Coversheet on evidence assessment by ATAGI using the GRADE framework for 20-valent pneumococcal conjugate vaccine (20vPCV) in adults

A summary of the use of the GRADE approach in the development of ATAGI and Australian Immunisation Handbook recommendations for 20vPCV use in adults

Background

- 20vPCV was approved by the Therapeutic Goods Administration in November 2022 for adults aged ≥18 years.
- In anticipation of the availability of this vaccine in Australia, the Australian Technical Advisory Group on Immunisation (ATAGI) undertook GRADE assessment of 20vPCV throughout 2022 to allow for informed recommendations on its use.
- In November 2022, the Pharmaceutical Benefits Advisory Committee recommended that 20vPCV be a designated vaccine, for the purposes of the *National Health Act 1953*, for the prevention of pneumococcal disease in non-First Nations adults aged ≥70 years, First Nations adults aged ≥25 years and individuals at increased risk of pneumococcal disease aged ≥18 years.
- At the time of this GRADE assessment (in 2022), ATAGI recommendations were for 13-valent pneumococcal conjugate vaccine (13vPCV) or 15-valent pneumococcal conjugate vaccine (15vPCV) for non-First Nations adults from age 70 years, and 13vPCV or 15vPCV followed by up to a maximum of 2 doses of 23-valent pneumococcal polysaccharide vaccine (23vPPV) for First Nations adults from age 50 years and for all adults aged ≥18 years with specified underlying risk conditions.
- 20vPCV includes all of the serotypes contained in 13vPCV and 15vPCV as well as seven serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) additional to 13vPCV and five serotypes (8, 10A, 11A, 12F, 15B) additional to 15vPCV.

Research questions

1. For non-First Nations people aged ≥ 70 years without underlying risk conditions, who are currently recommended 13vPCV or 15vPCV, what should the recommendation be for the use of 20vPCV?

Table 1 PICO 1: 20vPCV vs. 13vPCV

Population	Non-First Nations adults aged ≥70 years without special risk factors
Intervention	20vPCV
Comparator	13vPCV
Outcomes	*Critical* • Serious adverse events *Important* • OPA GMT ratios (follow-up: 27–49 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 • OPA GMFR (follow-up: 27–49 days) by vaccine serotypes • Local adverse events • Systemic adverse events

2. For First Nations adults aged ≥50 years without underlying risk conditions, who are currently recommended 13vPCV+23vPPV or 15vPCV+23vPPV, what should the recommendation be for the use of 20vPCV+23vPPV?

Table 2 PICO 2: 20vPCV+23vPPV vs. 13vPCV+23vPPV

Population	First Nations adults aged ≥50 years without special risk factors
Intervention	20vPCV+23vPPV
Comparator	13vPCV+23vPPV
Outcomes	*Critical* • Serious adverse events *Important* • OPA GMT ratios (follow-up: 27–49 days) by vaccine serotypes • % of participants ≥ 4-fold rise of GMT by vaccine serotypes pre- to post-vaccination • IgG GMFR (follow-up: 27–49 days) by vaccine serotypes • Local adverse events • Systemic adverse events

3. For adults aged ≥18 years with specific risk factors (as listed in the Australian Immunisation Handbook) who are currently recommended 13vPCV+23vPPV 15vPCV+23vPPV, what should the recommendation be for the use of 20vPCV+23vPPV?

Table 3 PICO 3: 20vPCV+23vPPV vs. 13vPCV+23vPPV

Population	Adults aged ≥18 years with specific risk factors (as listed in the Australian Immunisation Handbook)
Intervention	20vPCV+23vPPV
Comparator	13vPCV+23vPPV
Outcomes	*Critical* • Serious adverse events *Important* • OPA GMT ratios (follow-up: 27–49 days) by vaccine serotypes • % of participants ≥ 4-fold rise of GMT by vaccine serotypes pre- to post-vaccination • IgG GMFR (follow-up: 27–49 days) by vaccine serotypes • Local adverse events • Systemic adverse events

Literature search

A literature search was performed on 24/6/2022 and updated on 26/10/2022 to identify studies assessing immunogenicity, efficacy and/or safety outcomes of the 20vPCV vaccine in adults. Details of the search methods used are presented in Appendix A. Citations were selected for review if they met the following pre-defined inclusion criteria:

