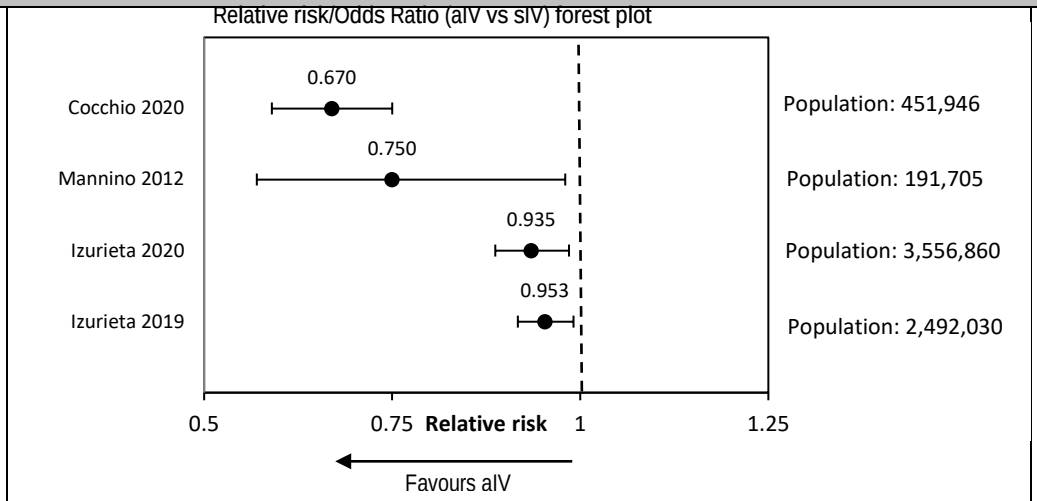
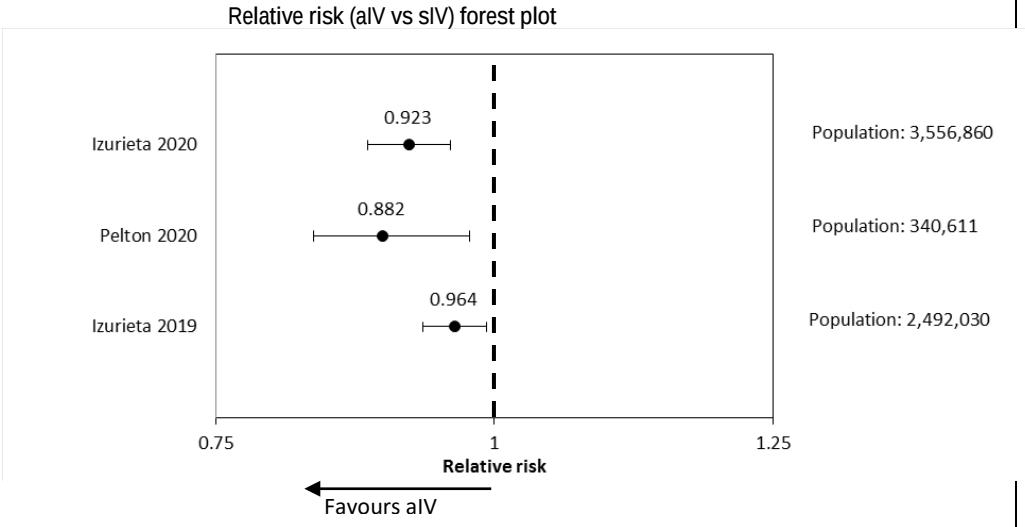
NCIRS is conducting GRADE in support of ATAGI and making pilot results available on the NCIRS website. Please read this material as a supplement to the Australian Immunisation Handbook Influenza Chapter and the ATAGI Annual Influenza Statement.

Summary of findings: MF-59 adjuvanted influenza vaccine compared with **standard dose influenza vaccine for people aged ≥65 years**

