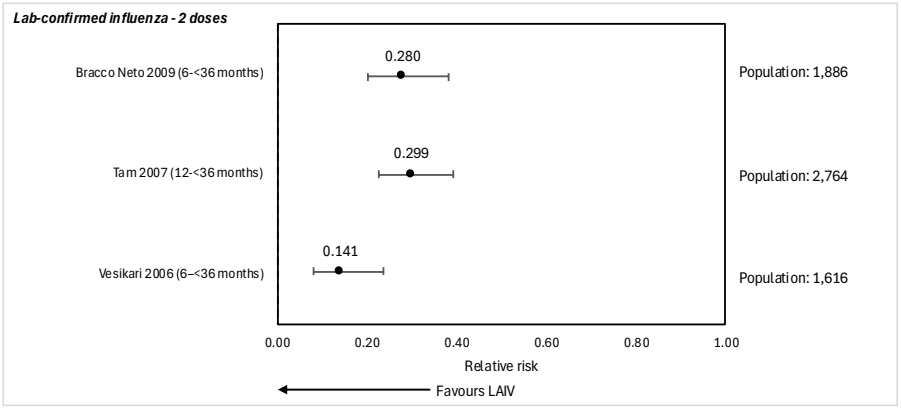
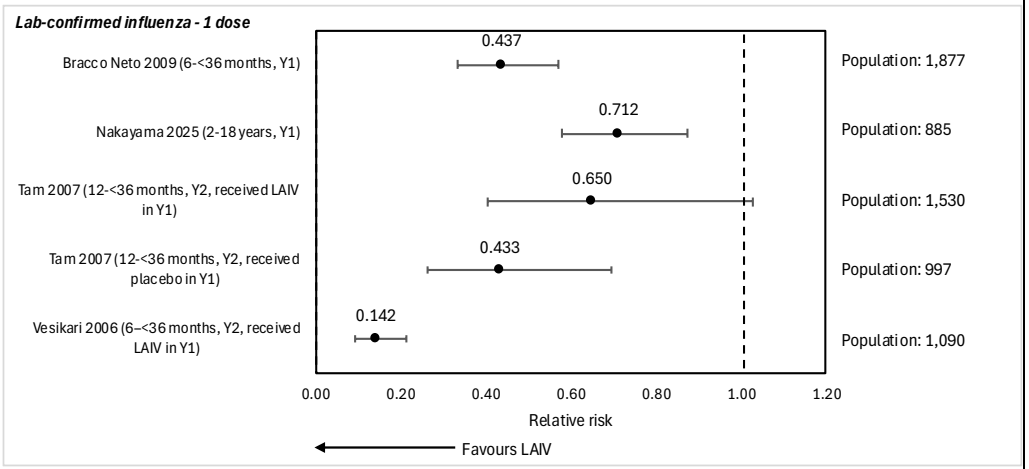
GRADE table: Comparison of live-attenuated influenza vaccine (LAIV; FluMist) with control (placebo/no vaccination) for prevention of influenza in children aged 2–17 years (PICO 1)

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.

LAIV (FluMist) compared with placebo for prevention of influenza in children aged 2–17 years

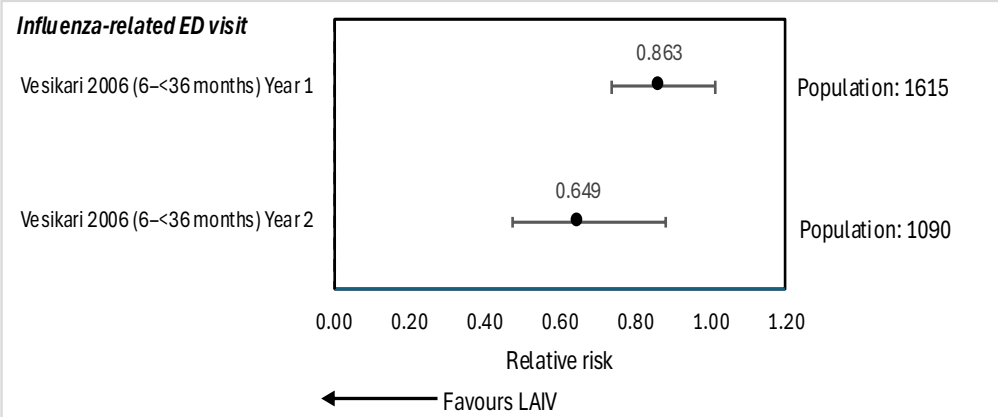
Patient or population: Children aged 2–17 years
Intervention: LAIV (FluMist)
Comparison: Placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Laboratory-confirmed influenza infection (LCI) Assessed with: culture/PCR Follow-up: range 11 days to 1 year	In most studies, LAIV is more effective than placebo in preventing laboratory-confirmed influenza infections. 2 doses of LAIV are more effective than placebo in preventing laboratory-confirmed influenza infections. 1 dose of LAIV is likely more effective than placebo in preventing laboratory-confirmed influenza infections, but results vary. Graphs below show LCI by number of doses of LAIV 	7,151 (4 RCTs)[1-4]	⨁⨁⨁◯ Moderate[a]	LAIV likely reduces LCI compared with placebo

LAIV (FluMist) compared with placebo for prevention of influenza in children aged 2–17 years				
Patient or population: Children aged 2–17 years **Intervention:** LAIV (FluMist) **Comparison:** Placebo				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
				

LAIV (FluMist) compared with placebo for prevention of influenza in children aged 2–17 years

Patient or population: Children aged 2–17 years
Intervention: LAIV (FluMist)
Comparison: Placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Laboratory-confirmed influenza emergency department (ED) visit (flu ED visit) Assessed with: culture/PCR Follow-up: range 11 days to 1 year	Estimates from a single study, with results reported separately for 2 influenza seasons  Note: Estimates reported are for ≥1 outpatient or emergency department visit	1,615 (1 RCT) [2]	⊕◯◯◯ Very low[b,c,d]	The evidence is very uncertain about the effect of LAIV on laboratory-confirmed ED visits compared with placebo

LAIV (FluMist) compared with placebo for prevention of influenza in children aged 2–17 years

Patient or population: Children aged 2–17 years
Intervention: LAIV (FluMist)
Comparison: Placebo

<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>Serious adverse events (SAEs) – randomised controlled trials (RCTs)</td><td>Frequency of SAEs was similar between LAIV and placebo groups across studies. (Table to be included with proportion/number of SAEs by study)
<table>
<tr><th>Study</th><th>Outcome</th><th>LAIV (%)</th><th>Placebo (%)</th><th>LAIV (n/N)</th><th>Placebo (n/N)</th></tr>
<tr><td>Bergen 2004, 1–17 years</td><td>SAEs</td><td>0.2%</td><td>0.2%</td><td>13/6,473</td><td>7/3,216</td></tr>
<tr><td>Bracco Neto 2009, 6–<36 months</td><td>SAEs, Year 1, single dose</td><td>3.8%</td><td>4.1%</td><td>NR/2,056</td><td>NR/515</td></tr>
<tr><td>Bracco Neto 2009, 6–<36 months</td><td>SAEs, Year 1, 2 doses</td><td>5.0%</td><td>4.1%</td><td>NR/1,023</td><td>NR/515</td></tr>
<tr><td>Bracco Neto 2009, 6–<36 months</td><td>SAEs, Year 2, dose 1</td><td>1.6%</td><td>2.4%</td><td>NR/1,451</td><td>NR/725</td></tr>
<tr><td>Nakayama 2025, 2–17 years</td><td>SAEs</td><td>0.7%</td><td>0.0%</td><td>4/608</td><td>0/302</td></tr>
<tr><td>Tam 2007, 12–<36 months</td><td>SAEs, Year 1</td><td>NR</td><td>NR</td><td>NR/1,831</td><td>NR/1,224</td></tr>
<tr><td>Tam 2007, 1–-<36 months</td><td>SAEs, Year 2</td><td>NR</td><td>NR</td><td>1/1,351</td><td>0/1,335</td></tr>
<tr><td>Vesikari 2006, 6–36 months</td><td>Lower respiratory tract illnesses reported as SAEs, Year 1</td><td>NR</td><td>NR</td><td>17/961</td><td>14/616</td></tr>
<tr><td>Vesikari 2006, 6–36 months</td><td>Lower respiratory tract illnesses reported as SAEs, Year 1</td><td>NR</td><td>NR</td><td>6/621</td><td>0/428</td></tr>
</table></td><td>1,7802 (5 RCTs) [1-5]</td><td>⊕⊕⊕⊕ High[e]</td><td>LAIV does not increase SAEs compared with placebo</td></tr>
</table>