- *Study type:* Randomized controlled trial (RCT), observational study
- *Population:* Adults aged 18 years and over
- *Intervention:* 20vPCV or 20vPCV+23vPPV
- *Comparator:* 13vPCV or 13vPCV+23vPPV
- *Outcomes:* Effectiveness, efficacy, immunogenicity, safety

A total of four citations met these criteria. All four studies included a comparison between 20vPCV and 13vPCV; two of the four studies included a comparison for 20vPCV and 13vPCV+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 20vPCV to 13vPCV were included. No studies that included efficacy or effectiveness against clinical outcomes were identified.
Population	Included population groups were selected on the basis that they are the groups of adults for whom pneumococcal vaccination is currently recommended in the Australian Immunisation Handbook.
Intervention 20vPCV 20vPCV+23vPPV	20vPCV alone or 20vPCV followed by 23vPPV to align with current 13vPCV and 23vPPV recommendations, by applicable population. No studies included the use of 20vPCV followed by 23vPPV.
Comparator 13vPCV 13vPCV+23vPPV	Non-First Nations adults aged ≥70 years without risk factors are currently recommended to receive 13vPCV or 15vPCV alone, and First Nations adults aged ≥50 years and all adults aged ≥18 years with specific risk factors are currently recommended to receive 13vPCV or 15vPCV followed by 23vPPV.
Outcomes	The outcomes included are as stated above in Table 1, Table 2 and Table 3. No studies were identified that included efficacy or effectiveness against clinical outcomes.
	Each important or critical outcome was discussed iteratively and ranked based on the consensus of ATAGI.
	General framework (depending on outcomes measured in available studies): *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 • Local 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 World Health Organization 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. Additionally, Essink et al.[2] define a non-inferiority margin, and this was also considered in the GRADE tables.

Abbreviations: EP = evidence profile; GMC = geometric mean concentration; GMT = geometric mean titres; GMFR = geometric mean fold rise; IgG = immunoglobulin; OPA = opsonophagocytic activity

