sponsor of 23vPPV), via the Consumer Comments facility on the PBS website. Seqirus questioned the timing of the submission for 13vPCV in the context of the upcoming cost-effectiveness review of 23vPPV on the NIP for older adults (see paragraph 3.5).

Clinical trials

6.3 Part of the key clinical evidence for 13vPCV and 23vPPV presented in the submission overlapped with the evidence presented in the submissions for adults aged ≥65 years and Indigenous adults aged ≥50 years (March 2015/July 2015/July 2016). The current submission was based on:

- One placebo-controlled efficacy trial (CAPiTA) of 13vPCV, which has previously been reviewed by the PBAC (PSD March 2015, July 2015 and July 2016);
- Thirty-six immunogenicity studies: 18 of 13vPCV and 18 of 7vPCV. None of the 18 immunogenicity trials presented for 13vPCV have been seen by the PBAC previously;
- A meta-analysis of seven randomised efficacy trials of 23vPPV. Two of the efficacy trials (French 2000 and Izumi 2017) have not been seen by the PBAC previously; and
- A meta-analysis of 28 non-randomised studies of 23vPPV. Sixteen of the 28 non-randomised trials have not been seen by the PBAC previously.

6.4 A listing of the trials presented in the submission is provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Proposed vaccine: 13vPCV studies		
13vPCV randomised trials		
CAPiTA	Study 3006. A phase 4, randomised, placebo-controlled clinical trial of 13-valent pneumococcal conjugate vaccine efficacy in prevention of vaccine-serotype pneumococcal community-acquired pneumonia and invasive pneumococcal disease. Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine pneumococcal pneumonia in adults. Huijts SM, van Werkhoven CH, Bolkenbaas M, Grobbee DE and Bonten MJM. Post-hoc analysis of a randomized controlled trial: Diabetes mellitus modifies the efficacy of the 13-valent pneumococcal conjugate vaccine in elderly. Isturiz R and Webber C. Prevention of adult pneumococcal pneumonia with the 13-valent pneumococcal conjugate vaccine: CAPiTA, the Community-Acquired Pneumonia immunization Trial in Adults. Suaya JA, Jiang Q, Scott Bonten M, Patterson S, van Werkhoven H, Scott D, Gruber W, Webber C Schmoele-Thoma B, Hall-Murray C, Sylvester G, Jodar L, Isturiz R. Post-hoc analysis of the 13-valent polysaccharide conjugate vaccine efficacy against vaccine-serotype pneumococcal community acquired pneumonia in at-risk older adults. Suaya JA, Jiang Q, Scott DA, Gruber WC, Webber C and Schmoele-Thoma B. Post hoc analysis of the efficacy of the 13-valent pneumococcal conjugate vaccine against vaccine-type community-acquired pneumonia in at-risk older adults van Werkhoven C, Huijts SM, Bolkenbaas M. Grobbee DE and Bonten MCJM. The impact of age on the efficacy of 13-valent pneumococcal conjugate vaccine in elderly. van Werkhoven C and Bonten MJM. The Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA): what is the future of pneumococcal conjugate vaccination in elderly?	22 May 2014 N Engl J Med 2015; 372:1114-25. Vaccine, 2017; 35(34):4444-4449 Human Vaccines & Immunotherapeutics, 2015; 11(7):1825—1827. 10th International Symposium on Pneumococci and Pneumococcal Diseases 2016; Poster #634 Vaccine, 2018; 36: 1477-1483 Clinical infectious diseases, 2015a; 61:1835-1838. Future Microbiol., 2015; 10(9):1405–1413.

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Trial ID	Protocol title/ Publication title	Publication citation
	Webber C, Patton M, Patterson S, Schmoele-Thoma, Huijts SM, Bonten MJM, for the CAPiTA Study Group. Exploratory efficacy endpoints in the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA).	Vaccine, 2017; 35:1266–1272.
13vPCV immunogenicity studies		
CAPiTA (immunogenicity)	Study 3006. Immunogenicity supplement to final report (supplemental clinical study report 2): a phase 4, randomized, placebo-controlled clinical trial of 13-valent pneumococcal conjugate vaccine efficacy in prevention of vaccine-serotype pneumococcal community-acquired pneumonia and invasive pneumococcal disease. Van Deursen AMM, van Houten MA, Webber C, Patton M, Scott DA, Patterson S, Sidhu M, Drews W, Gruber WC, Emini EA, Grobbee DE, Bonten MJM and Sanders EAM. Immunogenicity of the 13-valent pneumococcal conjugate vaccine in older adults with and without comorbidities in the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA). Webber C, Patton M, Scott D, Patterson S, van Deursen A, Sanders E, Grobbee D, Bonten M on behalf of the study team. A post-hoc analysis of immunogenicity of 13-valent pneumococcal conjugate vaccine in subjects with underlying medical conditions in Community Acquired Pneumonia Immunization Trial in Adults (CAPiTA).	22 May 2014 Clin Infect Dis. 2017; 65(5):787-795. 25th European Congress of Clinical Microbiology and Infectious Diseases; April 25–28, 2015
Study 3002	A phase 3, open-label, single-arm trial to evaluate the safety, tolerability, and immunogenicity of 2 and 3 doses of 13-valent pneumococcal conjugate vaccine in human immunodeficiency virus-infected subjects 6 years of age and older who have not been previously immunized with pneumococcal vaccine Bhorat AE, Madhi SA, Laudat F, Sundaraiyer V, Gurtman A, Jansen KU, Scott DA, Emini EA, William C. Gruber WC and Schmoele-Thoma B. Immunogenicity and safety of the 13-valent pneumococcal conjugate vaccine in HIV-infected individuals naive to pneumococcal vaccination.	2 October 2013 AIDS 2015, 29:000–000
Study 3003	A phase 3, open-label trial to evaluate the safety, tolerability, and immunogenicity of 13-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal polysaccharide vaccine in recipients of allogeneic hematopoietic stem cell transplant aged 2 years and older. Cordonnier C, Ljungman P, Juergens C, Maertens J, Selleslag D, Sundaraiyer V, Giardina PC, Clarke K, Gruber WC, Scott DA and Schmoele-Thoma B for the 3003 Study Group. Immunogenicity, safety, and tolerability of 13-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal polysaccharide vaccine in recipients of allogeneic hematopoietic stem cell transplant aged ≥ 2 years: an open-label study.	15 October 2013. Clinical Infectious Diseases, 2015.
Study 3014	A phase 3, open-label, single-arm trial evaluating the safety, tolerability, and immunogenicity of 13-valent pneumococcal conjugate vaccine in children with sickle cell disease previously immunized with 23-valent pneumococcal polysaccharide vaccine. De Montalembert M, Abboud MR, Fiquet A, Inati A, Lebensburger JD, Kaddah N, Mokhtar G, Piga A et al. 13-Valent Pneumococcal conjugate vaccine (pcv13) is immunogenic and safe in children 6-17 years of age with sickle cell disease previously vaccinated with 23-valent pneumococcal polysaccharide vaccine (PPSV23): results of a phase 3 study.	17 October 2013 Pediatr Blood Cancer, 2015
Study 3017	Study 3017. A phase 3, open-label, single-arm trial to evaluate the safety, tolerability, and immunogenicity of 3 doses of 13-valent pneumococcal conjugate vaccine in human immunodeficiency virus-infected subjects 18 years of age or older who have been previously immunized with 23-valent pneumococcal polysaccharide vaccine.	16 November 2012

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Trial ID	Protocol title/ Publication title	Publication citation
	Glesby MJ, Watson W, Brinson C, Greenberg RN, Lalezari JP, Skiest D, Sundaraiyer V, Natuk R, Gurtman A, Scott DA, Emini EA, Gruber WC and Schmoele-Thoma B. Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine in HIV-infected adults previously vaccinated with pneumococcal polysaccharide vaccine.	Journal of Infectious Diseases, 2014
Bamford 2014	Bamford A, Kelleher P, Lyall H, Haston M, Zancolli M, Goldblatt D and Kampmann B. Serological response to 13-valent pneumococcal conjugate vaccine in children and adolescents with perinatally acquired HIV infection.	AIDS 2014, 28:2033–2043
Dendle 2017	Dendle C, Stuart RL, Polkinghorne KR, Balloch A, Kanellis J, Ling J, Kummrow M, Moore C, Thursky K, BATTERY J, Mulholland K, Gan P-Y, Holdsworth SH and Mulley WR. Seroresponses and safety of 13-valent pneumococcal conjugate vaccination in kidney transplant recipients.	Transpl Infect Dis. 2018; e12866.
Hung 2017	Hung T-Y, Kotecha RS, Blyth CC, Steed SK, Thornton RB, Ryan AL, Cole CH and Richmond PC. Immunogenicity and safety of single-dose, 13-valent pneumococcal conjugate vaccine in pediatric and adolescent oncology patients.	Cancer, 2017.
Jallow 2017	Jallow S, Madhi SA, Madimabe R, Sipambo N, Violari A, Kala U, Petersen K, Naidoo S, Verwey C, Moore DP and Nunes MC. Immunogenicity of 13-valent pneumococcal conjugate vaccine among children with underlying medical conditions.	Vaccine, 2017; 35:4321–4329.
Kantsø 2015	Kantsø B, Halkjær SI, Thomsen OO, Belard E, Gottschalck IB, Jørgensen CS, Kroghfelt KA, Slotved H-CD, Ingels HD, Petersen AM. Immunosuppressive drugs impairs antibody response of the polysaccharide and conjugated pneumococcal vaccines in patients with Crohn's disease	Vaccine, 2015; 33 (41): 5464-5469
Lombardi 2016	Lombardi F, Belmonti S, Fabbiani M, Morandi M, Rossetti B, Tordini G, Cauda R, De Luca A, Di Giambenedetto S, Montagnani F. Immunogenicity and safety of the 13-valent pneumococcal conjugate vaccine versus the 23-valent polysaccharide vaccine in unvaccinated HIV-infected adults: a pilot, prospective controlled study.	PLoS ONE 11(6): e0156523.
Mitra 2016	Mitra S, Stein GE, Bhupalam S and Havlichek DH. Immunogenicity of 13-valent conjugate pneumococcal vaccine in patients 50 years and older with end-stage renal disease and on dialysis.	Clinical and Vaccine Immunology, 2016; 23(11):884-887.
Nived 2015	Nived P, Jørgensen CS, Bo Settergren B. Vaccination status and immune response to 13-valent pneumococcal conjugate vaccine in asplenic individuals.	Vaccine, 2015; 1688-1694.
Pittet 2016	Pittet LF, Posfay-Barbe KM, Chehade H, Rudin C, Wilhelm-Bals A, Rodriguez M, Siegrist CM and Parvex P. Optimizing seroprotection against pneumococcus in children with nephrotic syndrome using the 13-valent pneumococcal conjugate vaccine.	Vaccine, 2016; 34:4948–4954.
Rezai 2017	Rezai MS, Ghaffari J, Mahdavi M, et al. Conjugate and 23-valent pneumococcal polysaccharide booster vaccination in asplenic patients with thalassemia major: A randomized clinical trial study.	Caspian J Intern Med, 2017; 8(1): 16-22.
Svensson 2018	Svensson T, Kättström M, Hammarlund Y, Daniel Roth R, Andersson P-O, Svensson M, Nilsson I, Rombo L, Cherif H and Kimby E. Pneumococcal conjugate vaccine triggers a better immune response than pneumococcal polysaccharide vaccine in patients with chronic lymphocytic leukemia A randomized study by the Swedish CLL group.	Vaccine, 2018; 36:3701–3707.
Vandecasteele 2017	Vandecasteele SJ, De Bacquer D, Caluwe R, Onbelet S and Van Vlem B. Immunogenicity and safety of the 13-valent pneumococcal conjugate vaccine in 23-valent pneumococcal polysaccharide vaccine-naïve and pre-immunized patients under treatment with chronic haemodialysis: a longitudinal quasi-experimental phase IV study.	Clinical Microbiology and Infection, 2018; 24:65e71.
Zangenah 2017	Zangenah S, Björkhem-Bergman L, Norlin A-C, Hansen S, Lindqvist L, Henriques-Normark B and Bergman P. The Pneumocell-study: vaccination of IgG1- and IgG2-deficient patients with Pevnar13.	Vaccine, 2017; 35:2654–2660.