LAIV (FluMist) compared with placebo for prevention of influenza in children aged 2–17 years

Patient or population: Children aged 2–17 years
Intervention: LAIV (FluMist)
Comparison: Placebo

<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>SAEs – systematic review (SR)</td><td>Pooled estimates of frequency of SAEs reported for children aged 2-17 years, by year of vaccination and timeframe of follow up.
<table>
<tr><th>Study</th><th>Outcome</th><th>LAIV (%)</th><th>Placebo (%)</th><th>LAIV (n/N)</th><th>Placebo (n/N)</th></tr>
<tr><td>Ambrose 2011, 2–17 years</td><td>SAEs, 0–42 days, Year 1</td><td>0.5%</td><td>0.6%</td><td>NR/10,693</td><td>NR/5,677</td></tr>
<tr><td>Ambrose 2011, 2–17 years</td><td>SAEs, 0–42 days, Year 2</td><td>0.5%</td><td>0.6%</td><td>NR/3,212</td><td>NR/1,697</td></tr>
<tr><td>Ambrose 2011, 2–17 years</td><td>SAEs, 0–180 days, Year 1</td><td>2.9%</td><td>2.7%</td><td>NR/2,408</td><td>NR/1,546</td></tr>
<tr><td>Ambrose 2011, 2–17 years</td><td>SAEs, 0–180 days, Year 2</td><td>2.1%</td><td>1.7%</td><td>NR/2,295</td><td>NR/1,256</td></tr>
</table>
Note: Data for this outcome is from a multi-study integrated analysis of 20 RCTs of LAIV vs either IIV or placebo. It is unclear how many studies were LAIV vs placebo (study details not reported, only population numbers reported).</td><td>1,6370 (1 SR)[6] – includes 20 RCTs published before April 2008</td><td>⊕⊕⊕◯ Moderate[f]</td><td>LAIV does not increase SAEs compared with placebo</td></tr>
</table>

LAIV (FluMist) compared with placebo for prevention of influenza in children aged 2–17 years

Patient or population: Children aged 2–17 years
Intervention: LAIV (FluMist)
Comparison: Placebo

<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>Adverse event of special interest (AESI): asthma/wheeze – RCT</td><td>Frequency of medically attended asthma/wheezing was low in children aged 1-17 years, i.e. <1% in both LAIV and placebo groups.

The frequency of medically attended asthma/wheezing was slightly higher in children aged 18-35 months who received LAIV vs placebo.

<table>
<tr><th>Study</th><th>Outcome</th><th>LAIV (%)</th><th>Placebo (%)</th><th>LAIV (n/N)</th><th>Placebo (n/N)</th></tr>
<tr><td>Bergen 2004, 1–17 years</td><td>Asthma (medically attended)</td><td>0.9%</td><td>0.9%</td><td>NR/6,473</td><td>NR/3,216</td></tr>
<tr><td>Bergen 2004, 18–35 months</td><td>Asthma (medically attended)</td><td>2.1%*</td><td>0.5%*</td><td>15/728</td><td>2/369</td></tr>
</table>
* RR = 3.81 (90%CI: 1.20-16.82)</td><td>9,689 (1 RCT)[5]</td><td>⊕⊕⊕◯ Moderate[e]</td><td>LAIV likely results in little to no difference in asthma/wheeze compared with placebo</td></tr>
</table>

<table>
<tr>
<td>AESI: asthma/wheeze – SR</td>
<td>
Frequency of wheezing was low (≤1%) in children aged 2–17 years in LAIV and placebo groups, regardless of year of vaccination and number of doses received. Frequency of wheeze was similar between LAIV and placebo groups in children aged 24-35 months.
<table>
<tr><th>Age group</th><th>Outcome</th><th>LAIV (%)</th><th>Placebo (%)</th><th>LAIV (n/N)</th><th>Placebo (n/N)</th></tr>
<tr><td>2–17 years</td><td>Wheezing, 0–10 days, Year 1, Dose 1</td><td>0.7%</td><td>0.7%</td><td>22/3,278</td><td>14/2026</td></tr>
<tr><td>2–17 years</td><td>Wheezing, 0–10 days, Year 1, Dose 2</td><td>0.6%</td><td>1.0%</td><td>16/2,533</td><td>18/1,734</td></tr>
<tr><td>2–17 years</td><td>Wheezing, 0-10 days, Year 2</td><td>0.7%</td><td>0.6%</td><td>17/2,295</td><td>7/1,256</td></tr>
<tr><td>24–35 months</td><td>Wheezing, 0–10 days, Year 1, Dose 1</td><td>0.7%</td><td>0.7%</td><td>22/3,149</td><td>14/1,900</td></tr>
<tr><td>24–35 months</td><td>Wheezing, 0–10 days, Year 1, Dose 2</td><td>0.6%</td><td>1.0%</td><td>16/NR</td><td>18/NR</td></tr>
<tr><td>24–35 months</td><td>Wheezing, 0–10 days, Year 2</td><td>0.8%</td><td>0.9%</td><td>9/1,063</td><td>5/574</td></tr>
<tr><td>24–35 months</td><td>SAE wheezing, 0–42 days, Year 1</td><td>0.2%</td><td>0.2%</td><td>7/10,693</td><td>4/5,667</td></tr>
<tr><td>24–35 months</td><td>SAE wheezing, 0–42 days, Year 2</td><td>0.1%</td><td>0.0%</td><td>1/3,212</td><td>0/1,697</td></tr>
<tr><td>24–35 months</td><td>SAE wheezing, 0–180 days, Year 1</td><td>0.4%</td><td>0.3%</td><td>9/2,408</td><td>5/1,546</td></tr>
<tr><td>24–35 months</td><td>SAE wheezing, 0–180 days, Year 2</td><td>0.2%</td><td>0.0%</td><td>2/2,295</td><td>0/1,256</td></tr>
</table>
Note: Data for this outcome is from a multi-study integrated analysis of 20 RCTs of LAIV vs either IIV or placebo. It is unclear how many studies were LAIV vs placebo (study details not reported, only population numbers reported).
</td>
<td>5,304 (1 SR)[6] – includes 20 RCTs published before April 2008</td>
<td>⊕⊕⊕◯ Moderate[f]</td>
<td>LAIV likely results in little to no difference in asthma/wheeze compared with placebo</td>
</tr>
<tr>
<td>AESI (other than asthma/wheeze) – RCT</td>
<td>
Frequency of AESI were similar between LAIV and placebo groups.
<table>
<tr><th>Study</th><th>Outcome</th><th>LAIV (%)</th><th>Placebo (%)</th><th>LAIV (n/N)</th><th>Placebo (n/N)</th></tr>
<tr><td>Bergen 2004, 1–17 years</td><td>AESI: Acute respiratory tract infections, medically attended</td><td>16.1%</td><td>17.9%</td><td>1042/6473</td><td>577/3,216</td></tr>
<tr><td>Bergen 2004, 1–17 years</td><td>AESI: Seizure</td><td>0.0%</td><td>0.0%</td><td>1/6,473</td><td>0/3,216</td></tr>
</table>
</td>
<td>9,689 (1 RCT) [5]</td>
<td>⊕⊕◯◯ Low[e,g]</td>
<td>The evidence suggests that LAIV does not increase AESI compared with placebo</td>
</tr>
</table>

