Coversheet on evidence assessment by ATAGI using the GRADE framework for the use of 21-valent pneumococcal conjugate vaccine in adults

Summary of key methods and decisions on evidence assessment using GRADE for developing ATAGI recommendations on the use of 21-valent pneumococcal conjugate vaccine (21vPCV) in adults for the Australian Immunisation Handbook.

Background

- 21vPCV was TGA approved on 5 February 2025 for adults aged ≥18 years.
- ATAGI undertook GRADE assessment in 2024 to make relevant recommendations on its use in anticipation of the availability of this vaccine in Australia.
- In November 2025 PBAC recommended that 21vPCV be a designated vaccine for the purposes of the *National Health Act 1953*, for the prevention of pneumococcal disease in non-Indigenous adults aged ≥65 years, Aboriginal and Torres Strait Islander adults aged ≥25 years, and individuals at increased risk of pneumococcal disease aged ≥18 years.
- In 2024, when this GRADE assessment was undertaken, the ATAGI recommendations were: 13-valent pneumococcal conjugate vaccine (13vPCV), 15-valent pneumococcal conjugate vaccine (15vPCV) or 20-valent pneumococcal conjugate vaccine (20vPCV) for non-Indigenous adults from age 70 years, and 13vPCV, 15vPCV or 20vPCV followed by up to a maximum of 2 doses of 23-valent pneumococcal polysaccharide vaccine (23vPPV) for Aboriginal and Torres Strait Islander adults from age 50 years and all adults aged ≥18 years with specified underlying at risk conditions. ATAGI was also considering the optimal pneumococcal schedule for all adults.
- 21vPCV contains the following serotypes: 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B. Only 11 of these are contained in 20vPCV (3, 6A, 7F, 8, 10A, 11A, 12F, 15B, 19A, 22F, 33F) and only 4 are shared with 13vPCV (3, 6A, 7F, 19A).

Research questions

1. What should be recommended regarding the use of 21vPCV for non-Indigenous Australians aged ≥70 years without underlying risk conditions who are currently recommended 13vPCV, 15vPCV or 20vPCV?

Table 1: PICO 1: 21vPCV vs 20vPCV

Population	Non-Indigenous adults aged ≥70 years without special risk factors
Intervention	21vPCV
Comparator	20vPCV
Outcomes	*Critical* • Serious adverse events (SAEs) *Important* • OPA GMT ratios (follow-up: 30 days) by vaccine serotypes • IgG GMR ratios (follow-up: 30 days) by vaccine serotypes • % of participants ≥4-fold rise of GMT by vaccine serotypes pre to post vaccination • % of participants ≥4-fold rise of GMC by vaccine serotypes pre to post vaccination • Injection site adverse events • Systemic adverse events

1. What should be recommended regarding the use of 21vPCV for Aboriginal and Torres Strait Islander Australian adults aged ≥50 years without underlying risk conditions who are currently recommended 13vPCV+23vPPV, 15vPCV+23vPPV or 20vPCV+23vPPV?

Table 2: PICO 2: 21vPCV vs 15vPCV+23vPPV

Population	Aboriginal and Torres Strait Islander Australian adults aged ≥50 years without special risk factors
Intervention	21vPCV
Comparator	15vPCV+23vPPV
Outcomes	Critical • Serious adverse events (SAEs) Important • OPA GMT ratios (follow-up: 30 days) by vaccine serotypes • IgG GMR ratios (follow-up: 30 days) by vaccine serotypes • % of participants ≥ 4-fold rise of GMT by vaccine serotypes pre to post vaccination • % of participants ≥ 4-fold rise of GMC by vaccine serotypes pre to post vaccination • Injection site adverse events • Systemic adverse events

2. What should be recommended regarding the use of 21vPCV for adults aged ≥18 years with specific risk factors (as in Australian Immunisation Handbook (AIH) list) who are currently recommended 13vPCV+23vPPV, 15vPCV+23vPPV or 20vPCV+23vPPV?

