Coversheet on evidence assessment by ATAGI using the GRADE framework

Summary of key methods and decisions on evidence assessment using GRADE (Grading of Recommendations Assessment, Development and Evaluation) for developing ATAGI recommendations on the use of 15-valent pneumococcal conjugate vaccine (15vPCV) in adults for the Australian Immunisation Handbook

Background

- 15vPCV was TGA approved in January 2022 for adults aged ≥18 years.
- ATAGI undertook GRADE assessment in 2022 to make relevant recommendations on its use in anticipation of the availability of this vaccine in Australia
- In November 2021 PBAC recommended that 15vPCV be a designated vaccine for the purposes of the *National Health Act 1953*, for the prevention of pneumococcal disease in non-Indigenous adults aged ≥70 years, Indigenous adults aged ≥50 years, and individuals at increased risk of pneumococcal disease aged ≥18 years.
- At the time this GRADE assessment was undertaken (in 2022) ATAGI recommendations were 13-valent pneumococcal conjugate vaccine (13vPCV) for non-Indigenous adults from age 70 years and 13vPCV followed by up to a maximum of 2 doses of 23-valent pneumococcal polysaccharide vaccine (23vPPV) for Indigenous adults from age 50 years and for all adults with specified underlying at risk conditions.
- 15vPCV has all the serotypes contained in the 13vPCV and two additional serotypes (22F and 33F)

Research questions

1. For non-Indigenous Australians aged ≥ 70 years without underlying risk conditions, who are currently recommended 13vPCV, what should the recommendation be for the use of 15vPCV

Table 1 PICO 1: 15vPCV vs. 13vPCV

Population	Non-indigenous adults aged ≥70 years without special risk factors
Intervention	15vPCV
Comparator	13vPCV
Outcomes	Critical • Serious adverse events (SAE) Important • OPA GMT ratios (follow-up: 30 days) by vaccine serotypes • OPA GMT ratios (follow-up: 12 months) by vaccine serotypes • % of participants ≥ 4-fold rise of GMT by vaccine serotypes pre to post vaccination • IgG GMC ratios (follow-up: 30 days) by vaccine serotypes • % of participants ≥ 4-fold rise of GMC by vaccine serotypes pre to post vaccination • Injection site adverse events • Systemic adverse events

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

Table 2 PICO 2: 15vPCV+23vPPV vs. 13vPCV+23vPPV

Population	Indigenous Australian adults aged ≥50 years without special risk factors
Intervention	15vPCV+23vPPV
Comparator	13vPCV+23vPPV
Outcomes	Critical • Serious adverse events (SAE) Important • OPA GMT ratios (follow-up: 30 days) by vaccine serotypes

	• % of participants ≥ 4-fold rise of GMT by vaccine serotypes pre to post vaccination • IgG GMC ratios (follow-up: 30 days) by vaccine serotypes • % of participants ≥ 4-fold rise of GMC by vaccine serotypes pre to post vaccination • Injection site adverse events • Systemic adverse events

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

Table 3 PICO 3: 15vPCV+23vPPV vs. 13vPCV+23vPPV

Population	Adults aged ≥18 years with specific risk factors (as in Australian Immunisation handbook list)
Intervention	15vPCV+23vPPV
Comparator	13vPCV+23vPPV
Outcomes	Critical • Serious adverse events (SAE) Important • OPA GMT ratios (follow-up: 30 days) by vaccine serotypes • % of participants ≥ 4-fold rise of GMT by vaccine serotypes pre to post vaccination • IgG GMC ratios (follow-up: 30 days) by vaccine serotypes • % 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 3/3/2022 and updated on 24/6/2022 to identify studies assessing immunogenicity, efficacy and/or safety outcomes of the 15vPCV 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: randomized controlled trial (RCT), observational study
- Population: Adults 18 years old and over
- Intervention: 15vPCV or 15vPCV+23vPPV
- Comparator: 13vPCV or 13vPCV+23vPPV
- Outcomes: Effectiveness, efficacy, immunogenicity, safety

A total of eight citations met the above pre-defined inclusion criteria. Among those there were five studies where the comparison was between 15vPCV and 13vPCV and the other three were comparisons between 15vPCV+23vPPV 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 15vPCV to 13vPCV were included. 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
Intervention 15vPCV 15vPCV+23vPPV	15vPCV alone or 15vPCV followed by 23vPPV to align with current 13vPCV and 23vPPV recommendations, by applicable population
Comparator	

13vPCV 13vPCV+23vPPV	Non-indigenous adults aged ≥70 years without risk factors are currently recommended to receive 13vPCV alone and Indigenous Australian adults aged ≥50 years and all adults aged ≥18 years with risk factors are currently recommended to receive 13vPCV followed by 23vPPV.
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.
	Two of the included studies[2,3] were powered to assess non-inferiority and superiority based on pre-determined parameters for OPA GMT ratios or IgG GMC ratios by individual serotype (for all serotypes in 15vPCV). The WHO guidelines on clinical evaluation of vaccines[4] also define generic non-inferiority parameters for antibody GMT and GMC ratios for comparison of vaccines. All 3 assessment parameters were considered in the GRADE assessment. The most conservative of these parameters is applied in the EP table.

Abbreviations: ATAGI, Australian Technical Advisory Group on Immunisation; EP, evidence profile; GMC, geometric mean concentration; GMT, geometric mean titres; IgG, immunoglobulin; IPD, invasive pneumococcal disease; OPA, opsonophagocytic activity

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).