LAIV (FluMist) compared with placebo for prevention of influenza in children aged 2–17 years

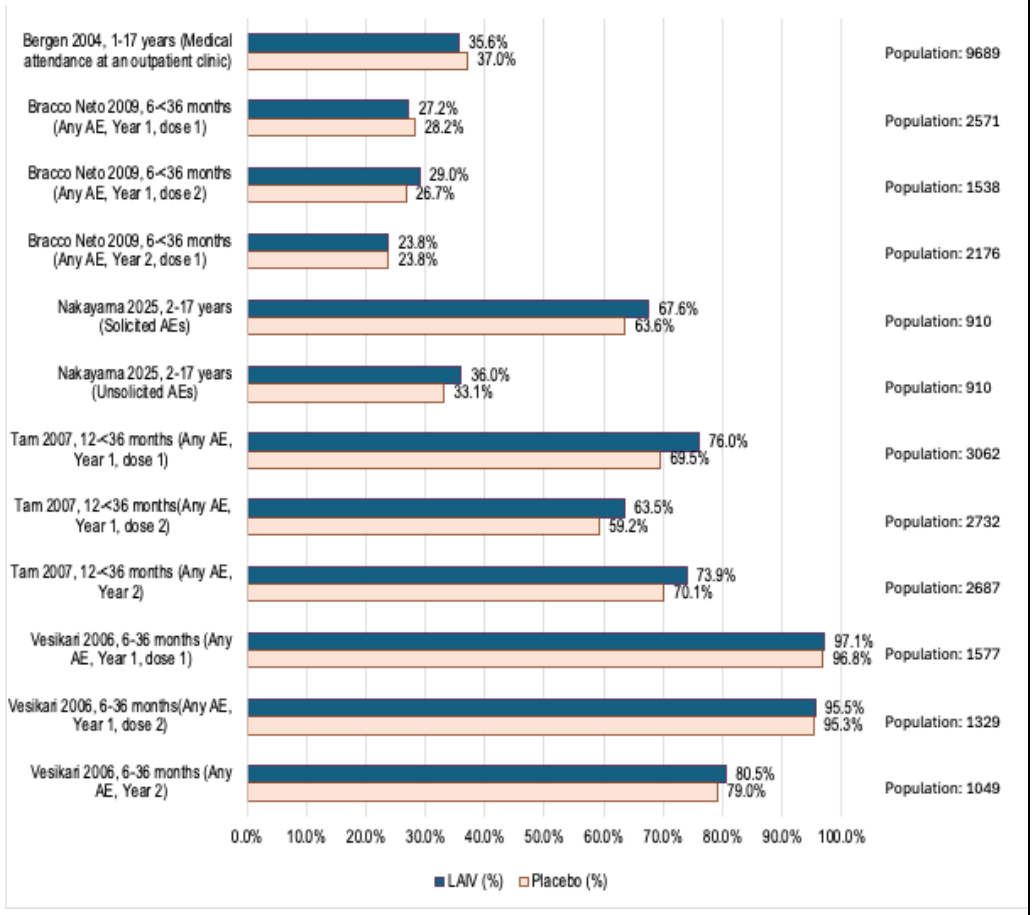
Patient or population: Children aged 2–17 years
Intervention: LAIV (FluMist)
Comparison: Placebo

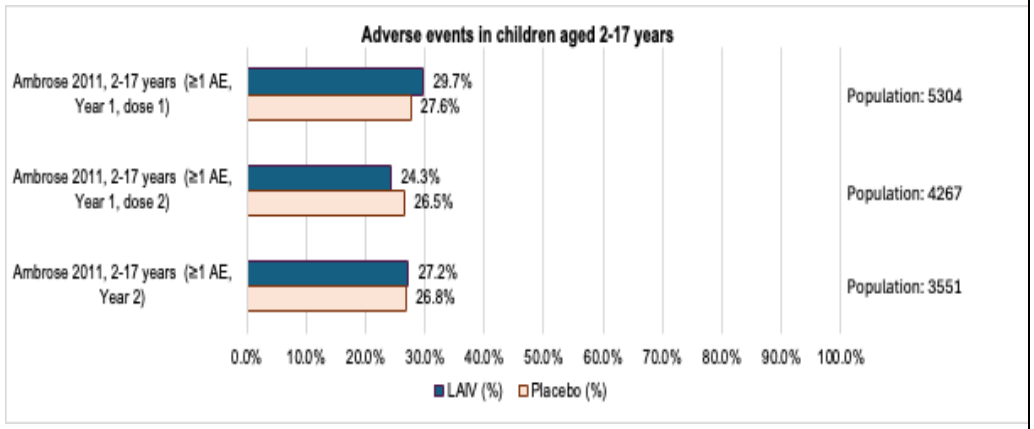
Outcomes	Impact						№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
	Bergen 2004, 1–17 years	AESI: Febrile seizure	0.1%	0.0%	5/6,473	1/3,216			
	Bergen 2004, 1–17 years	AESI: Epilepsy	0.0%	0.1%	2/6,473	2/3,216			

LAIV (FluMist) compared with placebo for prevention of influenza in children aged 2–17 years

Patient or population: Children aged 2–17 years
Intervention: LAIV (FluMist)
Comparison: Placebo

<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>AESI (other than asthma/wheeze) – SR</td><td>Frequency of AESI were low and similar between LAIV and placebo groups, regardless of follow up time (10, 42 or 180 days), year of vaccination and number of doses.
<table>
<tr><th>Age group</th><th>Outcome</th><th>LAIV (%)</th><th>Placebo (%)</th><th>LAIV (n/N)</th><th>Placebo (n/N)</th></tr>
<tr><td>2–17 years</td><td>AESI: LRI, 0–10 days, Year 1, Dose 1</td><td>1.8%</td><td>1.8%</td><td>58/3,278</td><td>37/2,026</td></tr>
<tr><td>2–17 years</td><td>AESI: LRI, 0–10 days, Year 1, Dose 2</td><td>1.9%</td><td>2.9%</td><td>48/2,533</td><td>51/1,734</td></tr>
<tr><td>2–17 years</td><td>AESI: LRI, 0–10 days, Year 2</td><td>1.7%</td><td>1.5%</td><td>40/2,295</td><td>19/1256</td></tr>
<tr><td>24–35 months</td><td>AESI: LRI, 0–10 days, Year 1, Dose 1</td><td>1.8%</td><td>1.9%</td><td>58/3,149</td><td>37/1,900</td></tr>
<tr><td>24–35 months</td><td>AESI: LRI, 0–10 days, Year 1, Dose 2</td><td>1.9%</td><td>2.9%</td><td>48/NR</td><td>51/NR</td></tr>
<tr><td>24–35 months</td><td>AESI: LRI, 0–10 days, Year 2</td><td>2.2%</td><td>1.6%</td><td>23/1,063</td><td>9/574</td></tr>
<tr><td>24–35 months</td><td>AESI: LRI, 0–42 days, Year 1</td><td>0.4%</td><td>0.4%</td><td>13/1,0693</td><td>8/5,667</td></tr>
<tr><td>24–35 months</td><td>AESI: LRI, 0–42 days, Year 2</td><td>0.4%</td><td>0.5%</td><td>4/3212</td><td>3/1,697</td></tr>
<tr><td>24–35 months</td><td>AESI: LRI, 0–180 days, Year 1</td><td>1.2%</td><td>1.0%</td><td>28/2,408</td><td>15/1,546</td></tr>
<tr><td>24–35 months</td><td>AESI: LRI, 0–180 days, Year 2</td><td>0.7%</td><td>0.7%</td><td>7/2,295</td><td>4/1,256</td></tr>
</table>
Note: Data for this outcome is from a multi-study integrated analysis of 20 RCTs of LAIV vs either IIV or placebo. It is unclear how many studies were LAIV vs placebo (study details not reported, only population numbers reported).</td><td>5,304 (1 SR)[6]</td><td>⊕⊕◯◯ Low[f,h]</td><td>The evidence suggests that LAIV does not increase AESI compared with placebo</td></tr>
</table>