Risk of bias assessment

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

Appendix A: Literature search strategy

Database: MEDLINE(R) All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946-current> Search Strategy: --- 1 exp Streptococcus pneumoniae/ (24148) 2 (streptococc$ adj5 pneumo$).tw. (27527) 3 exp Pneumococcal Infections/ (22070) 4 exp Pneumococcal Vaccines/ (8569) 5 pneumococc$.tw. (28722) 6 1 or 2 or 3 or 4 or 5 (52740) 7 (twenty valen$ or twenty-valen$ or 20 valen$ or 20-valen$ or 20valen$).tw. (40) 8 (20v or 20vPCV$ or PCV 20$ or PCV-20$ or PCV20$).tw. (166) 9 7 or 8 (191) 10 6 and 9 (48) 11 Apexxnar$.tw. (0) 12 ("prevnar 20" or prevnar-20 or prevnar20).tw. (2) 13 11 or 12 (2) 14 10 or 13 (50) 15 exp Immunogenicity, Vaccine/ (3057) 16 immunogen$.tw. (85054) 17 exp Antibodies, Bacterial/ (51965) 18 exp Antibody Formation/ (63069) 19 (antibod$ adj2 (respons$ or form$)).tw. (59465) 20 (immun$ adj2 (respon$ or protect$)).tw. (334169) 21 exp Seroconversion/ (1086) 22 seroconver$.tw. (20574) 23 seroprotect$.tw. (1879) 24 exp Treatment Outcome/ (1199091) 25 efficac$.tw. (1002963) 26 effective$.tw. (2312764) 27 exp Safety/ (87415) 28 exp Safety-Based Drug Withdrawals/ (413) 29 exp "Drug-Related Side Effects and Adverse Reactions"/ (127560) 30 exp Product Surveillance, Postmarketing/ (17568) 31 exp Drug Evaluation/ (42037) 32 exp Adverse Drug Reaction Reporting Systems/ (8505) 33 (adverse adj2 (effect$ or event$)).tw. (418345) 34 (safe or safety or aefi or aesi).tw. (936581) 35 ((post marketing or post-marketing or postmarketing or post licensure or post-licensure or postlicensure) adj2 (surveillance or monitor$)).tw. (3417)	Database: Embase <1974 to 2022 October 26> Search Strategy: --- 1 exp Streptococcus pneumoniae/ (47062) 2 (streptococc$ adj5 pneumo$).tw. (33980) 3 exp pneumococcal infection/ (18049) 4 exp Pneumococcus vaccine/ (22027) 5 pneumococc$.tw. (34488) 6 1 or 2 or 3 or 4 or 5 (80623) 7 ("twenty valen$" or twenty-valen$ or 20 valen$ or 20-valen$ or 20valen$).tw. (37) 8 (20v or 20vPCV$ or PCV 20$ or PCV-20$ or PCV20$).tw. (361) 9 7 or 8 (375) 10 6 and 9 (69) 11 Apexxnar$.tw. (0) 12 ("prevnar 20" or prevnar-20 or prevnar20).tw. (8) 13 11 or 12 (8) 14 10 or 13 (76) 15 exp vaccine immunogenicity/ (5200) 16 immunogen$.tw. (111121) 17 exp bacterium antibody/ (26498) 18 exp antibody production/ (60806) 19 (antibod$ adj2 (respons$ or form$)).tw. (67473) 20 (immun$ adj2 (respon$ or protect$)).tw. (431527) 21 exp seroconversion/ (26790) 22 seroconver$.tw. (26810) 23 seroprotect$.tw. (2354) 24 exp drug efficacy/ (960312) 25 efficac$.tw. (1460467) 26 effective$.tw. (3013084) 27 exp drug safety/ (497867) 28 exp postmarketing surveillance/ (37947) 29 exp drug surveillance program/ (26584) 30 exp adverse drug reaction/ (587207) 31 (adverse adj2 (effect$ or event$)).tw. (657803) 32 (safe or safety or aefi or aesi).tw. (1413534) 33 ((post marketing or post-marketing or postmarketing or post licensure or post-licensure or postlicensure) adj2 (surveillance or monitor$)).tw. (5238) 34 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 (6288004) 35 14 and 34 (27) 36 limit 35 to (adult <18 to 64 years> or aged <65+ years>) (21) 37 exp adult/ (9824004)

36 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 or 34 or 35 (5038345) 37 14 and 36 (15) 38 limit 37 to ("adult (19 to 44 years)" or "middle age (45 to 64 years)" or "all aged (65 and over)") (8) 39 exp Adult/ (7810481) 40 exp Middle Aged/ (4685372) 41 exp Aged/ (3404016) 42 exp "Aged, 80 and over"/ (1007091) 43 (adult$ or elder$ or senior$ or geriatr$).tw. (1754958) 44 39 or 40 or 41 or 42 or 43 (8589153) 45 37 and 44 (12) 46 38 or 45 (12)	38 (adult$ or elder$ or senior$ or geriatr$).tw. (2350208) 39 37 or 38 (10609350) 40 35 and 39 (22) 41 36 or 40 (22)

Cochrane Library Central Register of Controlled Trials (CENTRAL): 20 valent pneumococcal conjugate vaccine in adults – immunogenicity, efficacy and safety (as at 26.10.22)

