

Coversheet on evidence assessment by ATAGI using the GRADE framework for the use of MF59-aIIV (Fluad) in adults aged 50–64 years

Summary of key methods and decisions on evidence assessment using GRADE for developing ATAGI recommendations on the use of Fluad in individuals aged 50–54 years for the Australian Immunisation Handbook.

Background

- MF59-adjuvanted inactivated influenza vaccine (aIIV, brand name: Fluad) was Therapeutic Goods Administration (TGA) approved in October 2002 for protecting people aged 65 years and older against influenza.
- In March 2018, PBAC recommended Fluad to be funded for older adults aged 65 years and older.
- In 2020, the trivalent version was replaced on the NIP by Fluad Quad (quadrivalent).
- ATAGI undertook GRADE assessment in 2021 to make relevant recommendations on its use in people aged 65 years and older.
- In 2024, Fluad was registered in European Medicines Agency for people from 50 years of age. In Australia, an application for lowering the age indication has been approved by TGA in September 2025.
- An additional GRADE assessment was undertaken in 2025 to make a relevant recommendation for the extended age group.

Research questions

1. Should adults aged 50-64 years use MF59-aIIV?

Table 1: Population, Intervention, Comparator, Outcomes (PICO) 1: MF59-aIIV vs. standard IIV, adults aged 50–64 years

Population	Aged 50–64 years
Intervention	MF59-aIIV
Comparator	Standard IIV
Outcomes	<p><i>Critical</i></p> <ul style="list-style-type: none"> • Serious adverse events (SAE) • Adverse events of special interest (AESI) <p>Not available:</p> <ul style="list-style-type: none"> • Laboratory-confirmed influenza infection • Influenza-related hospitalisations/emergency department visits <p><i>Important</i></p> <ul style="list-style-type: none"> • Adverse events (local/systemic) • Seroconversion • Geometric mean titre (GMT) ratio

Literature search

A literature search was undertaken using Embase (1974 to 2025 May 23) and Medline (1946 to 2025 May 23) to identify studies assessing immunogenicity, efficacy and/or safety outcomes of Fluad in adults aged 50–64 years. 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 up to 65 years

- *Intervention:* MF59-aIV
- *Comparator:* Standard IIV
- *Outcomes:* Effectiveness, efficacy, immunogenicity, safety

A total of 992 citations met the above pre-defined inclusion criteria. Of these, 2 eligible studies were included (2 RCTs). The included studies are summarised in Appendix B.

Inclusion criteria and rationale

Table 2. Rationale for PICO and inclusion criteria

Inclusion criteria	Rationale
Study type: Observational or RCTs	Observational studies and RCTs were considered most suitable to reporting efficacy/effectiveness and safety for this PICO. Only relevant studies found were RCTs.
Population: 50-64 years	The registered age for aIV (Fluad) has been expanded from adults aged ≥ 65 years old to include those aged 50-64 years. An evidence review is needed to ensure its effectiveness/safety is needed in this particular age group and to inform clinical recommendations in Australia.
Intervention MF59-aIV	MF59 is an adjuvant used in IIV that has been recommended for older adults aged ≥ 65 years for enhanced their vaccine response. This is the vaccine under assessment.
Comparator Standard IIV	Standard IIV vaccines are the main type of influenza vaccine in use with some brands funded on the immunisation program for certain population groups.
Outcomes: Efficacy/effectiveness	Efficacy in RCTs is not available for this age population and the effectiveness studies were also not available. Therefore, immunogenicity studies are included to assess any benefit of aIV over standard IIV.
Safety	Safety of aIV vaccine being recommended should continually be assessed over risk of vaccination.

Abbreviations: aIV=adjuvanted inactivated influenza vaccine; IIV=inactive influenza vaccine; RCT=randomised controlled trial

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

1. Frey S, Poland G, Percell S, Podda A. Comparison of the safety, tolerability, and immunogenicity of a MF59-adjuvanted influenza vaccine and a non-adjuvanted influenza vaccine in non-elderly adults. *Vaccine*. 2003 Oct 1;21(27-30):4234-7. doi: 10.1016/s0264-410x(03)00456-0.
2. Poder A, Oberije J, Meyer J, Heymer P, Molrine D, Versage E, Isakov L, Zhang Q, Hohenboken M. Immunogenicity and Safety of MF59-Adjuvanted Quadrivalent Influenza Vaccine Compared with a Nonadjuvanted, Quadrivalent Influenza Vaccine in Adults 50–64 Years of Age. *Vaccines*. 2023; 11(10):1528. doi: 10.3390/vaccines11101528.

