## GRADE table: Comparison of MF59 adjuvanted inactivated influenza vaccine (aIIV, Fluad) with standard IIV for prevention of influenza in adults aged 50 to 64 years

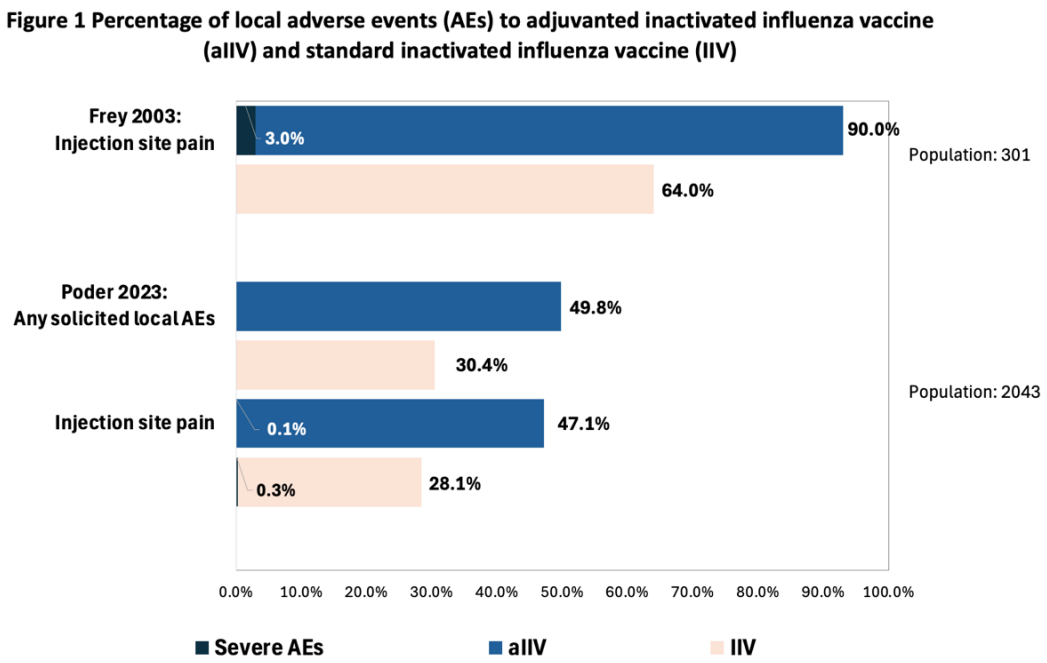
*NCIRS is conducting GRADE assessments in support of the Australian Technical Advisory Group on Immunisation (ATAGI) and making pilot results available on the Centre's website. Please read this material as a supplement to the Australian Immunisation Handbook Influenza (flu) chapter.*

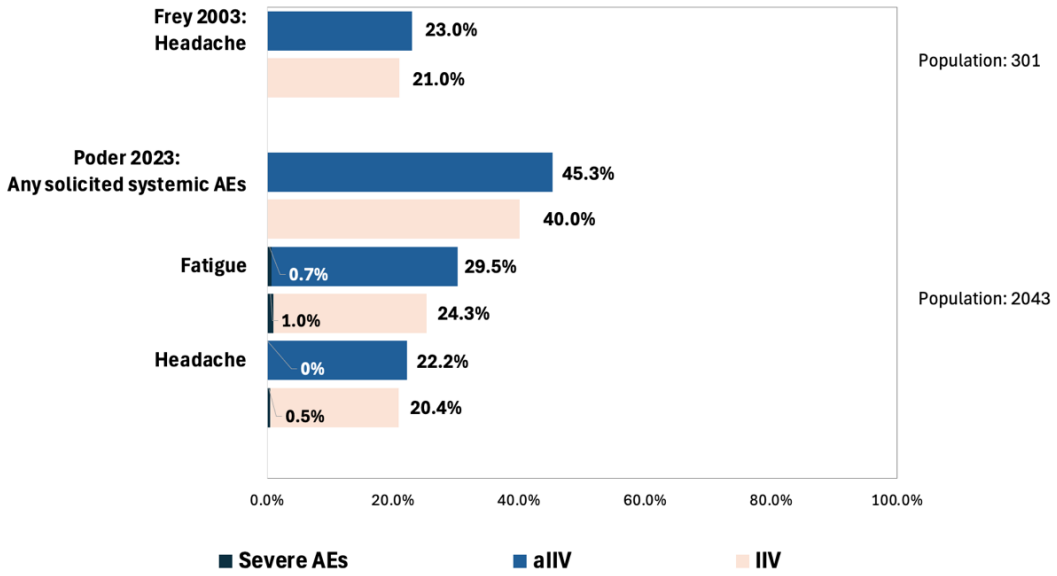
**MF59 adjuvanted inactivated influenza vaccine compared with standard IIV for prevention of influenza in adults aged 50 to 64 years**