References

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2. Platt HL, Cardona JF, Haranaka M, et al. A phase 3 trial of safety, tolerability, and immunogenicity of V114, 15-valent pneumococcal conjugate vaccine, compared with 13-valent pneumococcal conjugate vaccine in adults 50 years of age and older (PNEU-AGE). *Vaccine* 2022;40(1):162-72.
3. Stacey HL, Rosen J, Peterson JT, et al. Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine (PCV-15) compared to PCV-13 in healthy older adults. *Human Vaccines and Immunotherapeutics* 2019;15(3):530-9.
4. 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.
5. Peterson JT, Stacey HL, MacNair JE, et al. Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine compared to 13-valent pneumococcal conjugate vaccine in adults >=65 years of age previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Human Vaccines and Immunotherapeutics 2019;15(3):540-8.
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7. Hammitt L, Quinn D, Janczewska E, et al. Phase 3 Trial to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by 23valent Pneumococcal Polysaccharide Vaccine 6 Months Later in At-risk Adults Aged 18-49 Years (PNEU-DAY): A Subgroup Analysis by Baseline Risk Factors. Open Forum Infectious Diseases 2021;8(SUPPL 1):S614-S5.
8. Mohapi L, Pinedo Y, Osiyemi O, et al. Safety and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine, in adults living with HIV. Aids 2022;36(3):373-82.
9. Simon JK, Staerke NB, Hemming-Harlo M, et al. Lot-to-lot consistency, safety, tolerability, and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine, in healthy adults aged >=50 years: A randomized phase 3 trial (PNEU-TRUE). Vaccine 2022;40(9):1342-51.
10. Song JY, Chang CJ, Andrews C, et al. Safety, tolerability, and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine, followed by sequential PPSV23 vaccination in healthy adults aged>=50years: A randomized phase III trial (PNEU-PATH). Vaccine 2021;39(43):6422-36.

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 (fifteen valen$ or fifteen-valen$ or 15 valen$ or 15-valen$ or 15valen$).tw. (55) 8 (15v or 15vPCV$ or PCV 15$ or PCV-15$ or PCV15$).tw. (174) 9 7 or 8 (208) 10 6 and 9 (62) 11 V114.tw. (36) 12 vaxneuvance$.tw. (5) 13 11 or 12 (39) 14 10 or 13 (77) 15 exp Immunogenicity, Vaccine/ (3057)	Database: Embase <1974 to 2022 June 22> Search Strategy: --- 1 exp Streptococcus pneumoniae/ (47028) 2 (streptococc$ adj5 pneumo$).tw. (33962) 3 exp pneumococcal infection/ (18019) 4 exp Pneumococcus vaccine/ (22013) 5 pneumococc$.tw. (34463) 6 1 or 2 or 3 or 4 or 5 (80557) 7 (fifteen valen$ or fifteen-valen$ or 15 valen$ or 15-valen$ or 15valen$).tw. (75) 8 (15v or 15vPCV$ or PCV 15$ or PCV-15$ or PCV15$).tw. (356) 9 7 or 8 (405) 10 6 and 9 (90) 11 V114.tw. (82) 12 vaxneuvance$.tw. (13) 13 11 or 12 (89) 14 10 or 13 (137) 15 exp vaccine immunogenicity/ (5176) 16 immunogen$.tw. (110935) 17 exp bacterium antibody/ (26493)

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)
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 (32)
38 limit 37 to ("adult (19 to 44 years)" or "middle age (45 to 64 years)" or "all aged (65 and over)") (17)
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 (22)
46 38 or 45 (22)

18 exp antibody production/ (60776)
19 (antibod$ adj2 (respons$ or form$)).tw. (67336)
20 (immun$ adj2 (respon$ or protect$)).tw. (430775)
21 exp seroconversion/ (26730)
22 seroconver$.tw. (26757)
23 seroprotect$.tw. (2351)
24 exp drug efficacy/ (959194)
25 efficac$.tw. (1457813)
26 effective$.tw. (3007682)
27 exp drug safety/ (496645)
28 exp postmarketing surveillance/ (37930)
29 exp drug surveillance program/ (26586)
30 exp adverse drug reaction/ (586471)
31 (adverse adj2 (effect$ or event$)).tw. (656362)
32 (safe or safety or aefi or aesi).tw. (1410710)
33 ((post marketing or post-marketing or postmarketing or post licensure or post-licensure or postlicensure) adj2 (surveillance or monitor$)).tw. (5229)
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 (6277489)
35 14 and 34 (53)
36 limit 35 to (adult <18 to 64 years> or aged <65+ years>) (32)
37 exp adult/ (9805269)
38 (adult$ or elder$ or senior$ or geriatr$).tw. (2346533)
39 37 or 38 (10590143)
40 35 and 39 (36)
41 36 or 40 (36)
42 limit 41 to dd=20220303-20220622 (2)
43 limit 41 to dc=20220303-20220622 (8)
44 42 or 43 (8)

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
Peterson 2019[5]	Immunogenicity	Low	Low	Low	Low	Some concerns[a]	Some concerns[a]
	Safety	Low	Low	Low	Low	Some concerns[a]	Some concerns[a]
Ermlich 2018[6]	Immunogenicity	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low
Hammit 2021[7]	Immunogenicity	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low
Mohapi 2022[8]	Immunogenicity	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low
Platt 2022[2]	Immunogenicity	Low	Low	Low	Low	Low	Low

	Safety	Low	Low	Low	Low	Low	Low
Simon 2022[9]	Immunogenicity	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low
Stacey 2019[3]	Immunogenicity	Low	Low	Low	Low	Some concerns[a]	Some concerns[a]
	Safety	Low	Low	Low	Low	Some concerns[a]	Some concerns[a]
Song 2021[10]	Immunogenicity	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low

a. trial protocol could not be identified