Table 3: PICO 3: 21vPCV vs. 15vPCV+23vPPV

Population	Adults aged ≥18 years with specific risk factors that (as in AIH list)
Intervention	21vPCV
Comparator	15vPCV+23vPPV
Outcomes	Critical • Serious adverse events (SAEs) Important • OPA GMT ratios (follow-up: 30 days) by vaccine serotypes • IgG GMR ratios (follow-up: 30 days) by vaccine serotypes • % of participants ≥ 4-fold rise of GMT by vaccine serotypes pre to post vaccination • % of participants ≥ 4-fold rise of GMC by vaccine serotypes pre to post vaccination • Injection site adverse events • Systemic adverse events

Literature search

A literature search was performed on 15/03/2024 to identify studies assessing immunogenicity, efficacy and/or safety outcomes of the 21vPCV vaccine in adults. Details of the search methods are presented in Appendix A. The citations were selected for review if they met the following criteria:

- *Study type:* Randomised controlled trial (RCT), observational study
- *Population:* Adults 18 years old and over
- *Intervention:* 21vPCV or 21vPCV+23vPPV
- *Comparator:* 13vPCV or 13vPCV+23vPPV
- *Outcomes:* Effectiveness, efficacy, immunogenicity, safety

Three citations met the above pre-defined inclusion criteria. One study was included for PICO 1 and had a comparison between 21vPCV and 20vPCV. The other two studies were included for PICO 2 and 3 and had a comparison between 21vPCV and 15vPCV+23vPPV.

Inclusion criteria and rationale

Table 4: Rationale for PICO and inclusion criteria

Inclusion criteria	Rationale
Study type: RCT, observational study	All study types comparing 21vPCV to 20vPCV or 15vPCV+23vPPV were part of the inclusion criteria, but only RCTs were available. No efficacy or effectiveness studies with clinical outcomes were identified.
Population	Included population groups were selected on the basis that they are the groups of adults for whom currently pneumococcal vaccination is recommended in the Australian Immunisation Handbook (AIH). For PICO 1 the population in the STRIDE-3 study was all adults aged ≥18 years with outcomes reported by two cohorts (18–49 years and ≥50 years). The ≥50-year age cohort was selected as the reported population for PICO 1 and was not downgraded for indirectness as it was considered reasonably aligned with the population of interest of ≥70 years. For PICO 2 and 3 the same studies were included. STRIDE-7 and STRIDE-8 were in people with risk conditions but neither included Indigenous adults and PICO 2 outcomes were downgraded for indirectness.
Intervention: 21vPCV 20vPCV+23vPPV	21vPCV alone or 21vPCV followed by 23vPPV to align with current 13vPCV and 23vPPV recommendations, by applicable population. None of the studies reported data on 21vPCV+23vPPV.
Comparator: 13vPCV 13vPCV+23vPPV	Non-indigenous adults aged ≥70 years without risk factors are currently recommended to receive 13vPCV, 15vPCV or 20vPCV alone and Aboriginal and Torres Strait Islander Australian adults aged ≥50 years and all adults aged ≥18 years with risk factors are currently recommended to receive 13vPCV, 15vPCV or 20vPCV followed by two doses of 23vPPV. The ideal comparator was 13vPCV as this is the only vaccine with efficacy data in adults. None of the studies for any PICOs had this as the comparator.
Outcomes	Included outcomes as stated above in Table 1, Table 2 and Table 3. No studies were identified which included efficacy or effectiveness against clinical outcomes.
	Ranking of importance of each important or critical outcome discussed iteratively reaching consensus with the ATAGI full panel.
	General framework (depending on outcomes measured in studies available): *Critical* • Mortality due to invasive pneumococcal disease • Invasive pneumococcal disease • Pneumococcal pneumonia • Serious adverse events *Important* • OPA GMT ratios • % of participants ≥4-fold rise of GMT pre to post vaccination • IgG GMC ratios • % of participants ≥4-fold rise of GMC pre to post vaccination • Injection site adverse events • Systemic adverse events Note: some outcomes may be missing in GRADE projects due to absence of data from available studies. Additional outcomes specifically reported in studies were included due to relevance.
	The WHO guidelines on clinical evaluation of vaccines[1] define generic non-inferiority parameters for antibody GMT and GMC ratios for comparison of vaccines, and this was the parameter applied in the EP table. All three studies defined a non-inferiority margin which was also considered in the GRADE tables.

Abbreviations: ATAGI=Australian Technical Advisory Group on Immunisation; EP=evidence profile; GMC=geometric mean concentration; GMT=geometric mean titres; GMFR=geometric mean fold rise; IgG=immunoglobulin; IPD=invasive pneumococcal disease; OPA=opsonophagocytic activity; WHO=World Health Organization

Risk of bias assessment

Risk of bias (RoB) was assessed for all selected studies using the standard GRADE criteria. Two assessors independently undertook this using the ROB 2.0 tool for randomised controlled trials (Appendix B).

