Coversheet on evidence assessment by ATAGI using the GRADE framework for the use of LAIV vaccine in children aged 2–17 years

Summary of key methods and decisions on evidence assessment using GRADE (Grading of Recommendations Assessment, Development and Evaluation) for developing ATAGI recommendations for the use of LAIV vaccine in children aged 2–17 years for the Australian Immunisation Handbook.

Background

- Intranasally-administered FluMist Quadrivalent was originally approved by the TGA in October 2016 for those aged 24 months to <18 years. It was never supplied or used in Australia. Sponsor submitted for re-registration as a trivalent LAIV to be considered for use on the private market in 2026 for those aged 2–17 years.
- LAIV is used in the UK's school-based childhood influenza vaccination program, targeting school aged children (age 5 to 16 years).
- LAIV has also been used in USA since 2003. Concerns about the effectiveness of LAIV, especially against A/H1N1 viruses, prompted the Advisory Committee on Immunization Practices (ACIP) to recommend against the use of LAIV during the 2016–2017 and 2017–2018 influenza seasons. However, following changes to the A/H1N1 component of the vaccine since the 2018–2019 season, ACIP has since reinstated the recommendation to use LAIV for the prevention of influenza among people aged 2–49 years.
- ATAGI undertook a GRADE assessment in 2025 to make relevant recommendations on LAIV use in anticipation of the availability of this vaccine in Australia from 2026.
- As LAIV is a live vaccine and contraindicated in some people, continued supply of and access to current inactivated influenza vaccines (IIVs) is required for those who cannot receive LAIV.

Research questions

1. Should children aged 2–17 years use live attenuated influenza vaccine (LAIV) in preference to control?

Table 1: Population, Intervention, Comparator, Outcomes (PICO-1) – LAIV vs control (placebo/no vaccination), aged 2–17 years

Population	Children aged 2 to 17 years
Intervention	Live attenuated influenza vaccine (LAIV)
Comparator	Control
Outcomes	*Critical* • Laboratory-confirmed influenza infection • Influenza-related ED visits • Serious adverse events (SAE) • Adverse events of special interest (AESI) *Important* • Adverse events

2. Should children aged 2–17 years use live attenuated influenza vaccine (LAIV) in preference to inactivated influenza vaccine (IIV)?

Table 2: Population, Intervention, Comparator, Outcomes (PICO-2) – LAIV vs IIV, aged 2–17 years

Population	Children aged 2 to 17 years
Intervention	Live attenuated influenza vaccines (LAIV)
Comparator	Inactivated influenza vaccine (IIV)
Outcomes	*Critical* • Laboratory-confirmed influenza infection • Serious adverse events (SAE) • Adverse events of special interest (AESI) *Important* • Adverse events

Literature search

A literature search was undertaken on 21 March 2025 using the Medline, Embase and Cochrane Database of Systematic Reviews databases to identify studies assessing vaccine efficacy and/or safety outcomes of the live attenuated influenza vaccine (LAIV) compared to control or inactivated influenza vaccine (IIV) in children. Details of the search methods are presented in Appendix A. Due to the large number of studies, those conducted in or that utilised data from before the year 2000 were excluded. Additionally, only randomised controlled trials (RCTs) or systematic reviews of RCTs were included. The citations were selected for review if they met the following criteria:

- *Study type:* Randomised controlled trial (RCT) and systematic reviews of RCTs
- *Population:* Children aged 2 to 17 years
- *Intervention:* Live attenuated influenza vaccine (LAIV)
- *Comparator:* Control (placebo/no vaccination); inactivated influenza vaccine (IIV)
- *Outcomes:* Efficacy, safety

A total of 33 citations met the above pre-defined inclusion criteria. Of these, eight eligible publications were included. For PICO 1 (vs control), five RCTs and one systematic review (including 20 studies) were included. For PICO 2 (vs IIV), one systematic review/meta-analysis (including 19 studies) and one 'integrated analysis' of two RCTs were included. Studies included in this GRADE are shown under 'References'.