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Trial ID	Protocol title/ Publication title	Publication citation
Comparator Vaccine: 23vPPV studies		
23vPPV randomised trials		
Alfageme 2006	Alfageme I, Vazquez R, Reyes N, et al. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD.	Thorax 2006; 61:189–95
Furumoto 2008	Furumoto A, Ohkusa Y, Chen M, et al. Additive effect of pneumococcal vaccine and influenza vaccine on acute exacerbation in patients with chronic lung disease.	Vaccine 2008; 26:4284–9
Kawakami 2010	Kawakami K, Yasushi Ohkusa Y, Kuroki R, et al. Effectiveness of pneumococcal polysaccharide vaccine against pneumonia and cost analysis for the elderly who receive seasonal influenza vaccine in Japan.	Vaccine 2010; 28:7063–9
Maruyama 2010	Maruyama T, Taguchi O, Niedeman MS, et al. Efficacy of 23-valent pneumococcal conjugate vaccine in preventing pneumonia and improving survival in nursing home residents: double blind, randomised and placebo controlled trial.	BMJ 2010; 340:C1004
Örtqvist 1998	Örtqvist A, Hedlund J, Burman LA, et al. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. Swedish Pneumococcal Vaccination Study Group.	Lancet 1998; 351:399–403
French 2000	French N, Nakiyingi J, Carpenter LM, Lugada E, Watera C, Moi K, Moore M, Antvelink D, Mulder D, Janoff EN, Whitworth J and Gilks CF. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial.	The Lancet, 2000; 355: 2106-2111
Izumi 2017	Izumi Y, Akazawa M, Akeda Y, Tohma S, Hirano F, Ideguchi H, Masumura R, Miyamura T, Mori S, Fukui T, Iwanaga N, Jiuchi Y, Kozura H, Tsutani H, Saisyo K, Sugiyama T, Suenaga Y, Okado Y, Katayama M, Ichikawa K, Furukawa H, Kawakami K, Oishi K and Migita K. The 23-valent pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis: a double-blinded, randomized, placebo-controlled trial.	Arthritis Research & Therapy, 2017; 19(15)
Comparator vaccine: 23vPPV non-randomised studies		
Andrews 2004	Andrews RM, Counahan ML, Hogg GG, et al. Effectiveness of a publicly funded pneumococcal vaccination program against invasive pneumococcal disease among the elderly in Victoria, Australia.	Vaccine 2004; 23:132–8
Andrews 2012	Andrews N, Waight PA, George RC, et al. Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales.	Vaccine 2012; 30:6802-8
Dominguez 2005	Dominguez A, Salleras L, Fedson DS, et al. Effectiveness of pneumococcal vaccination for elderly people in Catalonia, Spain: a case-control study.	Clin Infect Dis 2005; 40:1250–7
Gutiérrez Rodríguez 2014	Gutiérrez Rodríguez MA, Ordoñas Gavin MA, García-Comas L, et al. Effectiveness of 23-valent pneumococcal polysaccharide vaccine in adults aged 60 years and over in the Region of Madrid, Spain, 2008-2011.	Euro Surveill 2014; 19:20922.
Jackson 2003	Jackson LA, Neuzil KM, Yu O, et al. Effectiveness of pneumococcal polysaccharide vaccine in older adults.	N Engl J Med 2003; 348:1747–55
Johnstone 2007	Johnstone J, Marrie TJ, Eurich DT, et al. Effect of pneumococcal vaccination in hospitalized adults with community-acquired pneumonia.	Arch Intern Med 2007; 167:1938-43
Leventer-Roberts 2015	Leventer-Roberts M, Feldman BS, Brufman I, et al. Effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive disease and hospital-treated pneumonia among people aged ≥65 years: a retrospective case-control study.	Clin Infect Dis 2015; 60:1472-80.
Menzies 2014	Menzies RI, Jayasinghe SH, Krause VL, et al. Impact of pneumococcal polysaccharide vaccine in people aged 65 years or older.	Med J Aust 2014; 200:112–5
Mooney 2008	Mooney JD, Weir A, McMenamin J, et al. The impact and effectiveness of pneumococcal vaccination in Scotland for those aged 65 and over during winter 2003/2004.	BMC Infect Dis 2008; 8:53

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Trial ID	Protocol title/ Publication title	Publication citation
Vila-Corcoles 2006	Vila-Corcoles A, Ochoa-Gondar O, Ansa X, et al. Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the Evan-65 study.	Clin Infect Dis 2006; 43:860–8
Vila-Corcoles 2010	Vila-Corcoles A, Ochoa-Gondar O, Guzmán JA, et al. Effectiveness of the 23-valent polysaccharide pneumococcal vaccine against invasive pneumococcal disease in people 60 years or older.	BMC Infect Dis 2010; 10:73
Wright 2013	Wright LB, Hughes GJ, Chapman KE, et al. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in people aged 65 years and over in the North East of England, April 2006-July 2012.	Trials Vaccinol 2013; 2:45-8.
Hsieh 2016	Hsieh M-J, Yu C-C, Hu H-C, Thai Y-H. No preventive effects of 23-valent pneumococcal polysaccharide vaccine in patients with chronic renal failure.	European Respiratory Journal. 2016;48(suppl 60).
Hung 2004	Hung C-C, Chen M-Y, Hsieh S-M, Hsai C-F, Sheng W-H and Chang S-C. Clinical experience of the 23-valent capsular polysaccharide pneumococcal vaccination in HIV-1-infected patients receiving highly active antiretroviral therapy: a prospective observational study.	Vaccine, 2004; 22:2006–2012.
Kuo 2015	Kuo C-S, Lu C-W, Chang Y-K, Yang K-C, Hung S-H, Yang M-C, Chang H-H, Huang C-T, Hsu C-C and Juang K-C. Effectiveness of 23-valent pneumococcal polysaccharide vaccine on diabetic elderly	Medicine, 2016; 95:26(e4064).
López-Paloma 2004	López-Palomo C, Martín-Zamorano M, Benítez E, Fernández-Gutiérrez C, Guerrero F, Rodríguez-Iglesias M, and Girón-González JA. Pneumonia in HIV-Infected Patients in the HAART Era: Incidence, risk, and impact of the pneumococcal vaccination.	Journal of Medical Virology, 2004; 72:517–524.
Rodriguez-Barrada 2008	Rodriguez-Barradas MC, Goulet J, Brown S, et al. Impact of pneumococcal vaccination on the incidence of pneumonia by HIV infection status among patients enrolled in the Veterans Aging Cohort 5-Site Study. Clinical infectious diseases	Infectious Diseases Society of America. 2008;46(7):1093-1100.
Tsai 2015	Tsai Y-H, Hsieh M-J, Chang C-J, Wen Y-W, Hu HC, Chao Y-N, Huang Y-C, Yang CT and Huang CC. The 23-valent pneumococcal polysaccharide vaccine is effective in elderly adults over 75 years old—Taiwan's PPV vaccination program.	Vaccine, 2015; 33:2897–2902.
Breiman 2000	Breiman RF, Keller DW, Phelan MA, Sniadack DH, Stephens DS, Rimland D, Farley MM, Schuchat A and Reingold AI. Evaluation of effectiveness of the 23-valent pneumococcal capsular polysaccharide vaccine for HIV-infected patients.	Arch Intern Med, 2000; 160:2633-2638.
Farr 1995	Farr BM, Johnston BL, Cobb DK, et al. Preventing pneumococcal bacteremia in patients at risk. Results of a matched case-control study.	Arch Intern Med 1995; 155:2336-40.
Grau 2005	Grau I, Pallares R, Tubau F, Schulze MH, Llopis F, Podzamczar D, Liñares J, Gudiol F for the Spanish Pneumococcal Infection Study Network (G03/103). Epidemiologic changes in bacteremic pneumococcal disease in patients with human immunodeficiency virus in the era of highly active antiretroviral therapy.	Arch Intern Med, 2005; 165:1533-1540.
Guerrero 1999	Guerrero M, Kruger S, Saitoh A, Sorvillo F, Cheng K-J, French C and Beall G. Pneumonia in HIV-infected patients: a case-control survey of factors involved in risk and prevention.	AIDS, 1999; 13:1971–1975.
Peñaranda 2007	Peñaranda M, Falco V, Payeras A, Jordano Q, Curran A, Samperiz G, Dalmau G, Ribera E and Riera M. Effectiveness of polysaccharide pneumococcal vaccine in HIV-infected patients: A case-control study.	Clinical Infectious Diseases, 2007; 45: e82–7
Shapiro 1991	Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine.	N Engl J Med 1991; 325:1453-60.
Teshale 2008	Teshale EH, Hanson D, Flannery B, Phares C, Wolfe M, Schuchat A and Sullivan P. Effectiveness of 23-valent polysaccharide pneumococcal vaccine on pneumonia in HIV-infected adults in the United States, 1998–2003.	Vaccine, 2008; 26:5830–5834.