**Patient or population:** Adults aged 50 to 64 years
**Intervention:** MF59-aIIV (Fluad)
**Comparison:** Standard IIV

| Outcomes | Impact | № of participants (studies) | Certainty of the evidence (GRADE) | Interpretation |
|---|---|---|---|---|
| **Serious adverse event (SAE)**<br><br>Follow-up: range 1 to 271days[a] | There were 31 SAEs reported in both aIIV and IIV groups during the extended follow-up period (271 days).<br>• One vaccine-related SAE reported in IIV group (hypertensive crisis on day 1) occurred in a subject with multiple cardiometabolic comorbidities.<br>• No vaccine-related SAE detected in aIIV group.<br>• One death in the aIIV group due to lung adenocarcinoma, which was assessed as unrelated to the study vaccine. | 2,044 (1 randomised controlled trial [RCT]) | ⨁⨁⨁⨁ High | aIIV results in little or no difference in SAE compared with standard IIV<br><br>Ref: 1 |

| MF59 adjuvanted inactivated influenza vaccine compared with standard IIV for prevention of influenza in adults aged 50 to 64 years | | | | |
|---|---|---|---|---|
| **Patient or population:** Adults aged 50 to 64 years<br>**Intervention:** MF59-aIIV (Fluad)<br>**Comparison:** Standard IIV | | | | |
| **Outcomes** | **Impact** | **№ of participants (studies)** | **Certainty of the evidence (GRADE)** | **Interpretation** |
| **Adverse events of special interest (AESI)**<br><br>Follow-up: range 1 to 271 days[a,b] | Two AESI reported in aIIV group, both events were assessed as unrelated to the study vaccine.<br>• One participant reported worsening of rheumatoid arthritis on day 164.<br>• Another participant reported autoimmune thyroiditis on day 228. | 2,044<br>(1 RCT) | ⨁⨁⨁⨁<br>High | aIIV results in little or no difference in AESI compared with standard IIV<br><br>Ref: 1 |

| | | | | |
|---|---|---|---|---|
| **Solicited local AE**<br><br>Follow-up: range 1 to 7 days[a] | Figure 1 Percentage of local AEs in aIIV and standard IIV groups<br>  <br><br>Severe AEs were not reported for any local AEs (Poder 2023) and IIV group in Frey 2003. | 2,344<br>(2 RCTs) | ⊕⊕⊕⊕<br>High[b] | aIIV results in a small increase in local AEs compared with standard IIV<br><br>Ref: 1,2 |

| | | | | |
|---|---|---|---|---|
| **Solicited systemic AE**<br><br>Follow-up: range 1 to 7 days[a] | Figure 2 Percentage of systemic AEs in aIIV and standard IIV groups<br><br>**Figure 2 Percentage of systemic adverse events (AEs) to adjuvanted inactivated influenza vaccine (aIIV) and standard inactivated influenza vaccine (IIV)**<br><br>  <br><br><br>Severe AEs were not reported for any systemic AEs (Poder 2023) and in Frey 2003. | 2,344<br>(2 RCTs) | ⊕⊕⊕⊕<br>High[b] | aIIV results in a small increase in systemic AE compared with standard IIV<br><br>Ref: 1,2 |