Appendix A: Literature search strategy

Database: Ovid MEDLINE® All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946-2024 March 15>
Search Strategy:
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1 exp Streptococcus pneumoniae/ (24985)
2 (streptococc$ adj5 pneumo$).tw. (29090)
3 exp Pneumococcal Infections/ (22723)
4 exp Pneumococcal Vaccines/ (9127)
5 pneumococc$.tw. (30277)
6 1 or 2 or 3 or 4 or 5 (55316)
7 ("twenty one valen$" or twenty-one valen$ or 21 valen$ or 21-valen$ or 21valen$ or 21v).tw. (31)
8 (21v or 21vPCV$ or PCV 21$ or PCV-21$ or PCV21$).tw. (36)
9 7 or 8 (45)
10 6 and 9 (10)
11 V116.tw. (15)
12 10 or 11 (20)
13 exp Immunogenicity, Vaccine/ (3439)
14 immunogen$.tw. (95669)
15 exp Antibodies, Bacterial/ (52650)
16 exp Antibody Formation/ (63898)
17 (antibod$ adj2 (respons$ or form$)).tw. (63762)
18 (immun$ adj2 (respon$ or protect$)).tw. (379141)
19 exp Seroconversion/ (1215)
20 seroconver$.tw. (22116)
21 seroprotect$.tw. (2045)
22 exp Treatment Outcome/ (1272614)
23 efficac$.tw. (1153905)
24 effective$.tw. (2670606)
25 exp Safety/ (89559)
26 exp Safety-Based Drug Withdrawals/ (419)
27 exp "Drug-Related Side Effects and Adverse Reactions"/ (135086)
28 exp Product Surveillance, Postmarketing/ (18626)
29 exp Drug Evaluation/ (42082)
30 exp Adverse Drug Reaction Reporting Systems/ (9031)
31 (adverse adj2 (effect$ or event$)).tw. (485613)
32 (safe or safety or aefi or aesi).tw. (1083913)
33 ((post marketing or post-marketing or postmarketing or post licensure or post-licensure or postlicensure) adj2 (surveillance or monitor$)).tw. (3763)
34 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (5681592)
35 12 and 34 (10)

Database: Embase <1974 to 2024 March 18>
Search Strategy:

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1 exp Streptococcus pneumoniae/ (51047)
2 (streptococc$ adj5 pneumo$).tw. (36291)
3 exp pneumococcal infection/ (13266)
4 exp Pneumococcus vaccine/ (24224)
5 pneumococc$.tw. (36814)
6 1 or 2 or 3 or 4 or 5 (85731)
7 ("twenty one valen$" or twenty-one valen$ or 21 valen$ or 21-valen$ or 21valen$ or 21v).tw. (57)
8 (21v or 21vPCV$ or PCV 21$ or PCV-21$ or PCV21$).tw. (74)
9 7 or 8 (83)
10 6 and 9 (9)
11 V116.tw. (29)
12 10 or 11 (33)
13 exp vaccine immunogenicity/ (7688)
14 immunogen$.tw. (126653)
15 exp bacterium antibody/ (27320)
16 exp antibody production/ (63569)
17 (antibod$ adj2 (respons$ or form$)).tw. (73768)
18 (immun$ adj2 (respon$ or protect$)).tw. (492882)
19 exp seroconversion/ (30465)
20 seroconver$.tw. (29322)
21 seroprotect$.tw. (2584)
22 exp drug efficacy/ (1046366)
23 efficac$.tw. (1681686)
24 effective$.tw. (3459060)
25 exp drug safety/ (595384)
26 exp postmarketing surveillance/ (39748)
27 exp drug surveillance program/ (26895)
28 exp adverse drug reaction/ (657685)
29 (adverse adj2 (effect$ or event$)).tw. (765309)
30 (safe or safety or aefi or aesi).tw. (1634761)
31 ((post marketing or post-marketing or postmarketing or post licensure or post-licensure or postlicensure) adj2 (surveillance or monitor$)).tw. (5816)
32 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 (7152295)
33 12 and 32 (14)

Cochrane Library Central Register of Controlled Trials (CENTRAL), Issue 2 of 12, February 2024: Pneumococcal vaccine - 21vPCV (as at 20.03.24)