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Trial ID	Protocol title/ Publication title	Publication citation
Veras 2007	Veras MA, Enanoria WTA, Castilho EA and Reingold AL. Effectiveness of the polysaccharide pneumococcal vaccine among HIV-infected persons in Brazil: a case control study.	BMC Infectious Diseases, 2007; 7:119.
Butler 1993	Butler JC, Breiman RF, Campbell JF, et al. Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations.	JAMA 1993; 270:1826-31.
Rudnick 2013	Rudnick W, Liu Z, Shigayeva A, et al. Pneumococcal vaccination programs and the burden of invasive pneumococcal disease in Ontario, Canada, 1995–2011.	Vaccine. 2013;31(49):5863-5871.

Source: Att Table 2.2.2 of the commentary; Table 2.2.1, p40-45 of the submission. Submission wrongly cited the title of Kantsø 2015 as Specific antibody response against pneumococcal polysaccharide and conjugated vaccine in Crohn's disease patients treated with immunosuppressive drugs alone or in combination with biological therapy or untreated. The year of publication for Kuo 2015 is 2016. This was wrongly cited in the submission.

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6.5 The key features of the 13vPCV and 23vPPV randomised efficacy trials, and the 23vPPV non-randomised study used in the economic evaluation, are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Primary outcome	Use in modelled evaluation	
13vPCV vs placebo							
CAPiTA	84,496	R, BD 4 years	Low	Aged ≥65 years	VT-CAP (VT pneumonia in mITT population)	VE for VT pneumonia and VT IPD	
23vPPV vs placebo or no vaccine							
Alfageme 2006	600	R, OL 2.7 years	Moderate	Mean age 68 years COPD	CAP of pneumococcal or unknown aetiology	VE for VT pneumonia	
Furumoto 2008	191	R, OL 2 years	Moderate	Aged 40-80 years Chronic lung disease	Pneumonia (all- cause)	VE for VT pneumonia	
Kawakami 2010	786	R, OL 2 years	Moderate	Aged ≥65 years Immunised against influenza Treated by pulmonary physician	Pneumonia (all- cause)	VE for VT pneumonia	
Maruyama 2010	1,006	R, DB 2.3 years	Low	Mean age 85 years Nursing home residents	Pneumococcal pneumonia	VE for VT pneumonia	
Örtqvist 1998	693	R, DB 2.5 years	Low	Aged 50-85 years Previously treated as inpatient for CAP	Pneumococcal pneumonia	VE for VT pneumonia	
French 2000	1392	R, DB 1.2 years	Low- moderate	Aged ≥15 years HIV infected adults living within 15km of the study clinic	Pneumonia (all- cause)	VE for VT pneumonia	
Izumi 2017	930	R, DB 1.7 years	Low	Clinically diagnosed rheumatoid arthritis who had been treated with biologics or immunosuppressive agents	Pneumonia (all- cause) Pneumococcal pneumonia	VE for VT pneumonia	
Meta-analysis	5,598	All studies included; Assessed pneumonia (all-cause), pneumococcal pneumonia, bacteraemic pneumococcal pneumonia, non-bacteraemic pneumococcal pneumonia and non bacteraemic pneumococcal pneumonia.					VE for VT pneumonia
23vPPV non-randomised study used in the economic evaluations							
Menzies 2014	900 IPD cases	Used screening method	High	IPD cases from NNDSS in adults ≥65 years	VT IPD	VE for VT IPD	
Rudnick 2013	1240 IPD cases	Used indirect cohort method	High	IPD cases from chart reviews in persons aged ≥2 years	VT IPD	VE for VT IPD	
Breiman 2000	167 IPD cases	Case control study	High	IPD cases from chart reviews in adults 18-55 years	IPD (all cause)	VE for IPD (all cause)	
Shapiro 1991	1054 IPD cases	Case control study	High	IPD cases from hospital records in HIV positive adults ≥18 years	VT IPD	VE for VT IPD	

Source: compiled during the evaluation

Abbreviations: CAP=community acquired pneumonia; COPD=chronic obstructive pulmonary disease; DB=double blind; IPD=invasive pneumococcal disease; OL=open label; mITT=modified intent to treat; NNDSS=National Notifiable Diseases Surveillance System; R=randomised; VE=vaccine efficacy; VT=vaccine type.

- 6.6 The inclusion criteria for CAPiTA differed from the proposed listing in that they recruited immunocompetent adults aged 65 years or older (average age 73 years), and excluded individuals previously vaccinated with a pneumococcal vaccine and individuals with immune deficiency or suppression. The proposed NIP listing is for at-risk individuals aged ≥ 5 to < 65 years, of which a large component are immunocompromised (immune deficient/suppressed). The submission also used efficacy from a per protocol population that excluded events in participants who developed immunocompromising conditions after recruitment; it may thus have overstated efficacy relative to that which may be associated with the proposed indication.
- 6.7 ATAGI noted there were limited data on the clinical efficacy of 13vPCV in individuals with at-risk conditions, which is a key area of uncertainty, although acknowledging that CAPiTA represents the available evidence (ATAGI pre-PBAC submission advice, June 2018, p23). ATAGI (pre-PBAC submission advice, June 2018, p1, pp15-16) considered that the effectiveness of pneumococcal vaccines is likely to vary across the different at-risk groups.
- 6.8 The main issues identified with regards to the transitivity of the participant characteristics in the randomised efficacy trials were due to the differences in participant enrolment. Two of the 23vPPV RCTs (French 2000 and Izumi 2017) enrolled immunocompromised individuals (French 2000) and patients with an autoimmune condition requiring treatment (Izumi 2017). Although, these studies included populations that are representative of the listing being sought, inclusion of these studies biased the analysis in favour of 13vPCV, as these patients are more susceptible to infections compared with the immunocompetent population in CAPiTA.
- 6.9 The CAPiTA study was conducted in immunocompetent individuals aged over 65 years, approximately half of whom had another risk factor, prior to the introduction of an infant 13vPCV immunisation program. The submission presented two post-hoc analyses to translate those results to the proposed at-risk population:
- Vaccine efficacy (VE) in immunocompromised individuals: Efficacy of 13vPCV in immunocompromised individuals was derived using the VE of 13vPCV in the PP population in CAPiTA, weighted by the ratio of the geometric mean fold rise (GMFR) from CAPiTA (as a measure of immunogenicity) and the GMFR averaged from multiple immunogenicity studies of 13vPCV and 7vPCV with immunocompromised individuals. This included an assessment of the impact on VE in immunocompromised individuals of prior exposure to 23vPPV. In the absence of acceptable alternative methods, ATAGI agreed in principle with the approach adopted in the submission (ATAGI pre-PBAC submission advice, June 2018, p16). The GMFR was an intermediate outcome from the immunogenicity studies (4-8 weeks post-vaccination). It is uncertain whether the short-term GMFR is generalisable to longer-term efficacy in this population, and sufficient to support a claim of superiority over 23vPPV in immunocompromised individuals. The ESC noted that the importance of this uncertainty depends on the number of

individuals who are immunocompromised as opposed to just having an at-risk condition.

- A post-hoc subgroup analysis of VE in ‘at-risk’ individuals (participants with pre-existing underlying medical conditions including heart disease, lung disease, asthma, diabetes, liver disease, smoking and splenectomy) compared with VE in individuals ‘without known risk’ (this was published as Suaya et al 2018).

Comparative effectiveness

6.10 The results for the primary and key secondary outcomes for CAPiTA for the modified ITT (mITT) population (all vaccinated individuals regardless of the occurrence of immunocompromising events), PP population, and subgroup analysis of participants with pre-existing underlying medical conditions are presented in Table 4. Based on the results from the overall study population (PP or mITT), the use of 13vPCV is associated with significantly fewer infection events than no vaccination.

Table 4: Results of pneumococcal CAP and IPD outcomes in CAPiTA

Outcome and case level population	13vPCV n with event/N (%)	Placebo n with event/N (%)	VE ^a (%) (95.2% CI ^b)	RD (%) (95% CI)	NNV
First episode confirmed VT pneumococcal CAP (primary outcome)					
Per-protocol	49/42,240 (0.116)	90/42,256 (0.213)	45.6 (21.8, 62.5)	-0.10 (-0.15, -0.04)	1,031
Post-hoc, per-protocol					
With at-risk conditions ^c	43/20,680 (0.208)	72/20,705 (0.348)	40.3 (11.4, 60.2)	-0.14(-0.24, -0.04)	
Without at-risk conditions	6/21,339 (0.028)	18/21,340 (0.084)	66.7 (11.7, 89.3)	-0.1 (-0.1,0.0)	
mITT	66/42,240 (0.156)	106/42,256 (0.251)	37.7 (14.3, 55.1)	-0.09 (-0.16, -0.03)	1,057
Immune-competent	51/42,240 (0.121)	93/42,256 (0.220)			
Immune-deficient/suppressed	14/42,240 (0.033)	11/42,256 (0.026)			
mITT (immunosuppressed) ^d	NR	NR	-27.3 (-212.1, 46.7)		
Post-hoc, mITT					
With at-risk conditions ^c	56/20,680 (0.271)	83/20,705 (0.401)	32.5 (3.9,53.0)	-0.13 (-0.24, -0.02)	
Without at-risk conditions	8/21,339 (0.037)	22/21,340 (0.103)	63.7 (14.7,86.1)	-0.1 (-0.1,0.0)	
First episode confirmed NB/NI VT pneumococcal CAP					
Per-protocol	33/42,240 (0.078)	60/42,256 (0.142)	45.0 (14.2, 65.3)	-0.06 (-0.11, -0.02)	1,566
mITT	43/42,240 (0.102)	73/42,256 (0.173)	41.1 (12.7, 60.7)	-0.07 (-0.12, -0.02)	1,409
Immune-competent	35/42,240 (0.083)	63/42,256 (0.149)			
Immune-deficient/suppressed	7/42,240 (0.017)	10/42,256 (0.024)			
mITT (immunosuppressed) ^d	NR	NR	30.0 (-105.5, 77.6)		
First episode VT IPD					
Per-protocol	7/42,240 (0.017)	28/42,256 (0.066)	75.0 (41.4, 90.8)	-0.05 (-0.08, -0.02)	2,012
Post-hoc, per-protocol					
With at-risk conditions ^{c,e}	5/20,680 (0.024)	22/20,705 (0.106)	77.3 (38.1, 93.4)		
Without at-risk conditions ^e	2/21,339 (0.009)	6/20,680 (0.029)	66.7 (-88.7, 96.8)		
mITT	8/42,240 (0.019)	33/42,256 (0.078)	75.8 (46.5, 90.3)	-0.06 (-0.09, -0.03)	1,690
Immune-competent	7/42,240 (0.017)	28/42,256 (0.066)			
Immune-deficient/suppressed	1/42,240 (0.002)	3/42,256 (0.007)			
mITT (immunosuppressed) ^d	NR	NR	66.7 (-315.1, 99.4)		

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Source: Table 2.5.1 p62, Table 2.5.2 p63 and Table 2.6.1 p72 of the submission; Suaya Table 3 p1480; ATAGI pre-PBAC submission advice, June 2018, Table 3.1 p16. Table 2.5.1p 57 of the commentary. Values in italics were calculated during the evaluation; values in bold are statistically significant.