**MF59 adjuvanted inactivated influenza vaccine compared with standard IIV for prevention of influenza in adults aged 50 to 64 years**

**Patient or population:** Adults aged 50 to 64 years
**Intervention:** MF59-aIIV (Fluad)
**Comparison:** Standard IIV

<table>
<tr><th>Outcomes</th><th>Impact</th><th>№ of participants (studies)</th><th>Certainty of the evidence (GRADE)</th><th>Interpretation</th></tr>
<tr>
<td>Geometric mean titre (GMT) ratio assessed with hemagglutination inhibition (HI) antibody assays[d]<br><br>Follow-up: range 22 to 28 days</td>
<td>Table 1: GMT ratios between pre-vaccination to post-vaccination at 1 month (22–28 days)
<table>
<tr><th>Study</th><th>Frey 2003*<br>(Adults aged 18-64 years)</th><th>Poder 2023**<br>(Adults aged 50-64 years)</th></tr>
<tr><td>Serotype</td><td>IIV (N=150)/aIIV (N=145)</td><td>IIV (N=985)/aIIV (N=983) (95% CI)</td></tr>
<tr><td>A(H1N1)</td><td>0.894</td><td>0.802 (0.738–0.871)</td></tr>
<tr><td>A(H3N2)</td><td>0.818</td><td>0.900 (0.819–0.989)</td></tr>
<tr><td>B/Victoria</td><td>NA</td><td>0.992 (0.923–1.067)</td></tr>
<tr><td>B/Yamagata</td><td>NA</td><td>0.944 (0.880–1.012)</td></tr>
<tr><td>B/Harbin</td><td>0.861</td><td>NA</td></tr>
</table>
NA = data not available<br>
* GMT ratio calculated by reviewers based on reported GMT at day 28 in IIV/aIIV group<br>
** Non-inferiority analysis of aIIV relative to IIV (i.e. upper limits of 95% CI for GMT ratios were <1.5)</td>
<td>2,263<br>(2 RCTs)</td>
<td>⊕⊕⊕◯<br>Moderate[b,c]</td>
<td>aIIV results in a small increase in GMT ratio compared with standard IIV<br><br>Ref: 1,2</td>
</tr>
</table>

**MF59 adjuvanted inactivated influenza vaccine compared with standard IIV for prevention of influenza in adults aged 50 to 64 years**

**Patient or population:** Adults aged 50 to 64 years
**Intervention:** MF59-aIIV (Fluad)
**Comparison:** Standard IIV

<table>
<tr><th>Outcomes</th><th>Impact</th><th>№ of participants (studies)</th><th>Certainty of the evidence (GRADE)</th><th>Interpretation</th></tr>
<tr><td>Seroconversion assessed with HI antibody assays[d]<br><br>Follow-up: range 22 to 28 days</td><td>Table 2: Percentage of participants seroconverted (≥4-fold rise of GMT pre-vaccination to 1-month post-vaccination)
<table>
<tr><th>Study</th><th colspan="2">Frey 2003<br>(Adults aged 18-64 years)</th><th colspan="2">Poder 2023*<br>(Adults aged 50-64 years)</th></tr>
<tr><td></td><td>IIV (N=150)</td><td>aIIV (N=145)</td><td>IIV (N=985)</td><td>aIIV (N=983)</td></tr>
<tr><td>Serotype</td><td>Seroconversion</td><td>Seroconversion</td><td>Seroconversion (95% CI)</td><td>Seroconversion (95% CI)</td></tr>
<tr><td>A(H1N1)</td><td>53%</td><td>61%</td><td>76.8 (74.04–79.42)</td><td>81.2 (78.57–83.58)</td></tr>
<tr><td>A(H3N2)</td><td>75%</td><td>77%</td><td>61.8 (58.61–64.82)</td><td>63.6 (60.46–66.63)</td></tr>
<tr><td>B/Victoria</td><td>NA</td><td>NA</td><td>40.6 (37.52–43.76)</td><td>44.5 (41.39–47.74)</td></tr>
<tr><td>B/Yamagata</td><td>NA</td><td>NA</td><td>41.0 (37.92–44.19)</td><td>43.4 (40.27–46.60)</td></tr>
<tr><td>B/Harbin</td><td>71%</td><td>83%**</td><td>NA</td><td>NA</td></tr>
</table>
NA = data not available<br>* Non-inferiority analysis of aIIV relative to IIV (i.e the upper limit of the 95% CI was ≤10% for the SCR difference)<br>** Statistically significant higher seroconversion rate in aIIV compared to IIV, p<0.05</td><td>2,263<br>(2 RCTs)</td><td>⊕⊕⊕◯<br>Moderate[b,c]</td><td>aIIV results in a small increase in seroconversion compared with standard IIV<br><br>Ref: 1,2</td></tr>
<tr><td colspan="4">Abbreviations: AESI=adverse events of special interest; aIIV=adjuvanted inactivated influenza vaccine; CI=confidence interval; GMT=geometric mean titre ratio; HI=hemagglutination inhibition; IIV=inactivated influenza vaccine; SAE=serious adverse event</td><td></td></tr>
</table>