AEs – RCT	Frequency of any AEs were marginally higher among the LAIV group vs placebo in some studies 	17,809 (5 RCTs) [1,2,3,4,5]	⊕⊕⊕⊕ High	LAIV results in little to no difference in adverse events compared with placebo

LAIV (FluMist) compared with placebo for prevention of influenza in children aged 2–17 years				
Patient or population: Children aged 2–17 years **Intervention:** LAIV (FluMist) **Comparison:** Placebo				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
AEs – SR	Frequency of any AEs (i.e. ≥1 AE) was similar between LAIV and placebo groups  Note: Data for this outcome is from a multi-study integrated analysis of 20 RCTs of LAIV vs either IIV or placebo. It is unclear how many studies were LAIV vs placebo (study details not reported, only population numbers reported).	5,304 (1 SR)[6] – includes 20 RCTs published before April 2008	⊕⊕⊕◯ Moderate[f]	LAIV likely results in little to no difference in adverse events compared with placebo

Explanations

a. There was substantial variation in the point estimates for vaccine efficacy (VE) between studies.
b. Single study with estimates from 2 years. VE is statistically significant in one year only.
c. Outcome reported in Vesikari, et al does not measure the desired outcome. The study reports on medical outpatient and emergency department visits for influenza-like illness (outcome is laboratory-confirmed influenza ED visits). Additionally, population in the study is 6–<36 months of age, whereas the PICO population is children aged 2–17 years.
d. Imprecision considered serious due to wide confidence intervals.
e. One RCT (Bergen 2004) was assessed as having some concerns.
f. One systematic review (Ambrose 2011) was assessed as high risk of bias.
g. AESI examined in the included studies were seizures, febrile seizures and epilepsy. Other AESI of interest (such as Guillain-Barré syndrome, neurological disorders) were not reported.
h. Study only examined one AESI – lower respiratory infection. Other common AESI (such as Guillain-Barré syndrome, neurological disorders, seizures) were not reported.

Footnotes

* **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).

Abbreviations: AE=adverse event; AESI=adverse event of special interest; CI=confidence interval; LAIV=live-attenuated influenza vaccine; LCI=laboratory-confirmed influenza infection; LRTI=lower respiratory tract illness; ED=emergency department; RCT=randomised controlled trail; SAE=serious adverse event; SR=systematic review; VE=vaccine efficacy.

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: We have limited confidence in the effect estimate: 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.

GRADE evidence profile

Evidence profile: LAIV (FluMist) compared with control (placebo/no vaccination) for prevention of influenza in children aged 2–17 years (PICO 1)

Certainty assessment							Summary of findings
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Laboratory-confirmed influenza infection (LCI) (follow-up: range 11 days to 1 years; assessed with: culture/PCR)							
7,151 (4 RCTs)[1-4]	Not serious	Serious[a]	Not serious	Not serious	None	⨁⨁⨁◯ Moderate[a]	In most studies, LAIV is more effective than placebo in preventing LCIs. 2 doses of LAIV are more effective than placebo in preventing LCIs. 1 dose of LAIV is likely more effective than placebo in preventing LCIs, but results vary.
Laboratory-confirmed influenza ED visit (follow-up: range 11 days to 1 years; assessed with: culture/PCR)							
1,615 (1 RCT)[2]	Not serious	Serious[b]	Serious[c]	Serious[d]	None	⨁◯◯◯ Very low[b,c,d]	Estimates from a single study, with results reported separately for 2 influenza seasons (forest plot with estimates to be included). Results indicate that LAIV may be more effective than placebo in preventing influenza-related ED visits, noting the quality of evidence is very low.
Serious adverse events (SAEs)– randomised controlled trials (RCTs)							
17,802 (5 RCTs)[1-5]	Not serious[e]	Not serious	Not serious	Not serious	None	⨁⨁⨁⨁ High[e]	The frequency of SAEs was similar between LAIV and placebo groups across studies.

Certainty assessment							Summary of findings
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Serious adverse events – systematic review							
16,370 (1 RCT)[6] – includes 20 RCTs published before April 2008	Serious[f]	Not serious	Not serious	Not serious	None	⨁⨁⨁◯ Moderate[f]	Pooled estimates of frequency of SAEs reported for children aged 2–17 years, by year of vaccination and timeframe of follow up. **Year 1:** 0–42 days follow up: LAIV 0.5% vs placebo 0.6% 0–180 days follow up: LAIV 0.5% vs placebo 0.6% **Year 2:** 0–42 days follow up: LAIV 2.9% vs placebo 2.7% 0–180 days follow up: LAIV 2.1% vs placebo 1.7% Note: Data for this outcome is from a multi-study integrated analysis of 20 RCTs of LAIV vs either IIV or placebo. It is unclear how many studies were LAIV vs placebo (study details not reported, only population numbers reported).
Adverse event of special interest (AESI): asthma/wheeze – RCT							
9,689 (1 RCT)[5]	Serious[e]	Not serious	Not serious	Not serious	None	⨁⨁⨁◯ Moderate[e]	Frequency of medically attended asthma/wheezing was low in children aged 1-17 years, i.e. <1% in both LAIV and placebo groups: LAIV: 0.9% vs placebo: 0.9% The frequency of medically attended asthma/wheezing was slightly higher in children aged 18-35 months who received LAIV vs placebo: LAIV: 2.1% (n=15/728) vs placebo: 0.5% (n=2/369) RR = 3.81 (90%CI: 1.20–16.82)

Certainty assessment							Summary of findings
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Adverse event of special interest: asthma/wheeze – systematic review							
5,304 (1 RCT)[6] – includes 20 RCTs published before April 2008	Serious[f]	Not serious	Not serous	Not serious	None	⨁⨁⨁◯ Moderate[f]	The frequency of wheezing was low (≤1%) in children aged 2–17 years in both LAIV and placebo groups, regardless of year of vaccination and number of doses received. Frequency of wheeze was not higher in young children aged 24–35 months. Note: Data for this outcome is from a multi-study integrated analysis of 20 RCTs of LAIV vs either IIV or placebo. It is unclear how many studies were LAIV vs placebo (study details not reported, only population numbers reported).
Adverse events of special interest (other than asthma/wheeze) – RCT							
9,689 (1 RCT)[5]	Serious[e]	Not serious	Serious[g]	Not serious	None	⨁⨁◯◯ Low[e,g]	Frequency of AESI were similar between LAIV and placebo groups. (table to be included with % of outcomes)
Adverse events of special interest (other than asthma/wheeze) – systematic review							
5,304 (1 RCT)[6] – includes 20 RCTs published before April 2008	Serious[f]	Not serious	Serious[h]	Not serious	None	⨁⨁◯◯ Low[f,h]	Frequency of AESI were low and similar between LAIV and placebo groups, regardless of follow up time (10, 42 or 180 days), year of vaccination and number of doses. Note: Data for this outcome is from a multi-study integrated analysis of 20 RCTs of LAIV vs either IIV or placebo. It is unclear how many studies were LAIV vs placebo (study details not reported, only population numbers reported).