Abbreviations: 13vPCV=13-valent pneumococcal conjugate vaccine; CAP=community acquired pneumonia; CI=confidence interval; IPD=invasive pneumococcal disease; mITT=modified intent to treat; NB/NI=non-bacteraemic/ non-invasive; NNV=number needed to vaccinate; NR=not reported; RD=risk difference; RR=risk ratio; VE=vaccine efficacy; VT=vaccine type

a $VE = (1-RR) \times 100$

b O'Brien-Fleming adjustment for 1 interim analysis

c The conditions covered included heart disease, lung disease, asthma, diabetes, liver disease, smoking and splenectomy. Subjects who self-identified a history of splenectomy or did not respond to any of the questions in the screening list were excluded from the post-hoc analysis.

d VE of the mITT (immunosuppressed) were reported in the ATAGI pre-PBAC submission advice, June 2018.

e The results of the post-hoc analysis of VE of 13vPCV against IPD reported in Table 2.6.2 p76 of the submission could not be verified during the evaluation.

- 6.11 Based on the average GMFR across all 7vPCV and 13vPCV studies, the submission estimated that VE of 13vPCV would be reduced by 12% in immunocompromised patients. The impact of applying this weighting to the VE of 13vPCV is provided in Table 5. The VE of 13vPCV against VT-IPD and VT-CAP was recalculated based on the data verification during the evaluation; this resulted in an estimate of a 13% reduction of VE efficacy based on data from the immunogenicity studies. Using this method, efficacy of 13vPCV was reduced further in immunocompromised individuals with prior 23vPPV compared with those with no prior 23vPPV; ATAGI has previously identified the potential for “blunting” of vaccine efficacy in individuals with prior exposure to 23vPPV.
- 6.12 Results of the subgroup analysis comparing at-risk and non-at-risk individuals in CAPiTA showed that VE of 13vPCV against VT-CAP was less in the ‘at-risk’ group (40.3%; 95% CI: 11.4–60.2%) compared with those ‘without known risk’ (66.7%; 95% CI: 11.7–89.3%). However, the confidence intervals overlapped between groups, suggesting no difference. VE of 13vPCV against VT-IPD in the ‘at-risk’ group was 77.3% (95% CI: 38.1–93.4%); VE in those ‘without known risk’ was less precise due to low case numbers (66.7%; 95% CI: -89.0–96.8%). For efficacy against all pneumococcal CAP, the difference between the groups was much less (ATAGI pre-PBAC submission advice, June 2018, p15). The post-hoc sub-group analysis suggests that while the VE of 13vPCV in ‘at-risk’ individuals was numerically lower, VE did not differ from that in individuals ‘without known risk’.

Table 5: 13vPCV efficacy using immunogenicity studies

Pneumococcal disease	Estimates from Submission		Estimates calculated during evaluation ^e	
	VT-IPD	First episode of VT CAP	VT-IPD	First episode of VT CAP
CAPiTA	75.00 (41.43-90.78) ^a	45.56 (21.82-62.49)	75.00 (41.43-90.78)	45.56 (21.82-62.49)
Vaccine efficacy (immunocompetent)	75.00 (41.43-90.78) ^a	45.56 (21.82-62.49)	75.00 (41.43-90.78)	45.56 (21.82-62.49)
Vaccine efficacy (immunocompromised)	66.00 (36.46-79.89) ^b	40.09 (19.20-54.99) ^b	65.04 (35.93, 78.72)	39.51 (18.92, 54.19)
Weighted ≥15-<65 years ^c	74.37 (41.08-90.01)	45.17 (21.64-61.96)	74.30 (41.04, 89.93)	45.13 (21.62, 61.91)
Weighted ≥5-<15 years ^d	74.48 (41.14-90.15)	45.25 (21.67-62.06)	74.43 (41.11, 90.09)	45.21 (21.65, 62.01)

Source: Table 2.6.1, p130 of the submission

Abbreviations: 13vPCV=13-valent pneumococcal conjugate vaccine; CAP=Community-acquired pneumonia; IPD=Invasive pneumococcal disease; VT=Vaccine-type

a Source of data could not be verified during the evaluation.

b 12% lower than CAPiTA results (source: Table 2.6.1, p 33. Calculated as the percentage reduction from CAPiTA)

Submission calculated VE against IPD as: 75.00 (100% - 12%) = 66.00%.

Using formula provided by submission, VE against IPD, Efficacy_{immunocompromised} = 75.00 * (5.81/6.59) = 66.12 (95% CI:36.53, 80.04).

c 93% immunocompetent, 7% immunocompromised.

d 94% immunocompetent, 6% immunocompromised.

e During the evaluation VE estimates were recalculated using formula $VE^*(y/x)$ where y/x is a ratio of GMFR from immunogenicity studies in immunocompromised patients (y) and CAPiTA (x).

6.13 An indirect statistical comparison of 13vPCV and 23vPPV was not presented in the submission. This was reasonable given the substantial differences across the 13vPCV and 23vPPV trials with respect to inclusion criteria, incidence of pneumonia in the control groups, and outcomes assessed. As a result, however, a reliable estimate of the incremental efficacy was not available. A qualitative comparison of the efficacy outcomes in 13vPCV and 23vPPV is presented in Table 6. From these results it can be observed that the evidence from CAPiTA supported a difference between 13vPCV and no vaccination across all outcomes with the exception of all-cause pneumonia and non-bacteraemic pneumococcal pneumonia. In contrast, the only differences noted in favour of 23vPPV were for VT-IPD. The PBAC previously considered that the evidence for 13vPCV over no vaccination was of higher quality than that for 23vPPV over no vaccination (13vPCV PSD, July 2015, paragraph 7.6).

Table 6: Summary of the qualitative comparison of efficacy outcomes for 13vPCV and 23vPPV

Trial	13vPCV	23vPPV/PBO	RR (95% CI)	Event rate/100 patients			RD (95% CI)	
				13vPCV	23vPPV/PBO			
Benefits								
VT pneumococcal pneumonia								
	13vPCV	PBO	23vPPV	RR (95% CI)	Event rate/100 patients			RD (95% CI)
					13vPCV	PBO	23vPPV	
CAPiTA	66/ 42,240	106/ 42,256	-	0.62 (0.45, 0.86)	0.16	0.25	-	-0.0009 (-0.0016, -0.0003)
23vPPV	No 23vPPV studies available assessing VT pneumonia							
Pneumococcal pneumonia								
	13vPCV	PBO	23vPPV	RR (95% CI)	Event rate/100 patients			RD (95% CI)
					13vPCV	PBO	23vPPV	
CAPiTA	135/ 42,240	174/ 42,256	-	0.78 (0.62, 0.98)	0.3	0.4	-	-0.0009 (-0.0017, -0.0001)
23vPPV RCTs pooled, 4 trials	-	59/ 1,590	35/ 1,603	0.64 (0.24, 1.73) Heterogeneity p-value=0.02	-	3.7	2.2	-0.01 (-0.04, 0.01) Heterogeneity p-value=0.00001
Pneumonia (all-cause)								
	13vPCV	PBO	23vPPV	RR (95% CI)	Event rate/100 patients			RD (95% CI)
					13vPCV	PBO	23vPPV	
CAPiTA	747/ 42,240	787/ 42,256	-	0.95 (0.86, 1.05)	1.8	1.9	-	-0.0009 (-0.0027, 0.0009)
23vPPV RCTs pooled, 7 trials	-	296/ 2,757	283/ 2,781	1.02 (0.77, 1.35) Heterogeneity p-value=0.007	-	10.7	10.2	-0.00 (-0.03, 0.03) Heterogeneity p-value=0.002
Breiman 2000	23vPPV: Non-randomised case control study, RR= 0.51 (0.30, 0.87)							
VT IPD								
	13vPCV	PBO	23vPPV	RR (95% CI)	Event rate/100 patients			RD (95% CI)
					13vPCV	PBO	23vPPV	
CAPiTA	8/ 42,240	33/ 42,256	-	0.24 (0.10, 0.54)	0.019	0.078	-	-0.0006 (-0.0009, -0.0003)
French 2000	-	10/695	15/697	1.50 (0.68, 3.31)	-	1.4	2.2	0.01 (-0.01, 0.02)
Menzies 2014	23vPPV: Non-randomised study using screening method, RR= 0.39 (0.33, 0.45)							
Rudnick 2013	23vPPV: Non-randomised study using indirect cohort method, RR= 0.54 (0.37, 0.78)							
Shapiro 1991	23vPPV: Non-randomised case control study, RR= 0.44 (0.33, 0.58)							
Bacteraemic pneumococcal pneumonia								
	13vPCV	PBO	23vPPV	RR (95% CI)	Event rate/100 patients			RD (95% CI)
					13vPCV	PBO	23vPPV	
CAPiTA	34/ 42,240	66/ 42,256	-	0.51 (0.33, 0.79)	0.08	0.16	-	-0.0008 (-0.0012, -0.0003)
23vPPV RCTs pooled, 3 trials	-	1/ 1,048	8/ 1,038	0.18 (0.03, 1.03) Heterogeneity p-value=0.85	-	0.10	0.77	Not reported
Non-bacteraemic pneumococcal pneumonia								
	13vPCV	PBO	23vPPV	RR (95% CI)	Event rate/100 patients			RD (95% CI)
					13vPCV	PBO	23vPPV	
CAPiTA	90/ 42,240	109/ 42,256	-	0.83 (0.62, 1.10)	0.21	0.26	-	-0.0004 (-0.0011, 0.0002)
23vPPV RCTs pooled, 3 trials	-	50/ 1,154	32/ 1,139	0.60 (0.16, 2.23) Heterogeneity p-value=0.005	-	4.33	2.81	Not reported

Source: Table 2.5.1 p58 and Table 2.5.2 p 59 of the commentary; Table 2.5.1 p62 and Table 2.5.1, p155 of the submission.