Inclusion criteria and rationale

Table 3: Rationale for PICO and inclusion criteria

Inclusion criteria	Rationale
Study type: • RCTs or systematic reviews/meta-analyses of RCTs	RCTs are typically considered to be higher quality evidence relative to observational studies. Several RCTs were available for the PICO questions. Due to the number of available RCT studies, only RCTs and systematic reviews of RCTs were included. Observational study data were considered as additional information in the Evidence to Decision framework.
Population: • Children aged 2–17 years	The population includes people who are recommended to receive influenza immunisation in Australia. LAIV is registered for use in people aged 2–17 years. This broad age group reflects age groups included in available RCTs. Studies have not consistently reported outcomes by more granular age groups (i.e. 2–4 years and 5–17 years for school age), so PICOs have been designed to encompass all studies of children aged 2–17 years.
Intervention: • LAIV	LAIV (QIV) was approved for use in Australia in 2016 for ages 2–17 years but has never been available for use in Australia. Sponsor is seeking to re-register as TIV and intends for supply for the first time in the 2026 season in Australia.
Comparator: • Control (placebo/no vaccination) (PICO 1) • IIV (PICO 2)	IIV vaccine is the current type of vaccine in use. Some brands of IIV are funded on the immunisation program for certain population groups (including children aged 6 months to <5 years).
Outcomes: • Efficacy/effectiveness	Studies on the efficacy of LAIV against influenza disease are necessary to assess any benefit of LAIV vaccine over control or IIV vaccines. This GRADE assessment focuses on evidence of efficacy from RCTs as these studies are considered to be higher quality evidence relative to observational studies. Results from selected pivotal large observational effectiveness studies in settings where LAIV has been used at a population level were considered for the purposes of the Evidence to Decision Framework.
• Safety	Safety of all vaccines being recommended should continually be assessed to weigh any benefit over risk of vaccination. Wheezing and exacerbation of asthma were assessed separately as a specific outcome (i.e. adverse events of special interest), as early clinical trials demonstrated an increased risk of hospitalisation and wheezing in young children.

Abbreviations: IIV=inactivated influenza vaccine; LAIV=live attenuated influenza vaccine; QIV=quadrivalent influenza vaccine; RCT=randomised controlled trial; TIV=trivalent influenza vaccine

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 and ROBIS for systematic reviews (Appendix B).

Appendix A: Literature search strategy

PICOs 1 and 2	
EMBASE: LAIV vs control or IIV in children – FINAL (as at 26.03.25) Database: Embase <1974 to 2025 March 24> Search Strategy: --- 1 exp immunization/ (415479) 2 exp vaccine/ (466140) 3 1 or 2 (633496) 4 exp influenza/ (118545) 5 3 and 4 (45358) 6 exp influenza vaccine/ (48426) 7 ((influenza or flu) adj2 (immunis$ or immuniz$ or vaccin$)).tw. (35991) 8 6 or 7 (57661) 9 5 or 8 (68232) 10 exp live vaccine/ (17691) 11 (live adj2 attentuate$).tw. (6) 12 LAIV.tw. (768) 13 10 or 11 or 12 (18291) 14 9 and 13 (3157) 15 exp intranasal drug administration/ (15198) 16 ((intranasal$ or nasal$) adj3 (administ$ or spray$)).tw. (20400) 17 (spray$ adj3 vaccin$).tw. (239) 18 15 or 16 or 17 (30886) 19 9 and 18 (1104) 20 flumist$.tw. (732) 21 14 or 19 or 20 (4448) 22 exp drug efficacy/ (1080917) 23 efficac$.tw. (1829863)	**MEDLINE: LAIV vs control or IIV in children – FINAL (as at 21.03.25)** Ovid MEDLINE® All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946-current> Search Strategy: --- 1 exp Immunization/ (222989) 2 exp Immunization Programs/ (16966) 3 exp Vaccines/ (296845) 4 1 or 2 or 3 (409184) 5 exp Influenza, Human/ (61114) 6 4 and 5 (21058) 7 exp Influenza Vaccines/ (28403) 8 ((influenza or flu) adj2 (immunis$ or immuniz$ or vaccin$)).tw. (29007) 9 7 or 8 (37898) 10 6 or 9 (39544) 11 exp Vaccines, Attenuated/ (13672) 12 (live adj2 attentuate$).tw. (7) 13 LAIV.tw. (665) 14 11 or 12 or 13 (13894) 15 10 and 14 (1968) 16 exp Administration, Intranasal/ (17337) 17 ((intranasal$ or nasal$) adj3 (administ$ or spray$)).tw. (15134) 18 (spray$ adj3 vaccin$).tw. (220) 19 16 or 17 or 18 (25603) 20 10 and 19 (1240) 21 flumist$.tw. (104) 22 15 or 20 or 21 (2873)