Patient or population: people ≥65 years | **Intervention**: MF-59 adjuvanted influenza vaccine (aIV) | **Comparison**: standard dose influenza vaccine (sIV)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (aIV vs sIV) (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sIV	Risk with aIV				
CRITICAL OUTCOMES						
Influenza- or pneumonia-related hospitalisation assessed with: Identified by ICD-9 and ICD-10 codes follow up: range 3 weeks to 17 weeks					⊕⊕◯◯ LOW [a,b]	Adjuvanted influenza vaccine may provide a small reduction in influenza or pneumonia-related hospitalisation compared with standard influenza vaccine Note: Izurieta 2019, 2020 values for hospitalisation overlap with outcome below for hospitalisation/emergency department (ED) visits below Refs: 1-4
Influenza-related hospital encounters assessed with: Inpatient hospitalisation/ED visits, using ICD-9 and ICD-10 codes Follow up: range 14 days after vaccination to end of season (up to 12 months)					⊕⊕⊕◯ MODERATE [b]	Adjuvanted influenza vaccine probably provides a small reduction in influenza-related hospital encounters compared with standard influenza vaccine Note: Izurieta 2019, 2020 values for hospitalisation/ED visits overlap with outcome above for hospitalisation Refs: 3-5

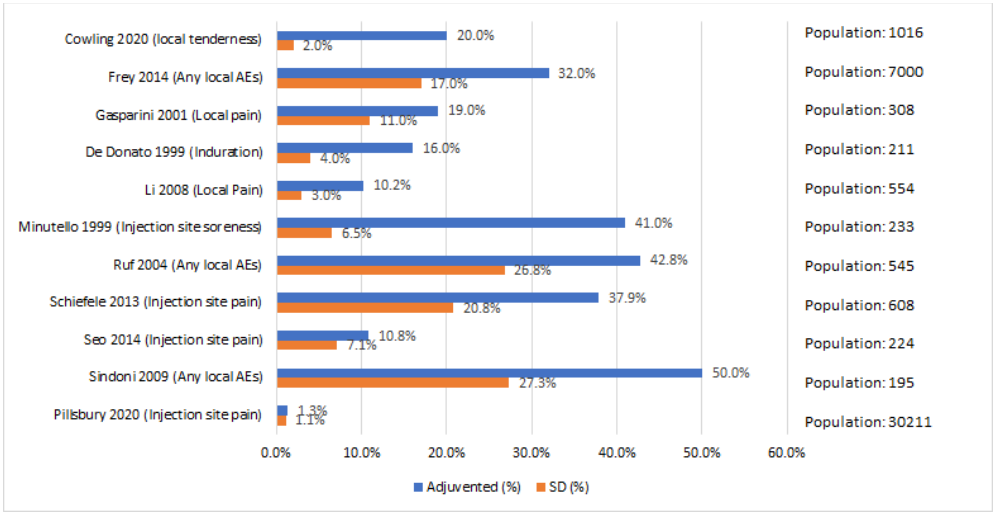
Summary of findings: MF-59 adjuvanted influenza vaccine compared with **standard dose influenza vaccine for people aged ≥65 years**

Patient or population: people ≥65 years | **Intervention**: MF-59 adjuvanted influenza vaccine (aIV) | **Comparison**: standard dose influenza vaccine (sIV)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (aIV vs sIV) (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sIV	Risk with aIV				
IMPORTANT OUTCOMES						
Laboratory-confirmed influenza assessed with: PCR Follow up: 4 months	Cases = 65, Control=162 aTIV = 42 cases, 123 controls SD-TIV = 23 cases, 39 controls		OR 0.37 (0.14 to 0.96)	65 cases 162 controls (1 observational study)	⨁◯◯◯ VERY LOW [d,e]	Adjuvanted influenza vaccine may reduce laboratory-confirmed influenza compared with standard influenza vaccine but the evidence is very uncertain Ref: 6
Influenza-related office visits assessed with: community-based physician office visits or hospital outpatient visits with a rapid influenza diagnostic test performed (CPT 87804) followed by a therapeutic course of oseltamivir (75 mg twice daily for 5 days) prescribed within 2 days after the test Follow up: range 14 days after vaccination to end of season (up to 12 months)	478 per 100,000	535 per 100,000 (517 to 554)	RR 1.119 (1.081 to 1.159)	2,492,030 (1 observational study)	⨁⨁◯◯ LOW [b,c]	Adjuvanted influenza vaccine may slightly increase influenza-related office visits compared with standard influenza vaccine Ref: 4
Influenza-like illness (ILI) assessed with: ≥37.2°C or feverishness and at least two of the following symptoms: headache, myalgia, cough, or a sore throat Follow up: range 23 days to 366 days	89 per 1,000	81 per 1,000 (63 to 103)	RR 0.91 (0.71 to 1.16)	7082 (1 RCT)	⨁⨁◯◯ LOW [b,f]	Adjuvanted influenza vaccine may result in little to no difference in ILI compared with standard influenza vaccine Ref: 7
ILI assessed with: sudden onset of acute respiratory disease, with axillary temp ≥38°C, at least one general symptom and at least one respiratory symptom Follow up: 4 months	259 per 1,000	187 per 1,000 (156 to 222)	OR 0.66 (0.53 to 0.82)	2094 (1 observational study)	⨁◯◯◯ VERY LOW [b,d]	Adjuvanted influenza vaccine may reduce ILI compared with standard influenza vaccine but the evidence is very uncertain Ref: 8