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Abbreviations: 13vPCV=13-valent pneumococcal conjugate vaccine; 23vPPV=23-valent pneumococcal polysaccharide vaccine; CI=confidence interval; CAP=community acquired pneumonia; PBO=placebo; RCT=randomized controlled trial; RD=risk difference; RR=risk ratio; VT=vaccine type.

Bold text indicates statistical significance.

Comparative harms

- 6.14 The harms data were the same as presented in the March 2015, July 2015 and July 2016 13vPCV submissions for older adults. No safety concerns were previously raised by the PBAC.
- 6.15 A number of published studies that assessed the adverse events profile of 13vPCV in individuals with at-risk conditions are available that primarily assessed the immunogenicity of one or more doses of 13vPCV in populations with an at-risk condition including HIV infection, HSCT, chronic renal disease, renal transplantation and receiving immunosuppressive therapy for cancers. ATAGI considered that overall there were no major safety concerns identified following receipt of 13vPCV in individuals with at-risk conditions (ATAGI pre-PBAC submission advice, June 2018, p17).

Benefits/harms

- 6.16 The qualitative nature of the indirect comparison presented in the submission did not allow for a quantitative comparison of the benefits and harms of 13vPCV with 23vPPV. Accordingly, a benefits/harms table has not been presented.

Clinical claim

- 6.17 The submission described 13vPCV as:
- superior in terms of comparative effectiveness for the prevention of VT-CAP and IPD over 23vPPV; and
 - equivalent to 23vPPV in terms of comparative safety.
- 6.18 The claim of superior comparative effectiveness was not supported by the qualitative nature of the indirect comparison presented in the submission. The following considerations arise with regard to the efficacy claim:
- The submission's claim that 13vPCV was superior to 23vPPV in terms of VE against IPD is inconsistent with the PBAC's previous recommendations for the use of 13vPCV in adults which were based on similar evidence (March/2015/July 2015/July 2016). The PBAC previously considered that efficacy of 13vPCV was at least likely to be 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 (13vPCV PSD July 2015, paragraph 7.6). The PBAC previously considered that, due to reduced serotype coverage of 13vPCV compared with 23vPPV, the claim of equivalent effectiveness for prevention of IPD was highly uncertain, and dependent not only on assumptions regarding the magnitude and duration of protection against VT-IPD for each vaccine, but also on the relative contribution of 23vPPV/non-13vPCV serotypes to IPD over time. If 13vPCV

serotypes are eventually eliminated as a result of the infant program, 13vPCV will become inferior to 23vPPV for IPD (13vPCV PSD July 2016 paragraph 6.17). The submission did not address the concerns raised previously by the PBAC.

- The PBAC previously accepted that 13vPCV is likely to be superior to 23vPPV in terms of prevention of VT-CAP, in the absence of directly comparative evidence between 13vPCV and 23vPPV. The PBAC considered that the magnitude of superiority, however, was unclear due to a lack of evidence of the efficacy of 23vPPV (13vPCV PSD, July 2016 paragraph 3.2 and paragraph 6.18 and 7.6).
- The listing requested for adults (≥ 15 to < 65 years) was in at-risk individuals (principally those who are immunocompromised or have other predisposing risk factors). The clinical evidence for 13vPCV from CAPITA was for an immunocompetent population aged over 65 years, approximately half of whom had another risk factor. Immunosuppressed individuals were excluded from CAPITA. The claim of vaccine efficacy of 13vPCV in immunocompromised individuals was supported using an intermediate outcome (GMFR, 4-8 weeks post-vaccination). While ATAGI agreed in principle with the approach (ATAGI pre-PBAC submission advice, June 2018, p16), the applicability of that intermediate outcome to the longer-term effectiveness of 13vPCV in immunocompromised individuals is unclear (see point 6.7).

6.19 The PBAC previously considered that the claim of equivalent comparative safety of 13vPCV with 23vPPV was reasonable (13vPCV PSD, July 2016 paragraph 6.19).

6.20 The ESC considered that

- the claim of superior clinical effectiveness for the prevention of IPD was not supported by the submission;
- the submission did not present a basis for the PBAC to reach a different conclusion with regards to the claim of superior clinical effectiveness for the prevention of VT-CAP for the requested population compared with older adults, i.e. 13vPCV is likely to be superior to 23vPPV in terms of prevention of VT-CAP but the magnitude of efficacy is unclear; and
- the claim of equivalent comparative safety was reasonable.

Economic analysis

6.21 The economic evaluations presented were a cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). The submission presented two versions of the model: one for at-risk individuals aged ≥ 5 to < 65 years, the other for Indigenous adults aged ≥ 25 years. Health benefits were reported as life years (LYs) and quality-adjusted life years (QALYs) gained. The model structure was the same as that presented in the March 2015, July 2015 and July 2016 submissions for adults aged ≥ 65 years/Indigenous adults aged ≥ 50 years. The model structure is summarised in Table 7.

Table 7: Summary of model structure and rationale

Component	Summary
Time horizon	Lifetime (ranging from 4 years in adults aged 62, to 59 years in children aged 7) in the model base case versus 2-4 years in the trials.
Outcomes	LYs and QALYs gained
Methods used to generate results	Cohort expected value analysis
Health states	Alive (no meningitis cx), Alive (with meningitis cx), Dead
Events modelled	IPD (bacteraemia; meningitis), Hospital treated CAP, GP treated CAP
Cycle length	1 year, half cycle correction applied
Transition probabilities	At risk population: aged ≥ 5 to < 65 years: Transition to 'Dead': Australian population death rates if no event or GP treated CAP; 3.6% for IPD (bacteraemia and meningitis) and hospitalised pneumonia. Transition to 'Alive, meningitis cx': 35% of meningitis events Indigenous adults: aged ≥ 25 years: Transition to 'Dead': Indigenous specific death rates if no event or GP treated pneumonia; 3.6% for IPD (bacteraemia and meningitis) and hospitalised pneumonia. Transition to 'Alive, meningitis cx': 35% of meningitis events

Source: Compiled during the evaluation.

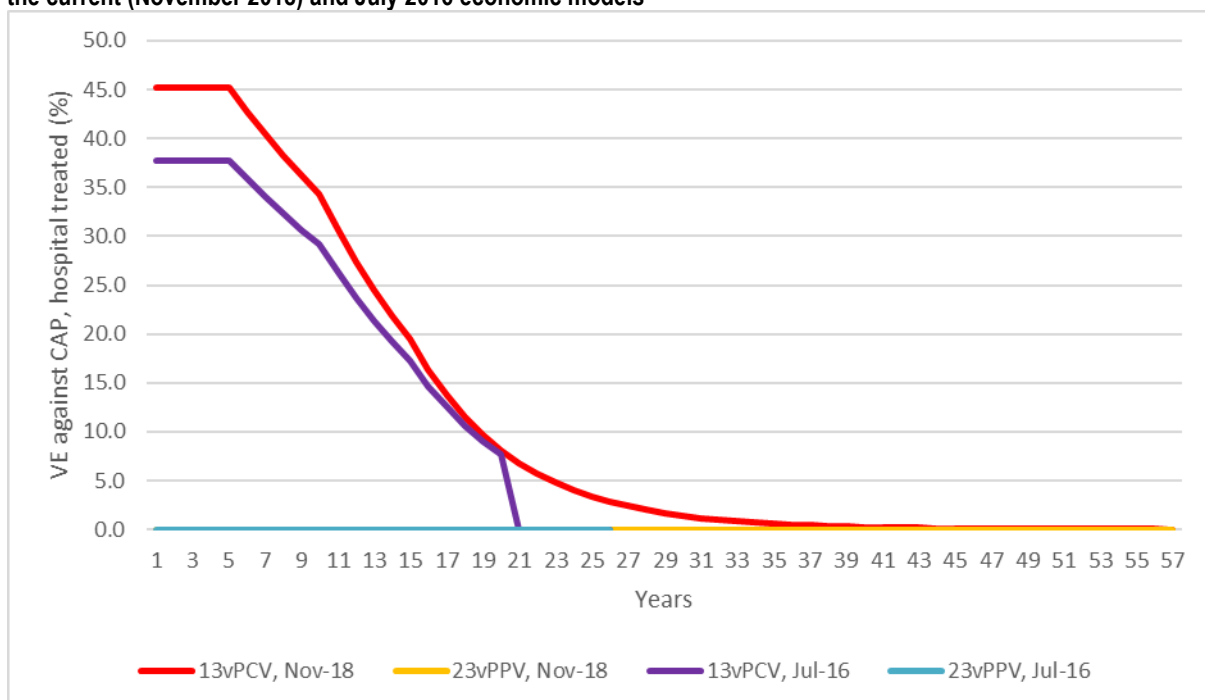
Abbreviations: CAP=Community acquired pneumonia; cx=complications; GP=General practitioner; IPD=invasive pneumococcal disease; LY=Life-year; QALY=Quality-adjusted life-year.