ID Search Hits
#1 MeSH descriptor: [Streptococcus pneumoniae] explode all trees 779
#2 (streptococc* NEAR/5 pneumo*):ti,ab,kw 2021
#3 MeSH descriptor: [Pneumococcal Infections] explode all trees 1032
#4 MeSH descriptor: [Pneumococcal Vaccines] explode all trees 1283
#5 pneumococc*:ti,ab,kw 2929
#6 #1 OR #2 OR #3 OR #4 OR #5 3917
#7 ("twenty one valent" OR "twenty-one valent" OR "21 valent" OR "21-valent" OR 21valent OR 21v):ti,ab,kw 9
#8 (21v OR 21vPCV OR "PCV 21" OR "PCV-21" OR PCV21):ti,ab,kw 6
#9 #7 OR #8 14
#10 #6 AND #9 8
#11 V116:ti,ab,kw 16
#12 #10 OR #11 16
#13 MeSH descriptor: [Immunogenicity, Vaccine] explode all trees 849
#14 immunogen*:ti,ab,kw 17354
#15 MeSH descriptor: [Antibodies, Bacterial] explode all trees 2103
#18 (immun* NEAR/2 (respon* OR protect*)):ti,ab,kw 17939
#19 MeSH descriptor: [Seroconversion] explode all trees 156
#20 seroconver*:ti,ab,kw 4719
#21 seroprotect*:ti,ab,kw 1381
#22 MeSH descriptor: [Treatment Outcome] explode all trees 200732
#23 efficac*:ti,ab,kw 454621
#24 effective*:ti,ab,kw 434216
#25 MeSH descriptor: [Safety] explode all trees 5136
#26 MeSH descriptor: [Safety-Based Drug Withdrawals] explode all trees 11
#27 MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees 5191
#28 MeSH descriptor: [Product Surveillance, Postmarketing] explode all trees 563
#29 MeSH descriptor: [Drug Evaluation] explode all trees 6560
#30 MeSH descriptor: [Adverse Drug Reaction Reporting Systems] explode all trees 185
#31 (adverse NEAR/2 (effect* OR event*)):ti,ab,kw 338246
#32 (safe OR safety OR aefi OR aesi):ti,ab,kw 348112
#33 (("post marketing" OR "post-marketing" OR postmarketing OR "post licensure" OR "post-licensure" OR postlicensure) NEXT/2 (surveillance OR monitor*)):ti,ab,kw 706

#16	MeSH descriptor: [Antibody Formation] explode all trees	1234	#34	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33	1034757
#17	(antibod* NEAR/2 (respons* OR form*)):ti,ab,kw	5786	#35	#12 AND #34	16

Appendix B: Risk of Bias: ROB 2.0

Study	Outcome	Randomisation process	Deviations from intervention	Missing data	Measurement of outcomes	Selection of the reported results	Overall bias
Platt et al (2024)[2] (P003)	Immunogenicity	Low	Low	Some concerns*/Low	Low	Low	Some concerns*/Low
	Safety	Low	Low	Low	Low	Low	Low
Pathirana et al (2025)[3] P007	Immunogenicity	Low	Low	Some concerns*/Low	Low	Low	Some concerns*/Low
	Safety	Low	Low	Low	Low	Low	Low
Scott et al (2026)[4] P008	Immunogenicity	Low	Low	Some concerns*/Low	Low	Low	Some concerns*/Low
	Safety	Low	Low	Low	Low	Low	Low

* Some concerns for the outcome of % participants with ≥4-fold rise in OPA GMT

References

1. World Health Organisation (WHO). Guidelines on clinical evaluation of vaccines: regulatory expectations.2017. Available from: https://www.who.int/publications/m/item/WHO-TRS-1004-web-annex-9
2. Platt HL, Bruno C, Buntinx E, et al. Safety, tolerability, and immunogenicity of an adult pneumococcal conjugate vaccine, V116 (STRIDE-3): a randomised, double-blind, active comparator controlled, international phase 3 trial. Lancet Infect Dis 2024;24:1141-50. Available from: https://www.ncbi.nlm.nih.gov/pubmed/38964361
3. Pathirana J, Ramgopal M, Martin C, et al. Safety, tolerability, and immunogenicity of an adult-specific pneumococcal conjugate vaccine, V116, in people living with HIV (STRIDE-7): a two-part, parallel-group, randomised, active comparator-controlled, international, phase 3 trial. *Lancet HIV* 2025;12:e679-e90. Available from: https://www.ncbi.nlm.nih.gov/pubmed/40953572
4. Scott PT, Pathirana J, Kato A, et al. A Phase 3, Randomized Trial Investigating the Safety, Tolerability, and Immunogenicity of V116, an Adult-Specific Pneumococcal Conjugate Vaccine, in Pneumococcal Vaccine-Naive Adults 18-64 Years of Age at Increased Risk of Pneumococcal Disease, STRIDE-8. *Clinical Infectious Diseases* 2026;82:e217-e26. Available from: https://www.ncbi.nlm.nih.gov/pubmed/41208546