24 effective$.tw. (3766413) 25 exp drug safety/ (656168) 26 exp postmarketing surveillance/ (40454) 27 exp drug surveillance program/ (26927) 28 exp adverse drug reaction/ (694782) 29 (adverse adj3 (effect$ or event$)).tw. (835336) 30 (safe or safety or aefi or aesi).tw. (1764089) 31 ((post marketing or post-marketing or postmarketing or post licensure or post-licensure or postlicensure) adj2 (surveillance or monitor$)).tw. (6117) 32 exp "severity of illness index"/ (26972) 33 exp critical illness/ (38482) 34 exp intensive care unit/ (344991) 35 ((intensive adj1 care) or icu).tw. (404111) 36 exp intensive care/ (970238) 37 (sever$ or critical$ or complicat$ or complex$).tw. (9765984) 38 exp mortality/ (1519992) 39 exp death/ (2203138) 40 (mortalit$ or death$ or fatal$ or case-fatal$ or lethal$ or died).tw. (3437290) 41 exp hospitalization/ (616997) 42 (hospitalis$ or hospitaliz$).tw. (627118) 43 (hospital adj2 (attend$ or present$ or admit$ or admission$)).tw. (147697) 44 exp hospital emergency service/ (11449) 45 (emergency adj2 (department$ or ward$ or attend$ or present$ or admit$ or admission$ or room$)).tw. (280643) 46 (urgent adj3 care).tw. (8220) 47 exp general practitioner/ (128633) 48 (general adj2 practitioner$).tw. (83576) 49 GP.tw. (79738) 50 (family adj2 (doctor$ or physician$ or practice$)).tw. (42592) 51 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 (17594709) 52 21 and 51 (3224) 53 limit 52 to (infant <to one year> or child <unspecified age>) (471)	23 limit 22 to "all child (0 to 18 years)" (798) 24 exp Infant/ (1303802) 25 exp Child/ (2257278) 26 exp Adolescent/ (2314874) 27 (baby or babies or infant$ or toddler$ or child$ or adolescen$ or teenage$ or pediatric$ or paediatric$).tw. (2569237) 28 24 or 25 or 26 or 27 (4844837) 29 22 and 28 (959) 30 23 or 29 (959) 31 exp Treatment Outcome/ (1335139) 32 exp Vaccine Efficacy/ (1452) 33 efficac$.tw. (1277238) 34 effective$.tw. (2961858) 35 exp Safety/ (91574) 36 exp Safety-Based Drug Withdrawals/ (423) 37 exp "Drug-Related Side Effects and Adverse Reactions"/ (139218) 38 exp Product Surveillance, Postmarketing/ (19768) 39 exp Drug Evaluation/ (42086) 40 exp Adverse Drug Reaction Reporting Systems/ (9809) 41 (adverse adj2 (effect$ or event$)).tw. (532877) 42 (safe or safety or aefi or aesi).tw. (1189123) 43 ((post marketing or post-marketing or postmarketing or post licensure or post-licensure or postlicensure) adj2 (surveillance or monitor$)).tw. (4013) 44 exp "Severity of Illness Index"/ (292647) 45 exp Critical Illness/ (42594) 46 exp Intensive Care Units/ (115396) 47 ((intensive adj1 care) or icu).tw. (250466) 48 exp Critical Care/ (69587) 49 (sever$ or critical$ or complicat$ or complex$).tw. (7620458) 50 exp Mortality/ (438806) 51 exp Death/ (171037) 52 (mortalit$ or death$ or fatal$ or case-fatal$ or lethal$ or died).tw. (2405460) 53 exp Hospitalization/ (313947)