- 6.22 The model did not consider that at-risk individuals would require a dose of 23vPPV one year after the initial 13vPCV or five years after the initial 23vPPV dose, and a further revaccination with 23vPPV five to 10 years later. Although the same proportion of individuals in both arms of the model would receive subsequent doses of 23vPPV, the incremental efficacy and safety of 23vPPV may differ based on whether the previous dose was 23vPPV or 13vPCV.
- 6.23 The submission included costs for vaccine acquisition, administration and the treatment of vaccine preventable events; this was appropriate. The submission did not include the costs associated with provider or community education regarding the availability of 13vPCV for the proposed immunisation program.
- 6.24 The submission applied a lifetime time horizon, defined as time until individuals in the at-risk population were 65 years old, and individuals in the Indigenous population were 50 years old. Empirical data from the trials (2 to 4 years in duration) were used to inform the extrapolation of the within trial data to a lifetime time horizon. The model assumed the incidence of IPD and CAP by serotype was constant over time; however, the distribution of serotypes causing IPD and CAP changes over time. The proportion of IPD and CAP prevented with 13vPCV and 23vPPV is uncertain and may be overestimated. The stability of serotype coverage over time is likely to change, thus a shorter model time horizon (within 20 years) would be more informative. The PSCR (p3) argued that serotype replacement was not considered in the economic evaluation because it was not known what patterns of serotypes replacement would be. The ESC noted the advice from the chair of ATAGI's Pneumococcal Working Party that extrapolations beyond 20 years are highly uncertain due to the potential for changes in the pattern and distribution of pneumococci serotypes and expected waning of antibody levels over time (Verbal advice from the chair of ATAGI's Pneumococcal Working Party, A/Prof Christopher Blyth; 22nd August 2018 and confirmed at the ESC

meeting). The ESC considered that not including serotype replacement over time in the economic model is likely to bias the results in favour of 13vPCV. In this regard, the ESC noted that in March 2015 the PBAC considered that serotype replacement by non-13vPCV serotypes could result in resurgence of IPD, especially for people without at risk conditions receiving only 13vPCV, which would attenuate the overall benefit of reducing disease caused by vaccine serotypes (13vPCV PSD March 2015 paragraph 7.9; 13vPCV PSD July 2015 paragraph 6.20).

- 6.25 ATAGI considered that the economic evaluation needed to include consideration of waning of 13vPCV efficacy over time. It is likely that the rate of any waning would be greater among immunocompromised individuals (ATAGI pre-PBAC submission advice, June 2018, p17). The extrapolation of the duration of protection of 13vPCV over the lifetime horizon favoured 13vPCV. The ESC noted that the longer assumed duration of protection for 13vPCV resulted in a larger number of cases of IPD prevented, relative to 23vPPV, despite 13vPCV covering fewer serotypes than 23vPPV (see Table 8). The difference also resulted in a large difference for the avoidance of CAP events with 13vPCV relative to 23vPPV, as shown in Figure 1 and Table 8.

Figure 1: Comparison of vaccine efficacy (VE) against hospital-treated CAP for 13vPCV and 23vPPV over 60 years in the current (November 2018) and July 2016 economic models

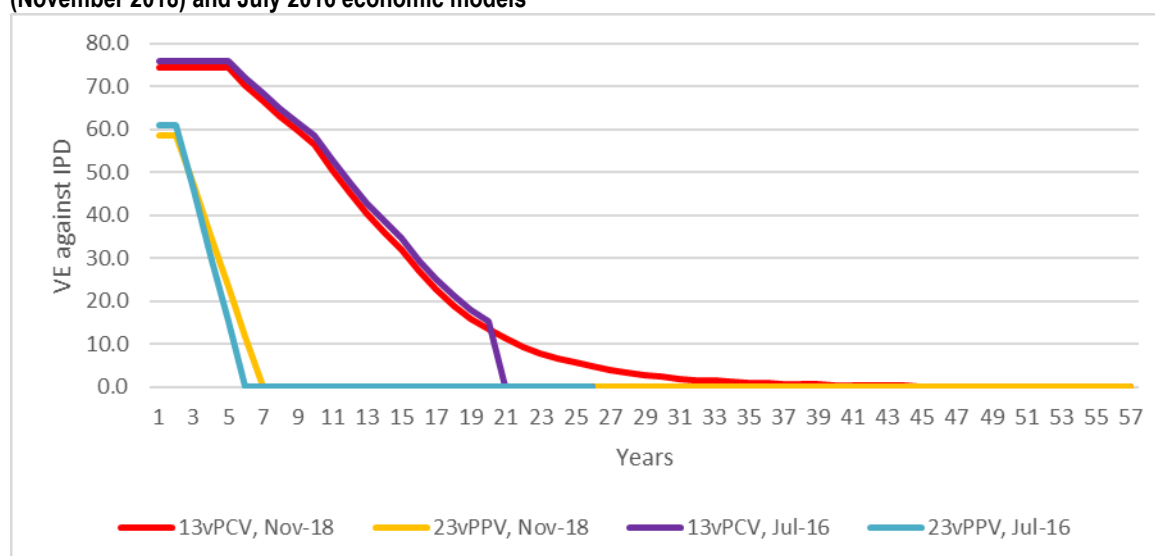


Source: Compiled during the evaluation; 'Eff' worksheet, Prevenar economic model - increased risk, July 2018.

Note: Data in the figure are only presented for the age group ≥ 15 to < 65 years of individuals at increased risk. Data from the November 2018 submission are based on the PP analysis of CAPiTA, while those from the July 2016 resubmission are from the mITT analysis.

Abbreviations: 13vPCV=13-valent pneumococcal conjugate vaccine; 23vPPV=23-valent pneumococcal polysaccharide vaccine; CAP=Community acquired pneumonia; VE=vaccine efficacy.

Figure 2: Comparison of vaccine efficacy (VE) against IPD for 13vPCV and 23vPPV over 60 years in the current (November 2018) and July 2016 economic models



Source: Compiled during the evaluation; 'Eff' worksheet, Prevenar economic model - increased risk, July 2018.

Note: Data in the figure are only presented for the age group ≥ 15 to < 65 years of individuals at increased risk. Data from the November 2018 submission are based on the PP analysis of CAPiTA, while those from the July 2016 resubmission are from the mITT analysis.

Abbreviations: 13vPCV=13-valent pneumococcal conjugate vaccine; 23vPPV=23-valent pneumococcal polysaccharide vaccine; IPD=invasive pneumococcal disease; VE=vaccine efficacy.

6.26 Table 8 presents a comparison of the number of cases of IPD and CAP with vaccination with 13vPCV compared with 23vPPV over 60 years in the economic model.

Table 8: Comparison of number of events over 60 years in the economic model

	IPD			CAP	
	Bacteraemia	Meningitis w/o cx	Meningitis w/ cx	PNE hosp	PNE GP visits
Submission base case: events per 1,000,000 individuals vaccinated					
23vPPV	3,119	211	107	22,819	22,819
13vPCV	2,946	199	102	21,462	22,169
Difference ^a	-174	-12	-6	-1,357	-649
Events based on expected vaccination in the year 2019 as estimated in the submission (N=1,209,590) (Table 11)					
23vPPV	3,773	255	130	27,601	27,601
13vPCV	3,563	241	123	25,960	26,816
Difference ^a	-210	-14	-7	-1,641	-786
Events based on expected vaccination in the year 2019 estimated in the Commentary (N=906,125) (Table 12)					
23vPPV	2,826	191	97	20,677	20,677
13vPCV	2,669	181	92	19,447	20,088
Difference ^a	-157	-10	-5	-1,230	-588

Source: Compiled during the evaluation; Table 4.2.4 and Table 4.2.5 of the Commentary; "Summary" and "IPD" worksheets, Prevenar economic model - increased risk, July 2018.

Note: Data in the table is only presented for model of individuals at increased risk.

^a Difference is the number of 13vPCV events minus the number of 23vPPV events.

Abbreviations: 13vPCV=13-valent pneumococcal conjugate vaccine; 23vPPV=23-valent pneumococcal polysaccharide vaccine; CAP=Community acquired pneumonia; cx=complications; GP=general practitioner; IPD=Invasive pneumococcal disease; PNE=pneumonia; w/=with; w/o=without.

6.27 The submission utilised baseline incidence data for pneumococcal disease from 2015-16, thereby effectively incorporating the impact on pneumococcal infection rates of the existing vaccination program. The testing of herd immunity via sensitivity analyses

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only was appropriate given the existing program of pneumococcal vaccination for infants and older persons, as those programs would be anticipated to generate the bulk of herd immunity effects in the prevention of pneumococcal disease.

6.28 A summary of the key drivers of the model (using the results for at-risk individuals aged ≥5 to <65 years) is shown in Table 9.

Table 9: Key drivers of the model

Description	Method/Value	Impact	\$/QALY ^a
Base case	Individuals at-increased risk of pneumococcal disease		\$ [REDACTED]
13vPCV efficacy for hospitalised CAP	Sourced from PP analysis in CAPiTA (N=84,496). VE of 13vPCV adjusted for immunocompromised individuals in a post-hoc analysis using ratio of GMFR from 13vPCV/7vPCV immunogenicity studies.	High	LL: \$ [REDACTED] UL: \$ [REDACTED]
13vPCV efficacy for IPD	Sourced from PP analysis in CAPiTA (N=84,496). VE of 13vPCV adjusted for immunocompromised individuals in a post-hoc analysis using ratio of GMFR from 13vPCV/7vPCV immunogenicity studies.	High	LL: \$ [REDACTED] UL: \$ [REDACTED]
23vPPV efficacy for CAP	Zero protective benefit assumed based on meta-analysis of underpowered RCTs in a total of 5,538 subjects	High, favours 13vPCV	UL: \$ [REDACTED]
Waning efficacy	<ul style="list-style-type: none"> 13vPCV: constant for 5 years, then declines over model duration. 23vPPV: constant for 2 years, then declines to 0 by 5 years. 	High, favours 13vPCV	13vPCV, VE=0 at: 20 years: \$ [REDACTED] 5 years: \$ [REDACTED]
Time horizon	Lifetime time horizon assumed from 2-4 year trial duration.	High, favours 13vPCV	4 years: \$ [REDACTED] 20 years: \$ [REDACTED]
Serotype distribution	Assumption IPD and CAP by serotype were constant over time; however, the distribution of incidence of IPD and CAP due to serotype changes over time.	Likely to be high and to favour 13vPCV if the proportion of 13v serotypes reduces over time	Sensitivity not done ^b
Case fatality rate of VT hospitalised CAP	Sourced from NNDSS (Toms 2016) for hospital treated pneumonia (3.6%).	High	LL: \$ [REDACTED] UL: \$ [REDACTED]
Utilities	High values for model health states taken from Hawthorne 2013 where median values were used.	Moderate, favours 13vPCV	Hawthorne 2013, mean values: \$ [REDACTED] Norman 2013, mean values: \$ [REDACTED]
Background rate of pneumococcal infection	Based on reported incidence of pneumococcal pneumonia in Australia 2015/16.		-10%: \$ [REDACTED] +10%: \$ [REDACTED]

Source: Compiled during the evaluation.