Certainty assessment							Summary of findings
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Adverse events – RCTs							
17,809 (5 RCTs)[1-5]	Not serious	Not serious	Not serious	Not serious	None	⨁⨁⨁⨁ High	Frequency of any AEs were marginally higher among the LAIV group vs placebo in some studies.
Adverse events – systematic review							
5,304 (1 RCT)[6] – includes 20 RCTs published before April 2008	Serious[f]	Not serious	Not serious	Not serious	None	⨁⨁⨁◯ Moderate[f]	Frequency of any AEs (i.e. ≥1 AE) was similar between LAIV and placebo groups Year 1, dose 1: LAIV 29.7% vs placebo 27.6% Year 1, dose 2: LAIV 24.3% vs placebo 26.5% Year 2 (dose 1): LAIV 27.2% vs placebo 26.8% Note: Data for this outcome is from a multi-study integrated analysis of 20 RCTs of LAIV vs either IIV or placebo. It is unclear how many studies were LAIV vs placebo (study details not reported, only population numbers reported).

Explanations

a. There was substantial variation in the point estimates for vaccine efficacy (VE) between studies.
b. Single study with estimates from 2 years. VE is statistically significant in one year only.
c. Outcome reported in Vesikari et al does not measure the desired outcome. The study reports on medical outpatient and emergency department visits for influenza-like illness (outcome is lab-confirmed influenza ED visits). Additionally, population in the study is 6–<36 months of age, whereas the PICO population is children aged 2–17 years.
d. Imprecision considered serious due to wide confidence intervals.
e. One RCT (Bergen 2004) was assessed as having some concerns.
f. One systematic review (Ambrose 2011) was assessed as high risk of bias.
g. AESI examined in the included studies were seizures, febrile seizures and epilepsy. Other AESI of interest (such as Guillain-Barré syndrome, neurological disorders) were not reported.
h. Study only examined one AESI - lower respiratory infection. Other common AESI (such as Guillain-Barré syndrome, neurological disorders, seizures) were not reported.

Abbreviations: AESI=adverse event of special interest; CI=confidence interval; IIV-inactivated influenza vaccine; LAIV=live-attenuated influenza vaccine; RCT=randomised controlled trail; SAE=serious adverse event; VE=vaccine efficacy.

References

1. Nakayama T, Hayashi T, Makino K, et al. The efficacy and safety of a quadrivalent live attenuated influenza nasal vaccine in Japanese children: A phase 3, randomized, placebo-controlled trial. Journal of Infection and Chemotherapy 2025;31:102460.

2. Vesikari T, Fleming DM, Aristegui JF, et al; AIV-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, et al; 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):619-628.

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.

6. Ambrose CS, Yi T, Falloon J. An integrated, multistudy analysis of the safety of Ann Arbor strain live attenuated influenza vaccine in children aged 2–17 years. Influenza and Other Respiratory Viruses 2011;5:389-397.

Evidence to Decision Framework

Evidence to Decision Framework: LAIV (FluMist) compared with control (placebo/no vaccination) for prevention of influenza in children aged 2–17 years (PICO 1)

Should LAIV be used in children aged 2–17 years for the prevention of influenza?					
Population	Children aged 2–17 years				
Intervention	LAIV				
Comparison	Control				
Main outcomes	Efficacy, effectiveness and safety				
Setting	High- and middle-income countries, with studies conducted in Asia, Africa, Europe and South America				
ASSESSMENT					
Problem *Is the problem a priority?*					
Don't know	Varies	No	Probably No	Probably Yes	Yes

Children experience high influenza notification and hospitalisation rates and are significant transmitters of disease. Further exacerbating the impact of influenza on children, influenza vaccination coverage is the lowest among children compared to other age groups and has been trending downward.

Burden and transmission

- Influenza notifications among children dropped during the COVID-19 pandemic years of 2020–2021 but were substantially increased in 2022–2024.
- During 2022–2024, notification rates were highest among those aged <5 years at 2,543.8 per 100,000 followed by those aged 5–17 years at 2,164.0 per 100,000. Rates were substantially lower in those aged 18–64 years, and lowest among those aged ≥65 years at 619.1 per 100,000.
- In 2022–2024, within the 5–17-year age group, notification rates were highest for those aged 5-9 years at 2,912.1 per 100,000.
- Hospitalisation rates were moderately higher in 2022 compared to rates in 2015–2019 (216.9 per 100,00 among children aged <5 years).
- Among older children aged 5–19 years, hospitalisation rates were estimated at 49.6 per 100,000 and similar to rates among those aged 20–64 years. Rates among older adults aged ≥65 years were estimated at 169.0 per 100,000.
- Children are known to shed influenza virus a day or two before becoming symptomatic and shed virus for longer than adults,[1] making them significant transmitters of influenza virus. A 2010–2011 study demonstrated that households with a younger average age of members were more likely to have influenza viral transmission events.[2]
- In addition to disease burden, influenza is responsible for significant economic burden related to disease in children due to the indirect costs of parents or carers having to take time off from work to care for sick children.[3]

Vaccination coverage

- Cumulative influenza vaccine coverage (AIR data; doses given) reached a high of 45% in 2020 for those aged 6 months–<5 years. In 2025, coverage in this age group was approximately 25.7%.
- For those aged 5–<15 years, 2020 coverage was approximately 27%; coverage has declined over time: 16% in 2023, 14% in 2024 and 14.5% in 2025.[4]

Desirable effects
How substantial are the desirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Based on four RCTs with approximately 7,000 participants comparing LAIV to placebo, LAIV was more effective than placebo in preventing lab-confirmed influenza infections in most studies.[5–8] Of note, 3 of the 4 RCTs[5–7] included children aged 6–<36 months, and only one study included people aged 2–18 years.[8]
- In the three placebo-controlled RCTs that included a 2-dose study arm, 2 doses of LAIV were more effective than placebo in preventing lab-confirmed influenza infections. 1 dose of LAIV appeared more effective than placebo in preventing lab-confirmed influenza infections, but results varied by the study. In a single study where children were given placebo in the first year of vaccination, the vaccine effectiveness of a single dose of LAIV versus placebo was statistically insignificant.[6]
- Among all 4 placebo-controlled RCTs, when analyses were limited to matched strains only, 1 dose of LAIV was more effective than placebo in preventing lab-confirmed influenza infection in all per-protocol efficacy analyses.[5–8]
- Across the four placebo-controlled RCTs, 2 doses of LAIV appeared more effective than a single dose in preventing lab-confirmed influenza infection. However, interpretation is affected by the fact that, in 2 RCTs, participants received 2 doses in the first year of the study and 1 dose in the second year, making it difficult to attribute the difference in effectiveness to the number of doses or other factors influencing vaccine effectiveness (e.g. seasonal variation in influenza strains). In the single study with both a 1-dose and 2-dose arm in the same year, vaccine effectiveness was higher in the 2-dose group (72.0%) compared to the 1-dose group (56.3%) – the relative vaccine efficacy of 2 vs 1 doses was 36.0% (95%CI: 8.5–55.6).[7]
- A single study with results reported separately for two influenza seasons suggested that LAIV may be more effective than placebo in preventing influenza-related emergency department visits, but the certainty of the evidence was considered to be very low.[5]
- A network meta-analysis including 24 RCTs encompassing 60,502 children aged <18 years and 5 vaccines reported an RR of 0.28 (95%CrI: 0.19–0.41) of trivalent LAIV versus placebo (but no difference in RR for quadrivalent LAIV versus placebo, RR = 0.71, 95%CrI: 0.21–2.4). Findings were similar in a subgroup analysis of children aged ≤5 years encompassing 19 RCTs and 53,93,973 participants. In children with pre-existing respiratory diseases, only the 3-LAIV vaccine was more efficacious than placebo (RR 0.09, 95%CrI 0.00−0.54; 5 RCTs, 5,801 participants, 3 vaccines).[9]
- In the UK, where a single-dose schedule of LAIV is used, adjusted vaccine effectiveness against lab-confirmed influenza among children ranged between 26.9% (95%CI: −32.6 to 59.7) and 65.8% (95%CI: 30.3–83.2) between the 5 seasons from 2014/15 to 2018-19.[10] In the 2015/16 season, adjusted vaccine effectiveness against lab-confirm influenza hospitalisations was 55% (95%CI: 32–68) in England and 63% (95% CI: 50–72) in Scotland.[10,11] Overall vaccine effectiveness against influenza-related hospitalisations in the 2013/14 to 2015/16 seasons in children aged 2–6 years was 50.1% (95% CI: 31.2–63.8). Vaccine effectiveness against primary care presentation for lab-confirmed influenza in the 2023/24 season in children aged 2–17 years was 65% (95%CI: 41–79).[12,13] Comparison of five UK-based countries found that GP ILI consultations and influenza-attributable mortality decreased in Scotland and Northern Ireland, where all primary school age children were vaccinated, relative to countries incrementally vaccinating (England and Wales) or not vaccinated primary school age children (Republic of Ireland).[14]
- In the UK, significant indirect benefits were observed in adults not targeted for vaccination with LAIV, including a 59% reduction in GP ILI consultations in pilot vs non-pilot areas; non-significant reductions were observed for emergency department respiratory attendances, influenza confirmed hospitalisations, and influenza ICU admissions. LAIV coverage ranged from 32.3–63.1% (average 56.8%) in pilot areas.[15]