Appendix A: Literature search strategy

PICO 1	
<p>Database: Ovid MEDLINE® All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations <1946-current></p> <p>Search Strategy:</p> <p>-----</p> <ol style="list-style-type: none"> 1 exp Immunization/ 2 exp Immunization Programs/ 3 exp Vaccines/ 4 1 or 2 or 3 5 exp Influenza, Human/ 6 4 and 5 (21166) 7 exp Influenza Vaccines/ 8 ((influenza or flu) adj2 (immunis\$ or immuniz\$ or vaccin\$)).tw. 9 7 or 8 10 6 or 9 11 exp Adjuvants, Immunologic/ 12 exp Squalene/ 13 adjuvant\$.tw. 14 mf59.tw. 15 11 or 12 or 13 or 14 16 10 and 15 17 fluad\$.tw. 18 (aTIV or aQIV or a-TIV or a-QIV).tw. 19 (aIIV3 or aIIV4 or a-IIV3 or a-IIV4).tw. 20 17 or 18 or 19 21 16 or 20 22 quadrivalen\$.tw. 23 (4-valen\$ or 4 valen\$ or 4valen\$).tw. 24 (four-valen\$ or four valen\$ or fourvalen\$).tw. 25 QIV.tw. 26 trivalen\$.tw. 27 (3-valen\$ or 3 valen\$ or 3valen\$).tw. 28 (three-valen\$ or three valen\$ or threevalen\$).tw. 29 TIV.tw. 30 (IIV3 or IIV4).tw. 	<p>Database: Embase <1974 to 2025 May 23></p> <p>Search Strategy:</p> <p>-----</p> <ol style="list-style-type: none"> 1 exp immunization/ 2 exp vaccine/ 3 1 or 2 4 exp influenza/ 5 3 and 4 6 exp influenza vaccine/ 7 ((influenza or flu) adj2 (immunis\$ or immuniz\$ or vaccin\$)).tw. 8 6 or 7 9 5 or 8 10 exp immunological adjuvant/ 11 exp squalene/ 12 adjuvant\$.tw. 13 mf59.tw. 14 10 or 11 or 12 or 13 15 9 and 14 16 fluad\$.tw. 17 (aTIV or aQIV or a-TIV or a-QIV).tw. 18 (aIIV3 or aIIV4 or a-IIV3 or a-IIV4).tw. 19 16 or 17 or 18 20 15 or 19 21 quadrivalen\$.tw. 22 (4-valen\$ or 4 valen\$ or 4valen\$).tw. 23 (four-valen\$ or four valen\$ or fourvalen\$).tw. 24 QIV.tw. 25 trivalen\$.tw. 26 (3-valen\$ or 3 valen\$ or 3valen\$).tw. 27 (three-valen\$ or three valen\$ or threevalen\$).tw. 28 TIV.tw. 29 (IIV3 or IIV4).tw. 30 (standard or standard-dose\$ or convention\$ or traditional\$).tw. 31 (non adjuvant\$ or non-adjuvant\$ or nonadjuvant\$).tw. 32 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31

31	(standard or standard-dose\$ or convention\$ or traditional\$).tw.	33	9 and 32
32	(non adjuvant\$ or non-adjuvant\$ or nonadjuvant\$).tw.	34	20 and 33
33	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	35	limit 34 to adult <18 to 64 years>
34	10 and 33	36	adult/
35	21 and 34	37	exp middle aged/
36	limit 35 to ("adult (19 to 44 years)" or "middle age (45 to 64 years)")	38	(working age\$ or working-age\$ or middle age\$ or middle-age\$).tw,kw.
37	Adult/	39	(non elderly or non-elderly).tw,kw.
38	exp Middle Aged/	40	36 or 37 or 38 or 39
39	(working age\$ or working-age\$ or middle age\$ or middle-age\$).tw,kw.	41	34 and 40
40	(non elderly or non-elderly).tw,kw.	42	35 or 41
41	37 or 38 or 39 or 40		
42	35 and 41		
43	36 or 42		

Appendix B: Risk of Bias Assessments

Table 1: Risk of bias assessments for randomised controlled trials using ROB 2.0

Study	Outcome	Randomisation process	Deviations from intervention	Missing data	Measurement of outcomes	Selection of the reported results	Overall bias
Frey 2003	Immunogenicity	Some concerns	Low	Low	Low	Some concerns	Some concerns
	Safety	Some concerns	Low	Low	Low	Low	Some concerns
Poder 2023	Immunogenicity	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low