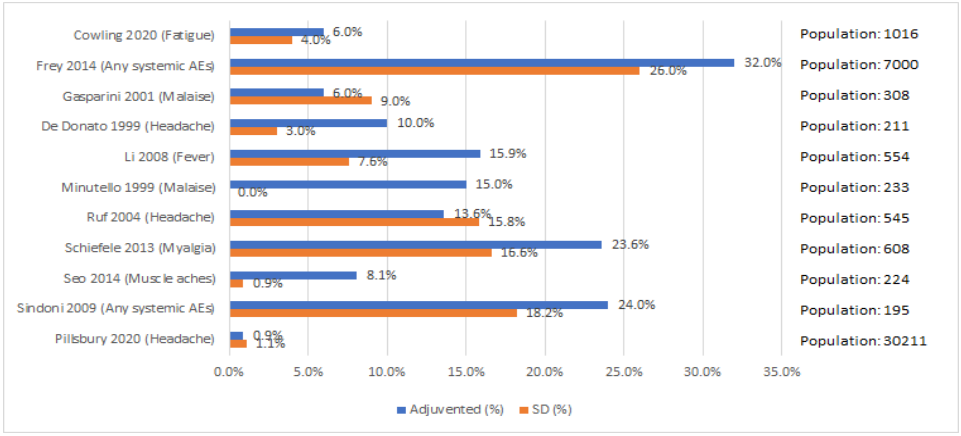
Summary of findings: MF-59 adjuvanted influenza vaccine compared with **standard dose influenza vaccine for people aged ≥65 years**

Patient or population: people ≥65 years | Intervention: MF-59 adjuvanted influenza vaccine (aIV) | Comparison: standard dose influenza vaccine (sIV)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (aIV vs sIV) (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sIV	Risk with aIV				
Hospitalisation for pneumonia, stroke and myocardial infarction assessed with: ICD-codes Follow up: range 28 days following entry to outcome, death, end of season or end of data availability (Mean: 12.5 weeks, max: 12 months)	Cases = 103, Controls=748 aTIV = 63 (61.2%) cases, 543 (72.6%) controls SD-TIV = 40 (38.8%) cases, 205 (27.4%) controls		OR 0.61 (0.39-0.96)	103 cases 748 controls (1 observational study)	⨁◯◯◯ VERY LOW [a,b,g]	Adjuvanted influenza vaccine may reduce hospitalisation for pneumonia, stroke and myocardial infarction slightly compared with standard influenza vaccine but the evidence is very uncertain Ref: 9
Solicited local adverse events assessed with: diaries Follow up: up to 7 days for solicited adverse events (AEs)	 Note: Estimates shown for “any local AE” or if not available most frequently reported local AE			⨁⨁⨁⨁ HIGH	Adjuvanted influenza vaccine increases local AEs slightly compared with standard influenza vaccine 10 RCTs[7,10,11,12,13,14,15,16,17,18]; 1 observational study[19]

Summary of findings: MF-59 adjuvanted influenza vaccine compared with **standard dose influenza vaccine for people aged ≥65 years**