| MF59 adjuvanted inactivated influenza vaccine compared with standard IIV for prevention of influenza in adults aged 50 to 64 years | | | | |
|---|---|---|---|---|
| **Patient or population:** Adults aged 50 to 64 years<br>**Intervention:** MF59-aIIV (Fluad)<br>**Comparison:** Standard IIV | | | | |
| **Outcomes** | **Impact** | **№ of participants (studies)** | **Certainty of the evidence (GRADE)** | **Interpretation** |
| **GRADE Working Group grades of evidence**<br><br>*High certainty:* We are very confident that the true effect lies close to that of the estimate of the effect.<br>*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.<br>*Low certainty:* We have limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.<br>*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. | | | | |

## Evidence Profile: MF59 adjuvanted inactivated influenza vaccine (aIIV) compared with standard IIV for adults aged 50 to 64 years

| Certainty assessment | | | | | | | Summary of findings |
|---|---|---|---|---|---|---|---|
| Participants (studies) | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Impact |
| **Serious adverse event (SAE) (follow-up: range 1 to 271 days)**[a] | | | | | | | |
| 2,044 (1 RCT) | Not serious | Not serious | Not serious | Not serious | None | ⨁⨁⨁⨁ High | There were 31 SAEs reported in both aIIV and IIV groups during the extended follow-up period (271 days). One vaccine-related SAE reported in IIV group (hypertensive crisis on Day 1) occurred in a subject with multiple cardiometabolic comorbidities.<br>No vaccine-related SAE detected in aIIV group.<br>There was one death in the aIIV group due to lung adenocarcinoma, which was assessed as unrelated to the study vaccine.<br>[1] |
| **Adverse events of special interest (follow-up: range 1 to 271 days)**[a] | | | | | | | |
| 2,044 (1 RCT) | Not serious | Not serious | Not serious | Not serious | None | ⨁⨁⨁⨁ High | Two AESI reported in aIIV group: one participant reported worsening of rheumatoid arthritis on study Day 164, another participant reported autoimmune thyroiditis on study Day 228. Both events were assessed as unrelated to the study vaccine.[1] |

| Certainty assessment | | | | | | | Summary of findings |
|---|---|---|---|---|---|---|---|
| **Solicited local adverse events (follow-up: range 1 to 7 days)**[a] | | | | | | | |
| 2,344 (2 RCTs) | Not serious | Not serious | Not serious[b] | Not serious | None | ⨁⨁⨁⨁ High[b] | One RCT reported 49.8% of the aIIV and 30.4% of the IIV groups experienced any solicited local AEs during the 7-day period after vaccination. The most frequently reported solicited local AEs were injection site pain (aIIV: 47.1%, 0.1% as severe; IIV: 28.1%, 0.3% as severe). The majority of solicited AEs were of short duration and rated as mild; less than 0.5% of subjects reported severe local AEs.<br><br>Another RCT reported that higher frequency of local pain (aIIV: 90%, 3% rated as severe vs. IIV: 64%, p≤0.05) and warmth (aIIV: 28% vs IIV: 18%, p≤0.05) in the aIIV group. [1,2] |