54 exp infant/ (1205380) 55 exp child/ (3317291) 56 exp adolescent/ (1918124) 57 (baby or babies or infant$ or toddler$ or child$ or adolescen$ or teenage$ or pediatric$ or paediatric$).tw. (3251261) 58 54 or 55 or 56 or 57 (5087978) 59 52 and 58 (968) 60 limit 59 to yr="2000 - 2025" (859) 61 remove duplicates from 60 (853)	54 (hospitalis$ or hospitaliz$).tw. (383651) 55 (hospital adj2 (attend$ or present$ or admit$ or admission$)).tw. (88199) 56 exp Emergency Service, Hospital/ (107213) 57 (emergency adj2 (department$ or ward$ or attend$ or present$ or admit$ or admission$ or room$)).tw. (177613) 58 (urgent adj3 care).tw. (5160) 59 exp General Practitioners/ (11833) 60 (general adj2 practitioner$).tw. (64089) 61 GP.tw. (53447) 62 exp Physicians, Family/ (17567) 63 (family adj2 (doctor$ or physician$ or practice$)).tw. (34169) 64 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 (13395192) 65 30 and 64 (647) 66 limit 65 to yr="2000 - 2025" (524) 67 remove duplicates from 66 (521)

Cochrane Library Central Register of Controlled Trials, Issue 3 of 12, March 2025: LAIV vs control or IIV in children (as at 26.03.25)

ID	Search Hits	ID	Search Hits
#1	MeSH descriptor: [Immunization] explode all trees 7332	#36	MeSH descriptor: [Severity of Illness Index] explode all trees 26078
#2	MeSH descriptor: [Immunization Programs] explode all trees 338	#37	MeSH descriptor: [Critical Illness] explode all trees 3729
#3	MeSH descriptor: [Vaccines] explode all trees 17341	#38	MeSH descriptor: [Intensive Care Units] explode all trees 6115
#4	#1 OR #2 OR #3 18921	#39	((intensive NEAR/1 care) or icu) 53338
#5	MeSH descriptor: [Influenza, Human] explode all trees 3629	#40	MeSH descriptor: [Critical Care] explode all trees 3028
#6	#4 AND #5 2415	#41	(sever* OR critical* OR complicat* OR complex*):ti,ab,kw 581789
#7	MeSH descriptor: [Influenza Vaccines] explode all trees 2115	#42	MeSH descriptor: [Mortality] explode all trees 18456
#8	((influenza OR flu) NEAR/2 (immunis* OR immuniz* OR vaccin*)):ti,ab,kw 4994	#43	MeSH descriptor: [Death] explode all trees 3529
#9	#7 OR #8 4994	#44	(mortalit* OR death* OR fatal* OR case-fatal* OR lethal* OR died) 204746
#10	#6 OR #9 5131	#45	MeSH descriptor: [Hospitals] explode all trees 5698
#11	MeSH descriptor: [Vaccines, Attenuated] explode all trees 999	#46	(hospitalis* OR hospitaliz*):ti,ab,kw 77566
#12	(live NEAR/2 attentuate*):ti,ab,kw 3		