Undesirable effects
How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Evidence suggests no difference in the frequency of serious adverse events after vaccination with LAIV compared to placebo.[5–8,16,17]
- In healthy children, the frequency of exacerbation of wheeze or asthma frequency was low similar between LAIV and placebo. In one placebo-controlled RCT, rates of medically attended asthma and wheeze were slightly higher in children aged 18-35 months who received LAIV vs placebo.[17] However, a systematic review that conducted an integrated post-hoc analysis including 20 RCTs (both placebo- and IIV-controlled) found that the frequency of wheeze was not higher in children aged <2 years.[16]
- Frequency of other adverse events of special interest (not including exacerbation of asthma/wheeze), particularly febrile seizures, were similar between LAIV and placebo groups.[17] Of note, the frequency of certain outcomes of interest for this GRADE assessment (e.g. frequency of GBS and other neurological outcomes) were not clearly reported.
- The frequency of any adverse event was marginally higher among LAIV recipients compared to placebo in some studies.[5–8,17] The most common adverse events reported after LAIV administration were nasal symptoms.[5–8,16]
- Children with egg allergy can safely receive LAIV – a phase IV study in the UK including approximately 780 children aged 2–18 years with egg allergy did not experience systemic allergic reactions; 9 children had mild symptoms consistent with a local, IgE mediated allergic reaction.[18]
- Studies examining the safety profiles of LAIV in children with specific conditions, including data from large passive safety surveillance systems in the US and phase IV studies in the UK, suggest LAIV is well-tolerated in children with asthma, cardiovascular conditions, diabetes, obesity, liver, renal disease, and other conditions that increase the risk of severe influenza.[19–23] All studies (including one with more than 387,000 immunisations) demonstrated no evidence of asthma exacerbation among children with asthma who received LAIV.[19–23] LAIV vaccination was also tolerated well among children who were mildly immunocompromised, specifically children with cystic fibrosis, HIV infection and those receiving cancer treatment; while some mild adverse events occurred more frequently relative to healthy children (mostly nasal symptoms), vaccine-related serious adverse events were not increased.[24–26] These studies also demonstrated absence of prolonged shedding in children with mildly immunocompromising conditions.
- As a precaution, IIV is preferred over LAIV in pregnancy as it is a live attenuated vaccine. However, there is no evidence of risk with LAIV use during pregnancy. A 2011 US study examining a health insurance claims database found no evidence of adverse maternal outcomes among women who had received LAIV; all adverse outcomes identified occurred at similar rates to those in unvaccinated women.[27] Data from case reports and spontaneous reports to the US Vaccine Adverse Event Reporting System (VAERS) have not identified any increased risk of adverse foetal outcomes following LAIV administration to pregnant women.[27]
- Because LAIV is a live attenuated vaccine, it is contraindicated in the following populations:
  - those who have experienced anaphylaxis with a previous dose of any influenza vaccine or after any component of an influenza vaccine
  - moderately and severely immunocompromised persons
  - children receiving salicylate therapy.

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

No Included Studies	Very Low	Low	Moderate	High

- Evidence of the benefits of LAIV compared with placebo came from 4 RCTs.[5–8] The evidence was assessed as moderate for the outcome of lab-confirmed influenza infection, which was downgraded due to variation in the point estimates for vaccine efficacy between studies and variation in efficacy estimates for matched versus all strains. The evidence for the outcome of lab-confirmed ED visits was assessed as very low as findings were obtained from a single study covering two influenza seasons, with estimates of vaccine efficacy being statistically significant in a single season only and included wide confidence intervals, and the study outcome did not match the desired outcome (the study included both ED visits and outpatient visits).

- Evidence of the potential harms of LAIV compared with placebo came from 5 RCTs and 1 systematic review with an integrated analysis of included studies.[5–8,16,17] The evidence for most safety-related outcomes (i.e. SAEs, asthma/wheeze and AEs) was assessed as high or moderate, with some outcomes being downgraded due to the inclusion of the systematic review that was assessed as having high risk of bias. Evidence for the outcome of AESI other than wheeze/asthma were assessed as low certainty of evidence due to the inclusion of the systematic review assessed as having high risk of bias, and because the included studies only reported findings for a narrow range of outcomes (excluding AESI such as GBS and neurological disorders).

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

- Overall, there is probably no important uncertainty or variability in how much parents/carers value protecting their children from influenza infection. However, due to widespread belief that influenza is not serious and that the influenza vaccine may not be effective, combined with increasing vaccine scepticism and hesitancy following the COVID-19 pandemic, this has meant that some parents/carers may not value vaccinating their children against influenza.
- In a quantitative and qualitative assessment of community attitudes towards influenza vaccination in 2021, parents of children aged 0–5 years were significantly less likely than most other subgroups to see influenza as a very serious disease, and viewed influenza vaccine as being significantly less important than a range of other vaccines included on the childhood immunisation schedule.[28] This has been evident in decreased influenza vaccine coverage rates in children.[29]

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

- Overall, the evidence indicates that, among healthy children aged 2–17 years, LAIV is likely more effective than preventing lab-confirmed influenza infection compared to placebo. Evidence on the effectiveness of LAIV in preventing other influenza-related outcomes is insufficient.
- The safety profile of LAIV is acceptable; serious adverse events and adverse events of special interest appear similar between LAIV and placebo, and the frequency of mild-moderate adverse events is slightly higher among LAIV recipients compared with placebo.

Acceptability

Is the intervention acceptable to key stakeholders?

Don't know	Varies	No	Probably no	Probably yes	Yes

- Data from a survey of 1,987 Australian parents indicated that 27% of children aged ≥4 years have an intense phobia of needles, and 13% have a phobia severe enough to stop them getting the influenza vaccine.[30] Intranasal administration avoids vaccination by injection, so LAIV may have greater acceptability by vaccine recipients and their parents compared with current influenza vaccinations available in Australia (i.e. intramuscular IIV).
- Studies of LAIV acceptability in other high-income countries show that parents have a preference for vaccinating their child with LAIV over intramuscularly administered IIV.[31–33] In a study of pilot implementation in schools in Canada, nurses administering vaccines perceived that children were calmer after LAIV administration compared with IIV administration.[34]
- Factors that may possibly adversely impact acceptability include perceptions of increased risk associated with being a live vaccine and objections to porcine gelatin contents of LAIV (particularly among some faith-based communities).