| Certainty assessment | | | | | | | Summary of findings |
|---|---|---|---|---|---|---|---|
| **Solicited systemic adverse events (follow-up: range 1 to 7 days)**[a] | | | | | | | |
| 2,344 (2 RCTs) | Not serious | Not serious | Not serious[b] | Not serious | None | ⨁⨁⨁⨁ High[b] | One RCT reported 45.3% of the aIIV and 40.0% of the IIV groups experienced any solicited systemic AEs. The most frequently reported solicited systemic AEs were fatigue (aIIV: 29.5%, 0.7% as severe vs IIV: 24.3%, 1% as severe) and headache (aIIV: 22.2%, none as severe vs IIV: 20.4%, 0.5% as severe).<br>Another RCT showed that the most frequent systemic AEs were headache (aIIV: 23%; IIV: 21%) and myalgia (aIIV: 15% vs IIV: 6%, p≤0.05).<br>[1,2] |

| Certainty assessment | | | | | | | Summary of findings |
|---|---|---|---|---|---|---|---|
| **GMT ratio (follow-up: range 22 to 28 days; assessed with HI antibody assays)** | | | | | | | |
| 2,263 (2 RCTs) | Not serious | Not serious | Serious[b,c] | Not serious | None | ⨁⨁⨁◯ Moderate[b,c] | Non-inferiority analysis (per-protocol data set, non-inferiority bound of 1.5) showed the derived GMT ratios of IIV/aIIV in aIIV group was non-inferior to IIV group for all vaccine strains reported in the pivotal RCT:<br>• A(H1N1): 0.802 (95%CI, 0.738–0.871)<br>• A(H3N2): 0.900 (95% CI, 0.819–0.989)<br>• B/Victoria: 0.992 (95%CI, 0.923–1.067)<br>• B/Yamagata: 0.944 (95%CI, 0.880–1.012).<br><br>Superiority analysis (intention to treat set, superiority bound = 1) showed GMT ratios in aIIV was superior to IIV for A(H1N1) and A(H3N2) with a GMT ratio of 0.808 (95% CI, 0.745 to 0.876) for A(H1N1) and 0.910 (95% CI, 0.829 to 0.998) for A(H3N2). The upper limits of the 95% CIs were >1 for the B-lineage strains.<br><br>In another RCT, no statistically significant between-group difference in GMT after first injection across all vaccine strains (A/H1N1: aIIV, 951 vs IIV, 850; A/H3N2: aIIV, 511 vs IIV, 418 and B: aIIV, 698 vs TIV, 601). After second injection, higher GMT was observed in aIIV group (112) compared to IIV group (71, $p<0.05$) for A/H3N2, but not for other strains. [1,2] |

| Certainty assessment | | | | | | | Summary of findings |
|---|---|---|---|---|---|---|---|
| **Seroconversion (follow-up: range 22 to 28 days; assessed with HI antibody assays)**[d] | | | | | | | |
| 2,263 (2 RCTs) | not serious | not serious | serious[b,c] | not serious | none | ⨁⨁⨁◯ Moderate[b,c] | The derived seroconversion rate (SCR) differences demonstrated that aIIV was non-inferior (non-inferiority bound = 10%) to IIV for all vaccine strains reported in the pivotal RCT:<br>• A(H1N1): −4.4 (95% CI, −7.97 to –0.74);<br>• A(H3N2): −1.8 (95% CI, −6.14 to 2.48);<br>• B/Victoria: −3.9 (95% CI, –8.31 to 0.45) and<br>• B/Yamagata: −2.4 (95% CI, −6.77 to 2.00).<br>In another RCT, a statistically significant SCR difference was seen in the aIIV group compared to IIV group for the B antigen (83% vs. 71%, p<0.05) but no difference observed for A/H1N1 (61% vs 52%) and A/H3N2 (77% vs 75%) strains.<br>[1,2] |

| Certainty assessment | Summary of findings |
|---|---|

**Explanations**

a. Clinical assessment during clinic visits, participants' eDiary and scheduled safety calls

b. The targeted population is people aged 50-64 years, while 1 small trial was conducted in people aged 18-64 years (N=301, approx. 12% of the total sample) – indirectness was not downgraded due to the small proportion.