ID	Search	Hits
#1	MeSH descriptor: [Streptococcus pneumoniae] explode all trees	604
#2	(streptococc* NEAR/5 pneumo*):ti,ab,kw	1848
#3	MeSH descriptor: [Pneumococcal Infections] explode all trees	796
#4	MeSH descriptor: [Pneumococcal Vaccines] explode all trees	1061
#5	pneumococc*:ti,ab,kw	2674
#6	#1 OR #2 OR #3 OR #4 OR #5	3618
#7	("twenty valen*" OR "twenty-valen*" OR "20 valen*" OR "20-valen*" OR 20valen*):ti,ab,kw	0
#8	(20v OR 20vPCV* OR "PCV 20*" OR "PCV-20*" OR PCV20*):ti,ab,kw	29
#9	#7 OR #8	29
#10	#6 AND #9	22
#11	Apexxnar*:ti,ab,kw	0
#12	("prevnar 20" or "prevnar-20" or prevnar20):ti,ab,kw	2
#13	#11 OR #12	2
#14	#10 OR #13	22
#15	MeSH descriptor: [Immunogenicity, Vaccine] explode all trees	501
#16	immunogen*:ti,ab,kw	14939
#17	MeSH descriptor: [Antibodies, Bacterial] explode all trees	1700
#18	MeSH descriptor: [Antibody Formation] explode all trees	1033
#19	(antibod* NEAR/2 (respons* OR form*)):ti,ab,kw	5280
#20	(immun* NEAR/2 (respon* OR protect*)):ti,ab,kw	15829
#21	MeSH descriptor: [Seroconversion] explode all trees	110
#22	seroconver*:ti,ab,kw	4280
#23	seroprotect*:ti,ab,kw	1292
#24	MeSH descriptor: [Treatment Outcome] explode all trees	152387
#25	efficac*:ti,ab,kw	397107
#26	effective*:ti,ab,kw	372409
#27	MeSH descriptor: [Safety] explode all trees	4144
#28	MeSH descriptor: [Safety-Based Drug Withdrawals] explode all trees	11
#29	MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees	3863
#30	MeSH descriptor: [Product Surveillance, Postmarketing] explode all trees	214
#31	MeSH descriptor: [Drug Evaluation] explode all trees	5750
#32	MeSH descriptor: [Adverse Drug Reaction Reporting Systems] explode all trees	95
#33	(adverse NEAR/2 (effect* OR event*)):ti,ab,kw	275639
#34	(safe OR safety OR aefi OR aesi):ti,ab,kw	300696

#35	(("post marketing" OR "post-marketing" OR postmarketing OR "post licensure" OR "post-licensure" OR postlicensure) NEXT/2 (surveillance OR monitor*)):ti,ab,kw 656
#36	#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 OR #34 OR #35 882957
#37	#14 AND #36 21
#38	MeSH descriptor: [Adult] explode all trees493133
#39	MeSH descriptor: [Middle Aged] explode all trees 333651
#40	MeSH descriptor: [Aged] explode all trees 220640
#41	MeSH descriptor: [Aged, 80 and over] explode all trees 56043
#42	(adult* OR elder* OR senior* OR geriatr*):ti,ab,kw 769443
#43	#38 OR #39 OR #40 OR #41 OR #42 862193
#44	#37 AND #43 15

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
Essink 2022[2]	Immunogenicity	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low
Hurley 2021[3]	Immunogenicity	Low	Low	Low	Low	Some concerns[a]	Some concerns[a]
	Safety	Low	Low	Low	Low	Some concerns[a]	Some concerns
Klein 2021[4]	Immunogenicity	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low
Fitz-Patrick 2021[5]	Immunogenicity	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low

Notes

a. Large portions of protocol could not be identified due to being redacted.

References

1. World Health Organization (WHO). Guidelines on clinical evaluation of vaccines: regulatory expectations [PDF]. October 2020. Available from: https://www.who.int/publications/m/item/WHO-TRS-1004-web-annex-9 (Accessed 28 September 2023).

2. Essink B, Sabharwal C, Cannon K, et al. Pivotal phase 3 randomized clinical trial of the safety, tolerability, and immunogenicity of 20-valent pneumococcal conjugate vaccine in adults aged ≥18 years. *Clinical Infectious Diseases* 2022;75:390-98.

3. Hurley D, Griffin C, Young M, et al. Safety, tolerability, and immunogenicity of a 20-valent pneumococcal conjugate vaccine (PCV20) in adults 60 to 64 years of age. *Clinical Infectious Diseases* 2021;73:e1489-e97.

4. Klein NP, Peyrani P, Yacisin K, et al. A phase 3, randomized, double-blind study to evaluate the immunogenicity and safety of 3 lots of 20-valent pneumococcal conjugate vaccine in pneumococcal vaccine-naive adults 18 through 49 years of age. *Vaccine* 2021;39:5428-35.

5. Fitz-Patrick D, Young M, Scott DA, et al. A randomized phase 1 study of the safety and immunogenicity of 2 novel pneumococcal conjugate vaccines in healthy Japanese adults in the United States. *Human Vaccines & Immunotherapeutics* 2021;17:2249-56.