- Intranasal administration may be challenging in very young children; current IIVs as an alternative are still required.
- Providers' willingness to stock and administer LAIV may be affected by the shorter shelf life of LAIV compared to currently available seasonal influenza vaccines, increased complexity in managing stock and predicting demand, additional storage requirements to stock both LAIV and IIV, increased time for consultations and shared decision-making with children and parents, and requirements for training on correct administration.
- England uses LAIV with delivery via schools and GPs and has achieved higher coverage than Australia. In 2023-2024, 55.1% of primary school children (through year 6) and 42.8% of secondary school children (year 7-year 11) were vaccinated.[35] In England in the 2024-2025 season, coverage of 2-4 year olds was 37.2%.[36]

Equity
What would be the impact on health inequities?

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

- The potential for easier administration via the intranasal route may mean that additional cadres of healthcare providers can administer vaccine, which can potentially increase access to influenza vaccination. This may help increase access to influenza vaccination and reduce inequities, including for high-risk groups.
- Intranasal administration of LAIV may assist in vaccinating specialised population groups who have traditionally been more challenging to vaccinate using intramuscular injections, such as those with needle phobia and people with intellectual and other disabilities including those living in disability accommodation settings. This can reduce inequities in vaccination.
- Despite the benefits of LAIV, some individuals are contraindicated to receive LAIV (particularly those with severe immunocompromising conditions) so continued access to currently available inactivated influenza vaccines is necessary to avoid any inadvertent difficulties in accessing influenza vaccination for these high-risk groups.
- As LAIV will not yet be available through the NIP, there may be potential inequities in access to LAIV for parents who will need to pay out-of-pocket. However, IIV is still available to these people.
- LAIV's shorter shelf life (relative to current influenza vaccines) may cause access issues for people living in rural or regional areas if few or no local providers can maintain adequate stock level.

Feasibility
Is the intervention feasible to implement?

Don't know	Varies	No	Probably no	Probably yes	Yes

- Implementation of an LAIV program, alongside the current influenza vaccination program with IIV, is considered feasible. Use of LAIV in a mass vaccination setting (e.g. school-based vaccination program) is also considered more feasible than the current intramuscularly administered IIV.
- Some individuals will continue to need access to currently used IIVs due to contraindication to LAIV or a preference for IIV over LAIV. Programmatic use of LAIV should complement the current influenza vaccination program utilising IIV.
- As LAIV is a new vaccine being introduced, a number of implementation considerations are necessary to ensure seamless implementation:
    - There are additional cold chain requirements and stock management challenges (such as forecasting demand and supply needs and additional refrigerator capacity) at all levels of the health system, due to the requirement to stock both IIV and LAIV.
    - Additional trainings are required for immunisation providers on nasal spray administration and handling of LAIV across different settings (e.g. primary care, pharmacy, tertiary hospital etc.), especially as vaccinating very young children can be more challenging.
    - Providers may need to provide extra time for pre-vaccination screening and counselling.
    - Shorter shelf life of LAIV (approximately 4 months) relative to IIV may create complexities for stock handling and storage.[37]

- Easier administration via the intranasal route increases the feasibility of using school-based vaccination delivery to increase vaccination coverage; however, this would be very resource intensive and require extensive planning and phased implementation over a period of several years.
- Updates are needed to existing vaccine surveillance and monitoring systems to monitor adverse events and vaccine effectiveness for LAIV, including updates to existing immunisation registries and reporting tools.

- Coadministration studies including LAIV are limited. Studies of LAIV co-administered with measles-mumps-rubella (MMR) vaccine, varicella vaccine and oral vaccine demonstrate similar immunogenicity compared to separate administration, and co-administration was well-tolerated.[38,39] Based on available evidence, there are no concerns about co-administering other routine vaccines with LAIV.
- There are no concerns about vaccinating children with LAIV across consecutive seasons. A systematic review of 4 placebo-controlled RCTs including 6,090 children investigating the efficacy of LAIV upon revaccination of children against lab-confirmed influenza infection in consecutive season found that there was no decrease in efficacy of LAIV when administered in 2 consecutive seasons.[40] A separate test-negative case-control study in the US including 3369 children aged 2–17 years observed across 3 influenza seasons found that protection against influenza A(H3N2) was significantly improved among children who were repeatedly vaccinated with LAIV.[41]

ATAGI RECOMMENDATION

- LAIV is recommended as an alternative to IIV for prevention of influenza in individuals aged 2–17 years.

JUSTIFICATION AND CONSIDERATIONS

- Influenza caused significant disease burden among children aged 2–17 years in Australia, including hospitalisations. Vaccination coverage among this age group remains low, despite a longstanding influenza vaccination program including NIP-funded vaccination for children aged <5 years.
- LAIV has been used widely for 2 decades in other countries (including in the USA since 2003 and the UK in a school-based program since 2013). A substantial body of evidence including RCTs and large observational studies of national-level programs demonstrate that LAIV is effective in preventing influenza infections and hospitalisations. Some evidence also suggests that herd protection to non-target populations is observed when high rates of coverage among children are achieved.
- Both RCTs and large observational studies indicate that LAIV is safe and has a similar safety profile to currently used IIVs and can be safely used in children with mild immunocompromising conditions and those with asthma. As a live vaccine, it is contraindicated in certain populations including moderate/severe immunocompromising conditions.
- LAIV is administered intranasally and may be more acceptable to intra muscularly administered IIVs, especially among children with needle phobia or others who are difficult to vaccinate due to pre-existing conditions. Therefore, use of LAIV may increase influenza vaccination coverage.
- LAIV has the potential to be used in mass vaccination programs in school-based settings to increase influenza vaccination coverage.

References

1. Nayak J, Hoy G, Gordon A. Influenza in children. Cold Spring Harbor Perspectives in Medicine 2021;11(1):a038430.
2. Petrie JG, Ohmit SE, Cowling BJ, et al. Influenza transmission in a cohort of households with children: 2010-2011. PLoS One 2013;8(9):e75339.
3. Nair H, Brooks WA, Katz M, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. The Lancet 2011;378(9807):1917–30.
4. National Centre for Immunisation Research and Surveillance. All persons: 2020–2025 (YTD) influenza vaccination coverage. 2025. Available from: https://ncirs.org.au/influenza-vaccination-coverage-data/all-persons-2020-2025-ytd-influenza-vaccination-coverage (accessed July 2025).
5. Vesikari T, Fleming DM, Aristegui JF, et al. 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.
6. Tam JS, Capeding MRZ, Lum LCS, et al. Efficacy and safety of a live attenuated, cold-adapted influenza vaccine, trivalent against culture-confirmed influenza in young children in Asia. Pediatric Infectious Disease Journal 2007;26(7):619–28.
7. Bracco Neto H, Farhat CK, Tregnaghi MW, et al. Efficacy and safety of 1 and 2 doses of live attenuated influenza vaccine in vaccine-naive children. Pediatric Infectious Disease Journal 2009;28(5):365–71.
8. Nakayama T, Hayashi T, Makino K, Oe K. The efficacy and safety of a quadrivalent live attenuated influenza nasal vaccine in Japanese children: a phase 3, randomized, placebo-controlled study. Journal of Infection and Chemotherapy 2025;31(2):102460.
9. Minozzi S, Lytras T, Gianola S, et al. Comparative efficacy and safety of vaccines to prevent seasonal influenza: a systematic review and network meta-analysis. EClinicalMedicine 2022;46:101331.
10. Kassianos G, MacDonald P, Aloysius I, et al. Implementation of the United Kingdom's childhood influenza national vaccination programme: a review of clinical impact and lessons learned over six influenza seasons. Vaccine 2020;38(36):5747–58.
11. Pebody R, Sile B, Warburton F, et al. Live attenuated influenza vaccine effectiveness against hospitalisation due to laboratory-confirmed influenza in children two to six years of age in England in the 2015/16 season. Euro Surveillance 2017;22(4):30450.
12. Whitaker H, Findlay B, Zitha J, et al. Interim 2023/2024 season influenza vaccine effectiveness in primary and secondary care in the United Kingdom. Influenza and Other Respiratory Viruses 2024;18(5):e13284.
13. Boddington NL, Mangtani P, Zhao H, et al. Live-attenuated influenza vaccine effectiveness against hospitalization in children aged 2-6 years, the first three seasons of the childhood influenza vaccination program in England, 2013/14-2015/16. Influenza and Other Respiratory Viruses 2022;16(5):897–905.
14. Sinnathamby MA, Warburton F, Reynolds AJ, et al. An intercountry comparison of the impact of the paediatric live attenuated influenza vaccine (LAIV) programme across the UK and the Republic of Ireland (ROI), 2010 to 2017. Influenza and Other Respiratory Viruses 2023;17(2):e13099.
15. Pebody RG, Green HK, Andrews N, et al. Uptake and impact of vaccinating school age children against influenza during a season with circulation of drifted influenza A and B strains, England, 2014/15. Euro Surveillance 2015;20(39).
16. Ambrose CS, Yi T, Falloon J. An integrated, multistudy analysis of the safety of Ann Arbor strain live attenuated influenza vaccine in children aged 2-17 years. Influenza Other Respiratory Viruses. 2011;5(6):389–97.