c. In the absent of vaccine effectiveness data (which was the planned critical outcome), immunogenicity outcomes were used – indirectness was downgraded.

d. Seroconversion rate is defined as the percentage of subjects with titers of HI antibody ≥160 and at least a 4-fold rise from baseline titers. (Frey 2003) and the percentage of subjects with both titers of HI antibody ≥160 and at least a 4-fold rise from baseline titers (Poder 2023).

## References

1. Poder A, Oberije J, Meyer J, et al. 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.

2. 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;21(27-30):4234-7.

## Evidence to Decision Framework: individual perspective

| **Should MF59 adjuvanted inactivated influenza vaccine (aIIV) be used in adults aged 50 to 64 years for prevention of influenza?** | |
|---|---|
| **Population** | Adults aged 50 to 64 years |
| **Intervention** | aIIV |
| **Comparison** | Standard IIV |
| **Main outcomes** | Immunogenicity (GMT ratio, seroconversion), serious adverse events (SAEs), adverse events (AEs) |
| **Setting** | High- and middle-income countries |

**ASSESSMENT**

**Problem**
*Is the problem a priority?*

| Don't know | Varies | No | Probably no | Probably yes | Yes |
|---|---|---|---|---|---|

- Although generally less than people aged ≥65 years, the burden of influenza reported in those aged ≥50 remains significant. There is also a need to outline the burden of influenza in this GRADE and acknowledge the considerations for influenza prevention within the 50–64 age-group as these populations account for a proportion of the workforce and play a central economic and social role.
- Based on NCIRS internal analysis, the 2022–24 influenza notification rates in Australia were similar between people aged 50-64 and ≥65 years, which were 638.3 and 619.1 per 100,000, respectively. Notably, hospitalisation rates during 2022 were 69.1 per 100,000 for adults aged 50–64 and 61.6 per 100,000 for those aged 20–49, markedly lower than the 169.0 per 100,000 observed in adults aged ≥65 years.
- A Canadian study investigated the burden of severe influenza in people aged 50-64 years old from 2010 to 2017.[1]
    - The study showed individuals aged 50–64 years had a 3-times higher rate of hospitalisation and a 9-fold higher mortality rate attributable to influenza than those aged 18–49 years, generating higher influenza-related hospitalisation costs.

- The average annual hospitalisation rate was 22.4, 45.9 and 408.7 per 100,000 in people aged 50–64, 65–74 and ≥75 years, respectively. The average annual mortality was 0.9 per 100, 000 and 2 per 100,000 in people aged 50–64 and 65–74 years, respectively.
- The average annual hospitalisation rate was 41/100,000 in those with any underlying condition, and highest in those with renal disease or immunocompromise (138 and 281 per 100,000, respectively).

- A 2017 Australian modelling study estimated the annual average respiratory hospitalisation rate of 78.9 (95%CI: 76.3, 81.4) per 100,000 population in Australian adults aged 50-64 due to seasonal influenza.[2] The corresponding respiratory mortality rates were 0.9 (95%CI: 0.7, 1.2) per 100,000 population. Influenza accounted for 1% of total myocardial infarction deaths in adults aged 50–64.
- Available data suggest that including healthy people aged 50–64 years in influenza vaccination recommendations would expand coverage to a broader population. However, this approach requires a socio-economic analysis and adjustments to public health prioritisation, program implementation etc. relevant to Australia context.[3]

**Desirable effects**

*How substantial are the desirable anticipated effects?*

| Don't know | Varies | Large | Moderate | Small | Trivial |
|---|---|---|---|---|---|