Abbreviations: 7vPCV=7-valent pneumococcal conjugate vaccine; 13vPCV=13-valent pneumococcal conjugate vaccine; 23vPPV=23-valent pneumococcal polysaccharide vaccine; CAP=Community acquired pneumonia; GMFR=geometric mean fold rise; IPD=Invasive pneumococcal disease; LL=lower limit; PP=per protocol; QALY=Quality-adjusted life-year; RCT=randomised controlled trial; UL=upper limit; VE=vaccine efficacy; VT=vaccine type.

a Sensitivity analyses presented in this table are only for the economic model of at-risk individuals.

b Sensitivity analysis varying serotype distribution were not presented in the submission or conducted during the evaluation.

The redacted table shows ICERs in the range of less than \$15,000 per QALY to more than \$200,000/QALY.

6.29 Results of the economic evaluation are presented in Table 10. The use of 13vPCV is estimated to be more cost-effective in at-risk individuals (\$15,000-\$45,000 per QALY

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gained) than Indigenous adults (\$75,000-\$105,000 per QALY gained). This result was an artefact of the differences in age ranges and the time horizons between the two modelled scenarios: the general at-risk population was aged 5-64 years and followed up until age 65 years, while the Indigenous population was aged 25-49 years and followed up until age 50 years.

Table 10: Results of the economic evaluation

Outcome	13vPCV	23vPPV	Increment
Individuals at-increased risk of pneumococcal disease			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY	13,580	13,579	0.373
\$ /LY gained			\$ [REDACTED]
QALY	12,231	12,231	0.343
\$ /QALY gained			\$ [REDACTED]
Indigenous adults ≥ 25 years			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY	10,030	10,030	0.184
\$ /LY gained			\$ [REDACTED]
QALY	9032	9031	0.165
\$ /QALY gained			\$ [REDACTED]

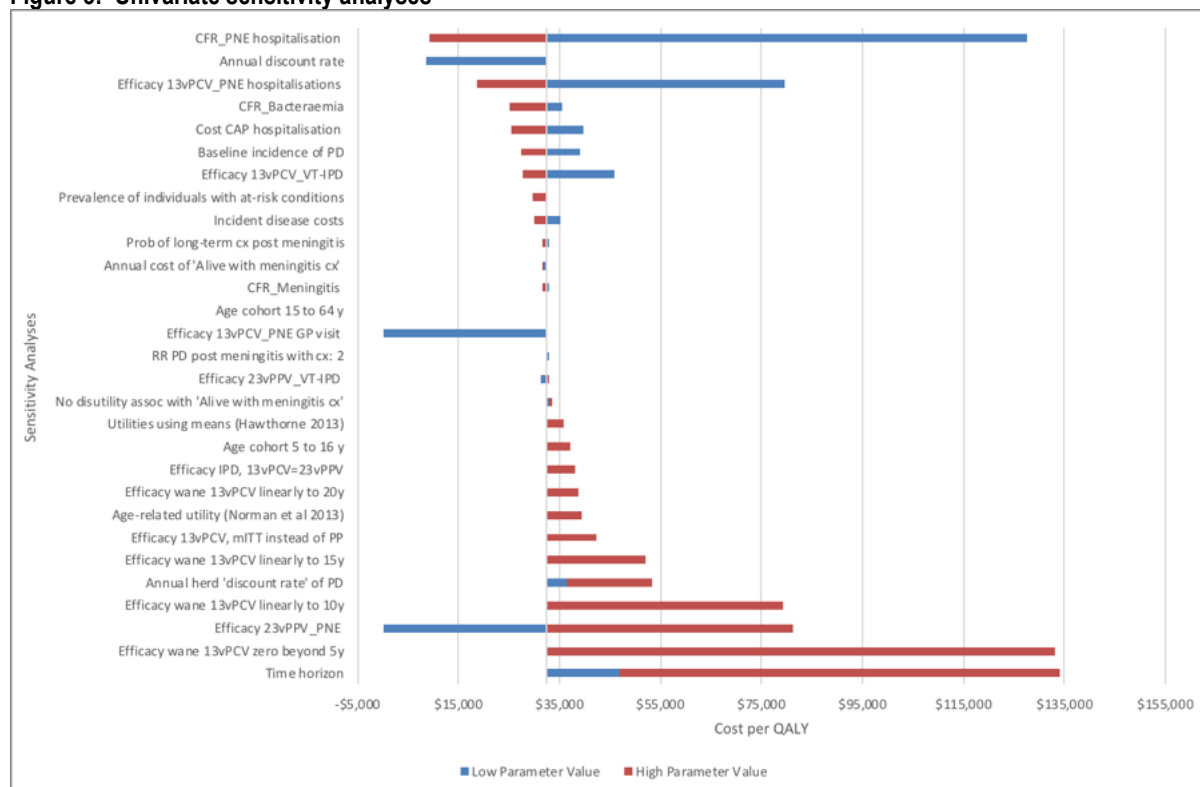
Source: Table A p204 and Table B p205 of the submission; compiled during the evaluation using "Summary", '13vPCV' and '23vPPV' worksheets of Prevenar economic model - increased risk, July 2018.

Abbreviations: 13vPCV=13-valent pneumococcal conjugate vaccine; 23vPPV=23-valent pneumococcal polysaccharide vaccine; LY=life-year; QALY= Quality-adjusted life-year.

The redacted table shows ICERs in the range of less than \$15,000 to 75,000 -\$105,000 per LY or QALY gained.

- 6.30 The pre-PBAC response (p3) proposed a reduced price of \$ [REDACTED] which resulted in ICERs of \$15,000 -\$45,000 per QALY gained for the at-risk population and \$45,000-\$75,000 per QALY saved for Indigenous adults.
- 6.31 Univariate sensitivity analyses were presented in the submission, with further analyses conducted during the evaluation. The results of the sensitivity analyses are presented in Figure 3. The model was most sensitive to: the duration of protection with 13vPCV (waning efficacy); the time horizon; discount rates; and parameters associated with the reduction in the number of hospital treated CAP events i.e. the 13vPCV efficacy, the baseline risk of hospital-treated CAP events and the cost of treating hospitalised CAP events. The model was also sensitive to the inclusion of herd immunity effects, the age-related utilities applied and the background incidence of pneumonia. The model results were less sensitive to parameters associated with the incidence of IPD due to the relatively low incidence of IPD. The model results were not sensitive to parameters associated with the incidence of GP treated CAP due to its low treatment cost and no impact on mortality.

Figure 3: Univariate sensitivity analyses



Source: Compiled during the evaluation using results from Table 3.9.2.

Abbreviations: 13vPCV=13-valent pneumococcal conjugate vaccine; 23vPPV=23-valent pneumococcal polysaccharide vaccine; ave=average; CFR=case fatality ratio; Ci=confidence interval; cx=complications; GP=general practitioner; ICER=incremental cost-effectiveness ratio; IPD=Invasive pneumococcal disease; QALY=Quality-adjusted Life-years; max=maximum; PD=pneumococcal disease; PNE=pneumonia; PP=per protocol; Prob=probability; RR=relative risk; VT=vaccine type; y=year.

The impact on the ICER of reducing the time horizon to 4 years (the within-trial duration) was excluded from the tornado plot as the resulting ICER (\$██████████ per QALY) would have swamped the impact of all other input variations.

6.32 The ESC noted that the key trial and the model structure was the same as that presented in the July 2016 13vPCV submission for older adults. The ESC and PBAC were previously concerned with the assumed magnitude and duration of protection against VT-IPD and VT-CAP and changes in the serotype distribution over time. In this regard, the ESC noted that the base case economic model accepted by the PBAC for older adults in July 2016 resulted in an ICER of less than \$15,000 per QALY gained and the ICER remained \$15,000-\$45,000 per QALY gained under a range of scenarios (13vPCV PSD, July 2016, paragraph 7.7). In July 2016, the PBAC indicated that these results provided it with greater confidence that the requested listing would be cost-effective compared with 23vPPV. The ESC noted that the concerns with the July 2016 model were also relevant to the current submission.

Drug cost/patient/dose: \$██████████

6.33 The 13vPCV cost per dose requested in the submission was \$██████████ (reduced to \$██████████ in the pre-PBAC response). The submission assumed individuals would only use one dose in their lifetime.

Estimated PBS usage & financial implications

- 6.34 This submission was not considered by DUSC.
- 6.35 The submission used an epidemiological approach in estimating the potential utilisation of 13vPCV on the NIP. The approach used by the submission assumed that each at-risk condition was mutually exclusive, potentially overestimating the proportion of people with an at-risk condition, as there is double-counting of individuals with multi-morbidity in an at-risk population. ATAGI advised that the appropriate estimate was the overall prevalence of individuals with a combined co-morbid condition, alcohol or smoking dependence (Table 2.3 p8 of the ATAGI pre-PBAC submission advice (June 2018) should have been used, not Table 2.1 p6). The PSCR (p3) stated that the utilisation estimates were conservative as they are higher than what would occur in reality.
- 6.36 A summary of the estimated use and financial implications for listing 13vPCV on the NIP and health budgets as estimated in the submission is provided in Table 11. At year 6 of listing, the estimated number of 13vPCV doses funded was over 200,000 and the net cost to the NIP was estimated to be around \$30-\$60 million. Estimates derived during the evaluation, taking into account the potential for multi-morbidity in determining risk-status as advised by ATAGI, are provided in Table 12.