Patient or population: people ≥65 years | Intervention: MF-59 adjuvanted influenza vaccine (aIV) | Comparison: standard dose influenza vaccine (sIV)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (aIV vs sIV) (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sIV	Risk with aIV				
Solicited systemic AEs assessed with: diaries Follow up: up to 7 days for solicited AEs	 Note: Estimates shown for "any systemic AE" or if not available most frequently reported systemic AE				⊕⊕⊕⊕ HIGH	Adjuvanted influenza vaccine results in little to no difference in systemic AEs compared with standard influenza vaccine 10 RCTs [7,10,11,12,13,14,15,16,17,18]; 1 observational study[19]
Serious adverse events (SAEs) assessed with: patient monitoring and active follow up Follow up: up to 366 days	All studies reported similar SAEs in both arms. In the largest study: SAEs were reported by 7% in both vaccine groups. One SAE in the aTIV group (bronchitis) and three SAEs in the SD-TIV group (asthmatic crisis, chronic obstructive pulmonary disease and Guillain–Barré syndrome [GBS]) were considered as possibly or probably vaccine-related Most studies did not report any SAEs in either group.			10,459 (9 RCTs)	⊕⊕⊕⊕ HIGH	Adjuvanted influenza vaccine results in little to no difference in SAEs compared with standard influenza vaccine 9 RCTs [7,10,11,12,13,14,16,17,18,19]
Adverse events of special interest assessed with: various (e.g. administrative data, insurance claims) Follow up: up to 6 months following vaccination	Risk of GBS: One surveillance study showed an increased risk of GBS in aTIV recipients compared with no increased risk in SD-TIV recipients (study compared vaccination to no vaccination): (aTIV vs no vaccination OR 3.75 [1.01–13.96]; SD-TIV vs no vaccination OR 1.00 [0.36–2.75]) Another observational study showed no statistically significant difference in hospitalisations due to AESIs between the groups.			4,651,769 (2 observational studies)	⊕◯◯◯ VERY LOW [c]	Adjuvanted influenza vaccine may have little to no effect on adverse events of special interest but the evidence is very uncertain 2 observational studies[20, 21]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; OR: Odds ratio; rVE: relative vaccine effectiveness

GRADE Working Group grades of evidence	
⊕⊕⊕⊕ High certainty	We are very confident that the true effect lies close to that of the estimate of the effect
⊕⊕⊕◯ Moderate certainty	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕◯◯ Low certainty	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⊕◯◯◯ Very low certainty	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Risk of bias judgement = serious - due to potential confounding
b. Not laboratory-confirmed influenza
c. Risk of bias judgement = moderate - due to confounding
d. Risk of bias judgement = very serious - due to risk of confounding
e. Few patients and events and thus wide confidence interval around the effect estimate
f. Risk of bias assessment downgraded -1 - for missing outcome data
g. Measured effect much greater than other studies

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Evidence Profile: MF-59 adjuvanted influenza vaccine (aIV) compared to standard dose influenza vaccine (sIV) **for people aged ≥65 years**

Certainty assessment							No. of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirect-ness	Imprecision	Other consider-ations	aIV	sIV	Relative (95% CI)	Absolute (95% CI)	
CRITICAL OUTCOMES											
Influenza- or pneumonia-related hospitalisation (follow up: range 3 weeks to 17 weeks; assessed with: identified by ICD-9 and ICD-10 codes)											
4	observational studies	serious [a]	not serious	serious [b]	not serious	none	All studies reported aIV was associated with lower influenza- or pneumonia-related hospitalisation than sIV Mannino 2012:[1] aTIV vs SD-TIV adjusted RR: 0.75 (95 %CI: 0.57–0.98) Number of cases/number of participants: aTIV 114/84,665, TIV 111/79,589. Cocchio 2020:[2] aTIV vs TIV vs SD adjusted OR: 0.67 (95% CI: 0.59–0.75) Number of cases/number of participants: aTIV 327/68,660, SD-TIV 2,849/410,737 Izurieta 2020:[3] aTIV vs SD-QIV: adjusted RR: 0.935 (95%CI 88.7–98.5) Number of cases/number of participants: aTIV 2874/2,101,606, SD-QIV 2790/1,455,254 Izurieta 2019:[4] aTIV vs SD-TIV: adjusted RR: 0.953 (95%CI 91.7–99.1) Number of cases/number of participants: aTIV 8202 /1,473,536, SD-TIV 4868 / 1,018,494 Note: Izurieta 2019, 2020 values for hospitalisation overlaps with outcome below for hospitalisation/emergency department (ED) visits below				⊕⊕◯◯ LOW
Influenza-related hospital encounters (follow up: range 14 days after vaccination to outcome of interest; assessed with: inpatient hospitalisation/ED visits, listing an ICD-10 code)											
3	observational studies	not serious [c]	not serious	serious [b]	not serious	none	All studies reported that aTIV was associated with a small reduction in inpatient hospitalisation/ED visits compared with SD-TIV and SD-QIV Izurieta 2020:[3] aTIV vs SD-QIV adjusted RR: 0.923 (95%CI 0.886-0.961) Number of cases/number of participants: aTIV 4,847/ 2,101,606, SD-QIV 4,582/ 1,455,254 Pelton 2020:[5] aTIV vs.SD-TIV adjusted RR: 0.888 (95%CI 0.806-0.977) Adjusted outcome rates per 1000: aTIV 5.27/1000 n= 234,313, SD-TIV 5.85/1000 n=106,491 Izurieta 2019:[4] aTIV vs SD-QIV adjusted RR: 0.964 (95%CI 0.936-0.993) Number of cases/number of participants: aTIV 9393/1,473,536, SD-TIV 8239/ 1,018,494 Note: Izurieta 2019, 2020 values for hospitalisation/ED visits overlaps with outcome above for hospitalisation				⊕⊕⊕◯ MODERATE