- The relative clinical effectiveness of aIIV compared to IIV is unclear in the 50-64 years age group due to a lack of evidence on clinical outcomes. Results from a cluster-randomised trial among 823 nursing homes (approximately 17% of residents were aged <65 years) estimated that aIIV resulted a 17% and 22% reduction than IIV for suspected and laboratory-confirmed influenza outbreaks, respectively.[4]
- Immunogenicity evidence from trials included in this GRADE summary of findings demonstrated that aIIV was largely non-inferior to IIV.[5,6] Poder et al 2023 demonstrated GMT ratios in aIIV were statistically significant superior to IIV for A(H1N1) and A(H3N2).[1]
- The immunogenicity of MF59-aIIV has also been examined in people with medical risk groups, including stem cell/organ transplant and chronic diseases.[7,8]
  - In 619 organ transplant recipients (67% kidney transplant) with a median age of 57 years old, use of aIIV resulted in a higher vaccine response rate compared to standard vaccine group (60% vs 42%, p <0.001).[9]
  - Of 238 adult subjects (18–60 years of age) with underlying chronic diseases (e.g. cancer, diabetes, cardiovascular and lung conditions), aIIV achieved superior seroprotection rate (titre ≥1:40) than a conventional subunit vaccine (75% vs 57.6%, p = 0.002).[10]
  - A recent study of 130 participants with haematologic cancer showed aIIV did not confer greater immunogencity than standard IIV, and a second IIV dose did not improve immune response.[11] Notably, the study population was older, with a median age of 64 years (IQR: 56–74).[XW1]

- A study in people 19–64 years undergoing hemodialysis showed seroconversion rates (≥4-fold increase in post-vaccination antibody titer) at 1 month post-vaccination were higher in the MF59-aIIV group than in the non-adjuvanted IIV group (46.3% vs 13.8% for A/H1N1; 40.3% vs 10.3% for A/H3N2; 31.3% vs 6.9% for B, p <0.01), although no significant between-group difference was found for seroprotection.[12]

**Undesirable effects**

*How substantial are the undesirable anticipated effects?*

| Don't know | Varies | Large | Moderate | Small | Trivial |
|---|---|---|---|---|---|

- The rate of local or systemic adverse events was higher in aIIV compared to IIV from clinical trials, but no serious adverse events or events of special interests related to aIIV in people aged 50–64 years old.[5,6]
- MF59-aIIV is well tolerated in people with various medical risk groups aged 18 to 64 years old.[7,8]
    - In 73 allogeneic hematopoietic stem cell transplant recipients, no statistically significant differences were found for local and systemic adverse effects in aIIV and non-adjuvanted IIV groups. New onset GVHD, or GVHD at a new site, occurred in 9/35 (25.7%) vs 10/38 (26.3%) patients in the adjuvanted and non-adjuvanted groups, respectively (p = 0.95).[8]
    - In study of 68 kidney transplant recipients, there were no significant differences in local and systemic adverse effects between the aIIV and non-adjuvanted groups, except local tenderness was significantly greater in the aIIV group (77.4% vs 51.6%; p = 0.034).[7]
    - There were no vaccine-related hospitalisations or deaths reported in the above studies.[7,8]

**Certainty of evidence**

*What is the overall certainty of the evidence of effects?*

| No Included Studies | Very Low | Low | Moderate | High |
|---|---|---|---|---|

- The overall certainty of evidence from the two eligible trials was considered as moderate (moderate for the immunogenicity outcomes and high for safety outcomes).
    - Indirectness was downgraded for immunogenicity outcomes in both studies because immunogenicity served as indirect evidence in the absence of vaccine effectiveness data, which was the planned critical outcome.