Table 11: Estimated use and financial implications (submission estimates)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
13vPCV						
At risk, aged 5-15 years	████████	████████	████████	████████	████████	████████
Uptake	53%	53%	53%	53%	53%	53%
At-risk, aged ≥ 15years	████████	████████	████████	████████	████████	████████
Uptake	53%	53%	53%	53%	53%	53%
Indigenous adults aged ≥ 25years	████████	████████	████████	████████	████████	████████
Uptake	35%	35%	35%	35%	35%	35%
Total 13vPCV doses	████████	████████	████████	████████	████████	████████
Total 13vPCV cost (NIP)	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████
23vPPV						
Volume of displaced 23vPPV units	████████	████████	████████	████████	████████	████████
Total cost ^a of substituted 23vPPV to PBS/RPBS/NIP	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████
Estimated costs						
Net cost to NIP (13vPCV minus 23vPPV)	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████
Net cost to PBS/RPBS/NIP (13vPCV minus 23vPPV)	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████
Net MBS cost	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████
Cost to overall health budget	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████	\$ ██████████

Source: Table 4.2.6, Table 4.2.7, Table 4.2.8, Table 4.2.9, Table 4.3.1, Table 4.3.2, Table 4.4.1, Table 4.5.1 and Table 4.5.2 pp251-255 of the submission; '2a. Patients - 5-15 yrs', '2a. Patients - epi >15 yrs', '2a. Patients - ATSI>25 yrs', and '3a. Volumes – new' worksheets of excel file Prevenar 13 Utilisation-and-cost-model - Incr risk and Indig.

Abbreviations: 13vPCV=13-valent pneumococcal conjugate vaccine; 23vPPV=23-valent pneumococcal polysaccharide vaccine; MBS= Medical Benefits Schedule; NIP=National Immunisation Program; PBS=Pharmaceutical Benefits Scheme; RPBS= Repatriation Schedule of Pharmaceutical Benefits

Note: Submission estimates are as presented and have not been corrected unless otherwise stated.

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a The submission applied the wrong formula in the “4c. Displaced – EFF” worksheet where “cost to PBS” was added to “less co-payments”. The formula in cells D30 through to I30 were corrected during the evaluation.

Table 12: Estimated use and financial implications (evaluation: at-risk individuals and Indigenous adults only)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
13vPCV						
At risk, aged 5-15 years						
Uptake	53%	53%	53%	53%	53%	53%
At-risk, aged ≥ 15years						
Uptake	53%	53%	53%	53%	53%	53%
Indigenous adults aged ≥ 25years						
Uptake	35%	35%	35%	35%	35%	35%
Total 13vPCV doses						
Total 13vPCV cost (NIP)	\$	\$	\$	\$	\$	\$
23vPPV						
Volume of displaced 23vPPV units						
Total cost of substituted 23vPPV to PBS/RPBS/NIP	\$	\$	\$	\$	\$	\$
Estimated costs						
Net cost to NIP (13vPCV minus 23vPPV)	\$	\$	\$	\$	\$	\$
Net cost to NIP/PBS/RPBS (13vPCV minus 23vPPV)	\$	\$	\$	\$	\$	\$
Net MBS cost	\$	\$	\$	\$	\$	\$
Cost to overall health budgets	\$	\$	\$	\$	\$	\$

Source: compiled during the evaluation; Table 4.2.5, Table 4.2.7, Table 4.3.2, Table 4.4.2, Table 4.5.2 of the Commentary.

Abbreviations: 13vPCV=13-valent pneumococcal conjugate vaccine; 23vPPV=23-valent pneumococcal polysaccharide vaccine; MBS= Medical Benefits Schedule; NIP=National Immunisation Program; PBS=Pharmaceutical Benefits Scheme; RPBS= Repatriation Schedule of Pharmaceutical Benefits.

The redacted table shows that at year 6, the estimated number of doses was more than 200,000 and the net cost to the NIP would be \$20-\$30 million.

- 6.37 The main sources of uncertainty pertain to the number of eligible patients and uptake rates. The net NIP cost is sensitive to these parameters. Another source of uncertainty is the likelihood of concurrent dosing of 13vPCV and 23vPPV. It is likely that there will be difficulty in ascertaining the status of prior pneumococcal vaccination dosing in individuals’ medical records. For this reason, the number of people that would have received two or more doses of 23vPPV was unknown.

Quality Use of Medicines

- 6.38 The submission quoted a statement from the ATAGI pre-PBAC submission advice (June 2018, p21) that raised a concern on how individuals with at-risk conditions on the immunisation register will be identified given that the population-based immunisation register does not capture information on risk factor status in individuals. ATAGI recommended that clear guidelines be provided in order to identify individuals with an at-risk condition requiring vaccination. The submission did not provide any further discussion of these issues.

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

7 PBAC Outcome

- 7.1 The PBAC decided not to recommend a change to the circumstances under which 13vPCV is available as a designated vaccine for the NIP. Specifically, the PBAC decided not to recommend vaccination of individuals with an at-risk condition (aged ≥ 5 to < 65 years) and Indigenous adults (aged ≥ 25 years) on the basis of unacceptably high and uncertain estimated ICERs.
- 7.2 The PBAC noted the advice from ATAGI that the current funding arrangements though the NIP and PBS for 23vPPV in at-risk populations are complicated, varying by age and Indigenous status. ATAGI expressed a “strong desire to simplify the current recommendations and funding arrangements while ensuring optimal protection for those at increased risk of pneumococcal disease” (post-submission advice, p1). To support simplification of the current recommendations, ATAGI advised that 13vPCV followed by two doses of 23vPPV could be considered for children and adults who are at increased risk of IPD. ATAGI also advised Indigenous adults (aged ≥ 25 years) without at-risk conditions could receive one dose of 13vPCV followed by one dose of 23vPPV.
- 7.3 The submission requested listing for one dose of 13vPCV for children and adults (aged ≥ 5 to < 65 years) with an at-risk condition and one dose of 13vPCV for Indigenous adults (aged ≥ 25 years) without at-risk conditions. The PBAC accepted that a single dose of 23vPPV was the appropriate main comparator in this setting.
- 7.4 The PBAC noted that the key clinical evidence for 13vPCV from CAPiTA was in immunocompetent individuals aged over 65 years. While approximately half of the trial population had an at-risk condition, immunosuppressed individuals were excluded from CAPiTA. The submission relied on the application of immunogenicity results from immunocompromised individuals (using GMFR) to infer the application of efficacy outcomes from CAPiTA to what might apply in an immunosuppressed population.
- 7.5 The TGA approved Product Information for 13vPCV (p3) notes that “if sequential administration of 13vPCV and 23vPPV is considered, 13vPCV should be given first for maximal efficacy and to avoid blunting of the immune response by 23vPPV”. ATAGI has also previously advised that there is a risk of “blunting” of the efficacy of 13vPCV where it is given subsequent to 23vPPV. The PBAC noted that the requested NIP listing for 13vPCV included use in adults previously vaccinated with 23vPPV. The PBAC considered that the magnitude of this “blunting” on the efficacy of 13vPCV for these individuals could not be quantified.
- 7.6 The PBAC noted the modest VE for 13vPCV compared with placebo against VT-CAP in ‘at-risk’ individuals in CAPiTA of 40.3% (95% CI: 11.4–60.2%). In the absence of direct comparative evidence or an indirect statistical comparison for 13vPCV and 23vPPV, the PBAC accepted 13vPCV is likely to be superior to 23vPPV for the prevention of CAP caused by the serotypes in 13vPCV but considered that the magnitude of superiority was uncertain.

- 7.7 The PBAC further considered 13vPCV is likely to be superior for the prevention of IPD caused by the serotypes common to both vaccines and is inferior to 23vPPV for the prevention of IPD caused by serotypes contained only within 23vPPV (23v-non-13v serotypes). The PBAC noted that the submission did not provide evidence of any cross-protective effect to non-13v serotypes. The comparative clinical effectiveness of 13vPCV for the prevention of IPD is therefore dependent on the relative contribution of the serotypes in 13vPCV, compared with 23v-non-13v serotypes, over time. If 13vPCV serotypes are substantially reduced in the population as a result of the infant program, 13vPCV may become inferior to 23vPPV for IPD. In this regard, the PBAC recalled that it recently recommended a change to the dosing schedule for the 13vPCV infant program which is expected to further decrease IPD rates [caused by those serotypes in 13vPCV] in the 0-4 year age group (March 2018 13vPCV PSD, paragraph 6.3).
- 7.8 The PBAC considered that the claim of equivalent comparative safety to 23vPPV was reasonable.
- 7.9 The PBAC considered that in the context of the uncertainties with the magnitude of clinical benefit, the ICERs presented in the submission were unacceptably high and sensitive to changes in key assumptions. Accordingly, the PBAC was not confident that 13vPCV would be cost effective for the proposed population at the requested price. In particular, the PBAC noted the following concerns:
- Serotype replacement was not considered in the economic evaluation which was likely to bias the results in favour of 13vPCV. ATAGI advised that the incidence of disease due to 13vPCV serotypes (both overall and in the target populations of this submission) is expected to continue to decline in the coming years, due to the indirect herd protection impact of the revised dosing schedule for the childhood 13vPCV program which has high coverage (post-submission advice, p9).
 - The extrapolation of the duration of protection of 13vPCV over the time horizon favoured 13vPCV. In the base case, protection of 13vPCV against VT-IPD and VT-CAP was assumed to be constant for the first 5 years then began to wane such that it reached zero at 50 years. By comparison, protection of 23vPPV against IPD was constant for the first 2 years and then waned to zero by 5 years (while a zero protective effect was assumed against VT-CAP).
 - The model was particularly sensitive to the assumption of a zero protective effect for 23vPPV against VT-CAP which resulted in a large difference in the avoidance of CAP events with 13vPCV relative to 23vPPV.
 - The large difference in CAP events avoided with 13vPCV meant that the model results were also sensitive to parameters relating to CAP events, including treatment costs and mortality associated with hospitalisations due to VT-CAP.
- 7.10 The PBAC noted that the cost effectiveness of the comparator, 23vPPV, has not been established in this setting.

- 7.11 The PBAC noted that the submission overestimated the number of adults eligible for vaccination (aged ≥ 15 to <65) by applying risk factors cumulatively, rather than allowing for multi-morbidity. The submission's estimates of the number of individuals aged 15 years and older were 23% higher than those of the evaluation (based on estimates provided by ATAGI), resulting in a potential overestimate of the cost to Government. The PBAC considered the significant opportunity cost of listing 13vPCV on the NIP (even after accounting for the overestimate in eligible adults) was a concern in the context of the uncertain magnitude of the clinical benefit and the unreliability of the ICER.
- 7.12 The PBAC noted that this submission is not eligible for an Independent Review as the submission was a request for listing on the NIP.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Pfizer Australia is disappointed that the PBAC did not recommend the NIP-listing of Prevenar 13 for individuals at increased risk of pneumococcal disease and remains committed to working with the PBAC to enable reimbursed access for this population.