Certainty assessment							No. of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirect-ness	Imprecision	Other consider-ations	aIV	sIV	Relative (95% CI)	Absolute (95% CI)	
IMPORTANT OUTCOMES											
Influenza-**like illness (follow up: range 23 days to 366 days; assessed with: ≥37.2°C or feverishness and at least two of the following** symptoms: headache, myalgia, cough or a sore throat)											
1	randomised trials	serious [d]	not serious	serious [b]	not serious	none	322/3,541 (9.1%)	314/3,541 (8.9%)	RR 0.91 (0.71 to 1.16)	8 fewer per 1,000 (from 26 fewer to 14 more)	⊕⊕◯◯ LOW
Influenza-related hospital encounters/office visits (follow up: range 14 days after vaccination to outcome of interest; assessed with: inpatient hospitalisation/emergency department visits, listing an ICD-10 code. J09.xx, J10.xx, J129)											
1	observational studies	serious [a]	not serious	serious [b]	not serious	none	8,202/147,3536 (0.6%)	4,868/ 1,018,494 (0.5%)	RR 1.119 (1.081 to 1.159)	57 more per 100,000 (from 39 more to 76 more)	⊕⊕◯◯ LOW
Laboratory-confirmed influenza (timing of exposure: 4 months; assessed with: PCR)											
1	observational studies	very serious [a]	not serious	not serious	serious [c]	none	Small case-control study, with 65 cases and 162 controls, who were either vaccinated with aTIV or SD-TIV. The adjusted relative odds ratio of influenza (aTIV vs SD-TIV) = 0.37 (95CI: 4 to 96).				⊕◯◯◯ VERY LOW
Influenza-**like illness (follow up: 4 months; assessed with: sudden onset of acute respiratory affection, with axillary fever ≥38°C, at** least one general symptom and at least one respiratory symptom)											
1	observational studies	very serious [a]	not serious	serious [b]	not serious	none	174/926 (18.8%)	302/1,168 (25.9%)	OR 0.66 (0.53 to 0.82)	71 fewer per 1,000 (from 103 fewer to 36 fewer)	⊕◯◯◯ VERY LOW

Certainty assessment							No. of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirect-ness	Imprecision	Other consider-ations	aIV	sIV	Relative (95% CI)	Absolute (95% CI)	
Hospitalisation for pneumonia, stroke and myocardial infarction (timing of exposure: range 28 days following entry to outcome, death, or end of data availability; assessed with: ICD-codes)											
1	observational studies	serious [a]	serious [g]	serious [b]	serious	strong association	Case–control study nested in a cohort of elderly vaccinated with aTIV or SD-TIV Cohort N=43,000, 28, 454 (66.2%) received aTIV and 14,546 (33.8%) received SD-TIV, Cases = 103, Control=748 The adjusted OR for aTIV is 0.61 (95%CI 0.39-0.96)				⊕◯◯◯ VERY LOW
Local adverse events (follow up: up to 7 days for solicited AEs and up to 6 months for unsolicited AEs; assessed with: Diaries)											
11	randomised trials 1 observational study	not serious	not serious	not serious	not serious	none	Generally, trials found higher rates of local reactions in aTIV vs SD-TIV trials. In trials with more than 100 participants per arm, the AE difference ranges from 5% to 20%. In the biggest study (over 3,000 participants in each arm) SD-TIV=17%, aTIV=32%.				⊕⊕⊕⊕ HIGH
Systemic adverse events (follow up: up to 7 days for solicited AEs and up to 6 months for unsolicited AEs; assessed with: diaries)											
11	randomised trials 1 observational study	not serious	not serious	not serious	not serious	none	Systematic reactions occurred at generally similar rates in both arms. In larger studies there were no statistically significant differences. In smaller studies, aTIV showed higher levels of myalgia (aTIV=23.6%, SD-TIV=16.6% reported in Schiefele 2013) (8.1% vs 0.9% in Seo 2014) However the number of participants in these studies in each arm ranged from <100 to ~300.				⊕⊕⊕⊕ HIGH
Serious adverse events (SAE) (follow up: up to 366 days; assessed with: patient monitoring and follow up)											
9	randomised trials	not serious	not serious	not serious	not serious	none	All studies reported similar SAEs in both arms. Most studies did not report any SAEs in either group.				⊕⊕⊕⊕ HIGH
Adverse events of special interest (assessed with: various (e.g. administrative data, insurance claims))											
2	observational studies	serious [c]	not serious	not serious	not serious	none	Risk of GBS: One surveillance study showed an increased risk of GBS. Other observational study showed no difference in hospitalisations due to adverse events of special interest between the groups.				⊕◯◯◯ VERY LOW