17. Bergen R, Black S, Shinefield H, et al. Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents. Pediatric Infectious Disease Journal 2004;23(2):138–44.
18. Turner PJ, Southern J, Andrews NJ, et al. Safety of live attenuated influenza vaccine in young people with egg allergy: multicentre prospective cohort study. BMJ 2015;351:h6291.
19. Millman AJ, Reynolds S, Duffy J, et al. Hospitalizations within 14 days of vaccination among pediatric recipients of the live attenuated influenza vaccine, United States 2010-2012. Vaccine 2017;35(4):529–35.
20. Caspard H, Steffey A, Mallory RM, et al. Evaluation of the safety of live attenuated influenza vaccine (LAIV) in children and adolescents with asthma and high-risk conditions: a population-based prospective cohort study conducted in England with the Clinical Practice Research Datalink. BMJ Open 2018 Dec 9;8(12):e023118.
21. Duffy J, Lewis M, Harrington T, et al. Live attenuated influenza vaccine use and safety in children and adults with asthma. Annals of Allergy, Asthma and Immunology 2017;118(4):439–44.
22. Ray GT, Lewis N, Goddard K, Ross P, et al. Asthma exacerbations among asthmatic children receiving live attenuated versus inactivated influenza vaccines. Vaccine 2017;35(20):2668–75.
23. Turner PJ, Fleming L, Saglani S, et al. Safety of live attenuated influenza vaccine (LAIV) in children with moderate to severe asthma. Journal of Allergy and Clinical Immunology 2020;145(4):1157-1164.e6.
24. Boikos C, Joseph L, Scheifele D, et al. Adverse events following live-attenuated intranasal influenza vaccination of children with cystic fibrosis: results from two influenza seasons. Vaccine 2017 Sept 5;35(37):5019–26.
25. Levin MJ, Song LY, Fenton T, et al. Shedding of live vaccine virus, comparative safety, and influenza-specific antibody responses after administration of live attenuated and inactivated trivalent influenza vaccines to HIV-infected children. Vaccine 2008;26(33):4210–17.
26. Halasa N, Englund JA, Nachman S, et al. Safety of live attenuated influenza vaccine in mild to moderately immunocompromised children with cancer. Vaccine;29(24):4110–5.
27. Toback SL, Beigi R, Tennis P, et al. Maternal outcomes among pregnant women receiving live attenuated influenza vaccine. Influenza and Other Respiratory Viruses 2012;6(1):44–51.
28. Snapcracker. Community Attitude Research on Influenza Vaccination 2021. 2022. Available from: https://www.health.gov.au/sites/default/files/documents/2022/09/community-attitude-research-on-influenza-vaccination-2021-research-report_0.pdf (accessed October 2025).
29. Steffens MS, Kaufman J, Bolsewicz KT, et al. Childhood influenza vaccination is not a priority for parents: a national, cross-sectional survey of barriers to childhood influenza vaccination in Australia. Vaccines (Basel) 2025;13(5).
30. The Royal Children's Hospital Melbourne. RCH National Child Health Poll: Flu vaccine plans: Knowledge gaps and needle phobia. 2025. Available from: https://rchpoll.org.au/polls/flu-vaccine-plans-knowledge-gaps-and-needle-phobia/ (accessed August 2025).
31. Marien AG, Hochart A, Lagrée M, et al. Parental acceptance of an intranasal vaccine: Example of influenza vaccine. Archives de Pédiatrie 2019;26(2):71–4.
32. Quach C. Vaccinating high-risk children with the intranasal live-attenuated influenza vaccine: the Quebec experience. Paediatric Respiratory Reviews 2014;15(4):340–7.
33. Yuan J, Li L, Dong M, et al. Parental vaccine hesitancy and influenza vaccine type preferences during and after the COVID-19 Pandemic. Communications Medicine (London). 2024;4(1):165.
34. Kwong JC, Pereira JA, Quach S, et al. Randomized evaluation of live attenuated vs. inactivated influenza vaccines in schools (RELATIVES) pilot study: a cluster randomized trial. Vaccine 2015;33(4):535–41.
35. UK Health Security Agency. Seasonal influenza vaccine uptake in children of school age in England: winter season 2023 to 2024. GOV.UK. 2025. Available from: https://www.gov.uk/government/statistics/seasonal-influenza-vaccine-uptake-in-children-of-school-age-winter-season-2023-to-2024/seasonal-influenza-vaccine-uptake-in-children-of-school-age-in-england-winter-season-2023-to-2024 (accessed October 2025).
36. Crofts J. England's influenza vaccination programme for school-aged children. Australian Technical Advisory Group on Immunisation (ATAGI) meeting 109; 2024 Dec 5. [Unpublished]

37. BC Centre for Disease Control. Trivalent Live Attenuated Influenza Vaccine (LAIV) FLUMIST. 2025. Available from: https://www.bccdc.ca/resource-gallery/Documents/Guidelines%20and%20Forms/Guidelines%20and%20Manuals/Epid/CD%20Manual/Chapter%202%20-%20Imms/Part4/Influenza_Flumist.pdf (accessed October 2025).
38. Nolan T, Bernstein DI, Block SL, et al. Safety and immunogenicity of concurrent administration of live attenuated influenza vaccine with measles-mumps-rubella and varicella vaccines to infants 12 to 15 months of age. Pediatrics 2008;121(3):508–16.
39. Breiman RF, Brooks WA, Goswami D, et al. A multinational, randomized, placebo-controlled trial to assess the immunogenicity, safety, and tolerability of live attenuated influenza vaccine coadministered with oral poliovirus vaccine in healthy young children. Vaccine 2009;27(40):5472–9.
40. Caspard H, Heikkinen T, Belshe RB, et al. A systematic review of the efficacy of live attenuated influenza vaccine upon revaccination of children. Human Vaccines and Immunotherapeutics 2016;12(7):1721–7.
41. McLean HQ, Caspard H, Griffin MR, et al. Association of prior vaccination with Influenza vaccine effectiveness in children receiving live attenuated or inactivated vaccine. JAMA Network Open 2018;1(6):e183742.