#13	LAIV:ti,ab,kw 171
#14	#11 OR #12 OR #13 1098
#15	#10 AND #14 330
#16	MeSH descriptor: [Administration, Intranasal] explode all trees 3390
#17	((intranasal* OR nasal*) NEAR/3 (administ* OR spray*)):ti,ab,kw 8835
#18	(spray* NEAR/3 vaccin*):ti,ab,kw 25
#19	#16 OR #17 OR #18 8842
#20	#10 AND #19 240
#21	flumist*:ti,ab,kw 49
#22	#15 OR #20 OR #21 476
#23	MeSH descriptor: [Treatment Outcome] explode all trees200291
#24	MeSH descriptor: [Vaccine Efficacy] explode all trees 115
#25	efficac*:ti,ab,kw 477670
#26	effective*:ti,ab,kw 456664
#27	MeSH descriptor: [Safety] explode all trees 4999
#28	MeSH descriptor: [Safety-Based Drug Withdrawals] explode all trees 14
#29	MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees 5106
#30	MeSH descriptor: [Product Surveillance, Postmarketing] explode all trees 580
#31	MeSH descriptor: [Drug Evaluation] explode all trees 6483
#32	MeSH descriptor: [Adverse Drug Reaction Reporting Systems] explode all trees 185
#33	(adverse NEAR/2 (effect* OR event*)):ti,ab,kw 348309
#34	(safe OR safety OR aefi OR aesi):ti,ab,kw 367631
#35	((post marketing OR post-marketing OR postmarketing OR post licensure OR post-licensure OR postlicensure) NEAR/2 (surveillance OR monitor*)):ti,ab,kw 1571
#47	(hospital NEAR/2 (attend* OR present* OR admit* OR admission*)):ti,ab,kw 17467
#48	MeSH descriptor: [Emergency Service, Hospital] explode all trees 3953
#49	(emergency NEAR/2 (department* OR ward* OR attend* OR present* OR admit* OR admission* OR room*)):ti,ab,kw 18490
#50	(urgent NEAR/3 care):ti,ab,kw 670
#51	MeSH descriptor: [General Practitioners] explode all trees 591
#52	(general NEAR/2 practitioner*):ti,ab,kw 9116
#53	GP:ti,ab,kw 7544
#54	MeSH descriptor: [Physicians, Family] explode all trees 539
#55	(family NEAR/2 (doctor* OR physician* OR practice*)):ti,ab,kw 5036
#56	#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 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 1369644
#57	#22 AND #56 372
#58	MeSH descriptor: [Infant] explode all trees 45268
#59	MeSH descriptor: [Child] explode all trees 81439
#60	MeSH descriptor: [Adolescent] explode all trees 135760
#61	(baby OR babies OR infant* OR toddler* OR child* OR adolescen* OR teenage* OR pediatric* OR paediatric*):ti,ab,kw371383
#62	#58 OR #59 OR #60 OR #61 371383
#63	#57 AND #62 219
#64	#63 with Cochrane Library publication date Between Jan 2000 and Mar 2025 180

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
Bracco Neto 2009	Efficacy	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low
Nakayama 2025	Efficacy	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low
Tam 2007	Efficacy	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low
Vesikari 2006	Efficacy	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low
Bergen 2004	Safety	Some concerns	Low	Low	Some concerns	Low	Some concerns
Ambrose 2012	Safety	Some concerns	Low	Low	Some concerns	Low	Some concerns

Table 2. Risk of Bias assessments for systematic reviews using ROBIS

Study	Outcome	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	Overall bias
Garai 2024	Efficacy	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low
Ambrose 2011	Safety	Low	Unclear	Unclear	High	High

References

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2. Vesikari T, Fleming DM, Aristegui JF, et al; CAIV-T Pediatric Day Care Clinical Trial Network. Safety, efficacy, and effectiveness of cold-adapted influenza vaccine-trivalent against community-acquired, culture-confirmed influenza in young children attending day care. Pediatrics 2006;118(6):2298-312.

3. Bracco Neto H, Farhat CK, Tregnaghi MW, et al; D153-P504 LAIV Study Group. Efficacy and safety of 1 and 2 doses of live attenuated influenza vaccine in vaccine-naïve children. The Pediatric Infectious Disease Journal 2009;28:365-371.

4. Tam JS, Capeding MR, Lum LC, Pan-Asian CAIV-T Pediatric Efficacy Trial Network. Efficacy and safety of a live attenuated, cold-adapted influenza vaccine, trivalent against culture-confirmed influenza in young children in Asia. The Pediatric Infectious Disease Journal 2007;26(7):619-28.

5. Bergen R, Black S, Shinefield H, et al. Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents. The Pediatric Infectious Disease Journal 2004:23:138-44.

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7. Garai R, Jánosi Á, Krivácsy P, et al. Head-to-head comparison of influenza vaccines in children: a systematic review and meta-analysis. Journal of Translational Medicine 2024;22(1):903.

8. Ambrose CS, Dubovsky F, Yi T, Belshe RB, Ashkenazi S. The safety and efficacy of live attenuated influenza vaccine in young children with asthma or prior wheezing. European Journal of Clinical Microbiology & Infectious Diseases 2012;31(10):2549-57.