a. Risk of bias judgement = serious - due to potential confounding
b. not laboratory-confirmed influenza
c. Risk of bias judgement = moderate - due to confounding
d. Risk of bias judgement = very serious - due to risk of confounding
e. Few patients and events and thus wide confidence interval around the effect estimate
f. RoB assessment downgraded -1 - for missing outcome data
g. Measured effect much greater than other studies

Evidence to Decision Framework: Individual perspective

Patients: ≥65 years old

Intervention: MF-59 adjuvanted influenza vaccines (aIV)

Comparison: Standard dose influenza vaccines (sIV)

Main outcomes:

- Influenza- or pneumonia-related hospitalisation
- Influenza-related hospitalisation/emergency department visits
- Influenza-related hospital encounters/office visits
- Laboratory-confirmed influenza
- Influenza-like illness
- Hospitalisation for pneumonia, stroke and myocardial infarction (during influenza season)
- Local adverse events
- Systemic adverse events
- Serious adverse events
- Adverse events of special interest

Setting: Global middle- to high-income settings (e.g. Italy, Canada, the United States of America, Columbia, Philippines)

Perspective: Individual

Background

Among adults aged ≥65 years, sIVs provide relatively poor protection against influenza disease. aIV aims to improve influenza vaccine effectiveness (VE) by enhancing the vaccine immunogenicity through the inclusion of an adjuvant. Whether aIV is more effective than sIV in reducing influenza related morbidity and mortality is the question.

ASSESSMENT

Problem

Is the problem a priority?

Don't know	Varies	No	Probably no	Probably yes	Yes

- High burden of influenza disease in older adults
- Relatively poor influenza VE of SIV

Desirable effects

How substantial are the desirable anticipated effects?

Don't know	Varies	Trivial	Small	Moderate	Large

- aIV is considered likely to be slightly more effective against influenza than sIV

Undesirable effects

How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Higher frequency of local adverse events following immunisation (AEFI); however, frequency of serious AEFI or adverse events of special interest appear similar between aIV and SIV recipients.

Certainty of evidence

What is the overall certainty of the evidence of effects?

No included studies	Very low	Low	Moderate	High

- Certainty of evidence on the effectiveness of aIV was downgraded because of the risk of bias due to potential confounding, with critical outcomes having low to moderate certainty of evidence. Most outcomes against influenza reported results favourable to the intervention. Most evidence on safety outcomes was of high certainty.

Values Is there important uncertainty about or variability in how much people value the main outcomes?						
Important uncertainty		Possibly important uncertainty or variability		Probably no important uncertainty or variability		No important uncertainty or variability
• Unlikely to be important uncertainty in how people value protection against influenza						
Balance of effects Does the balance between desirable and undesirable effects favour the intervention of the comparison?						
Don't know	Varies	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention
• The overall greater protection provided by aIV is likely to outweigh the additional frequency of non-serious AEFI						
Acceptability Is the intervention acceptable to key stakeholders?						
Don't know	Varies	No	Probably no	Probably yes	Yes	
• Large number of adjuvanted influenza vaccinations recorded on AIR indicate acceptability of vaccine[1]						
Feasibility Is the intervention feasible to implement?						
Don't know	Varies	No	Probably no	Probably yes	Yes	
• Minimal barriers in implementation, as vaccine delivery system already in use						

Reference

1. NCIRS. Exploratory analysis of the first 2 years of adult vaccination data recorded on AIR 2019. Available from: http://ncirs.org.au/sites/default/files/2019-12/Analysis%20of%20adult%20vaccination%20data%20on%20AIR_Nov%202019.pdf.

Note: The Australian Technical Advisory Group on Immunisation takes an individual perspective when using the GRADE framework and does not consider resources or cost-effectiveness, with agreement from the National Health and Medical Research Council.