- Indirectness on study population was downgraded in Frey et al 2003 as it consisted of 18-64 years old, the overall indirectness remained not serious due to the small proportion of the sample size among the overall population. Similarly, Frey et al 2003 had some concerns on missing reporting of serious adverse events outcomes, the overall risk of bias was not affected.[6]

**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 or the comparison?*

| Don't Know | Varies | Favours comparison | Probably favours comparison | Does not favour either comparison or intervention | Probably favours intervention | Favours intervention |
|---|---|---|---|---|---|---|

- Current evidence is insufficient to confirm that the slightly higher immunogenicity of aIIV translates into increased clinical effectiveness for this age group; consequently, these potential benefits do not outweigh the slightly higher frequency of non-serious adverse events following immunisation

**Equity**

*What would be the impact on health inequities?*

| Don't know | Varies | Increased | Probably increased | Probably no impact | Probably reduced | Reduced |
|---|---|---|---|---|---|---|

- The incremental clinical benefits of aIIV over standard IIV is unclear in this age group
- For healthy adults aged 50–64 in Australia, an out-of-pocket payment is usually required for any influenza vaccine, with aIIV costing more than IIV.
- Adults with medical conditions are eligible for free IIV under NIP but aIIV is not subsidised for them.
- In general, aIIV can be less accessible for low-income adults aged 50–65 if it is available only through the private market. This may result in a potential gap in access to enhanced vaccine options, especially for adults under 65 with medical risk conditions.

- Current influenza vaccine coverage among adults aged 50–64 ranges from 25.4% to 44.3% across jurisdictions.[13] If adjuvanted vaccines remain unsubsidised for this group, particularly for low-income adults with medical risk conditions, their ability to access enhanced vaccine options may be limited. However, given the uncertainty around incremental benefits of aIIV in this age group, the impact on health equity remains unclear.

**Acceptability**
*Is the intervention acceptable to key stakeholders?*

| Don't know | Varies | No | Probably no | Probably yes | Yes |
|---|---|---|---|---|---|

- The vaccination uptake of at least one dose of influenza vaccine recorded on the Australian Immunisation Register (AIR) increased progressively with age. In 2017, recorded uptake was 4.8% for people aged 18–50 years, 10.5% for those aged 50–65 years and 31.5% for those aged ≥65 years, increasing in each of these age groups in 2018 to 8.9%, 17.2% and 46.3%, respectively.[14]
- An analysis of 2018 Australian AIR records showed aIIV was well-accepted in adults aged ≥65 years (i.e. the eligible age group enhanced influenza vaccination was funded and recommended). Among vaccinated older adults, 52% of people received aIIV and the rest received high-dose IIV.[14]
- Adults aged 50–64 are usually employed, making it harder to access vaccination during business hours when workplace vaccination programs are not universally available.
- The cost for aIIV is much (2~3 times) higher than standard dose IIV in private market, which also further limit its acceptability.
- Healthcare providers do not currently routinely recommend influenza vaccination to this age group unless comorbidities are present.

**Feasibility**
*Is the intervention feasible to implement?*

| Don't know | Varies | No | Probably no | Probably yes | Yes |
|---|---|---|---|---|---|

- There are minimal barriers in implementation, as vaccine delivery system already in use.
- The adjuvanted IIV is currently recommended and funded for ≥65 years old in Australia. Expanding eligibility to include those aged 50–64 would require robust evidence.

| |
|---|
| • In addition, the vaccine uptake and coverage for this age are unlikely to increase without targeted strategies including tailored-communication, education and promotional campaigns directed at both healthcare providers and the public. |
| **ATAGI RECOMMENDATIONS** |
| • Adjuvanted inactivated influenza vaccine (aIIV) is recommended as an alternative to standard IIV in adults aged 50–64 years. |
| **JUSTIFICATION** |
| • Compared with standard dose IIV, aIIV may provide a modest benefit in preventing influenza based on immunogenicity data in people aged 50 to 64 years and prior vaccine effectiveness data in those aged ≥65 years.<br>• Due to a current lack of vaccine effectiveness data demonstrating clear incremental clinical benefits for people aged 50–64 years, ATAGI does not support a preferential recommendation for aIIV in this cohort.<br>• Compared with standard dose IIV, aIIV was associated with a small increase in non-serious adverse events, but little to no difference in serious adverse events or adverse events of special interest.<br>• Current evidence is insufficient to confirm that the slightly higher immunogenicity of aIIV translates into increased clinical effectiveness for this age group; consequently, these potential benefits do not outweigh the slightly higher frequency of non-serious adverse events following immunisation. |

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