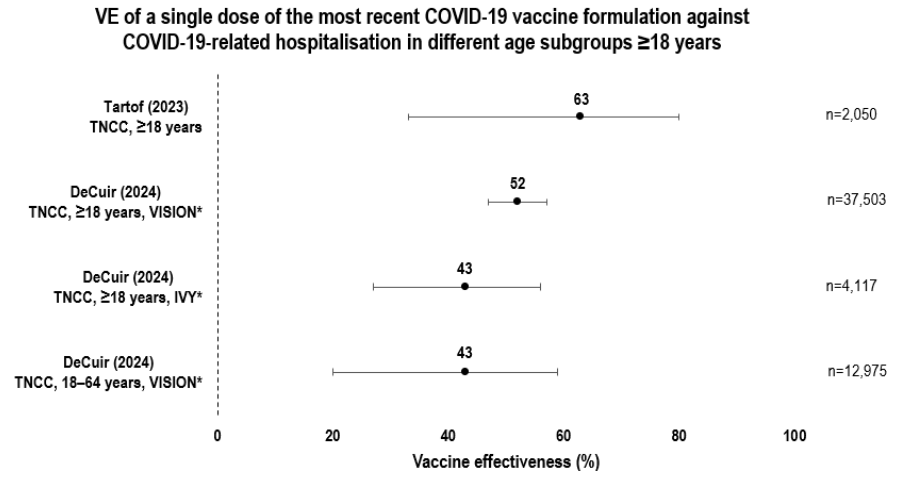
GRADE tables: Comparison of a dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months with no dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months in people aged 6 months and over

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 COVID-19 chapter.

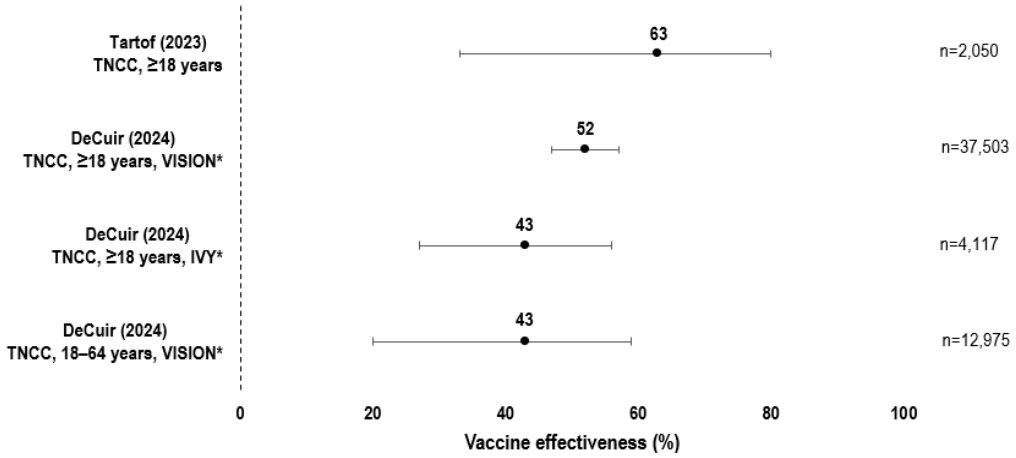
A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months compared with no dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months in people aged 6 months and over

Patient or population: People aged 6 months and over
Intervention: A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months
Comparison: No dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
CRITICAL OUTCOMES				
Vaccine effectiveness (VE) against COVID-19-related hospitalisation [mRNA COVID-19 vaccine] Assessed with: patients who were admitted to hospital with COVID-19-like illness (CLI) or acute respiratory infection (ARI) and were tested for SARS-CoV-2 using polymerase chain reaction (PCR) and/or hospitalisations where COVID-19 was the primary reason for hospital admission Follow-up: ≥7 days		1,105,156 (4 non-randomised studies)[1-4]	⨁⨁⨁◯ Moderate[a]	A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months likely results in a moderate reduction in hospitalisation compared with no dose of the most recent COVID-19 formulation within the past 6–12 months.

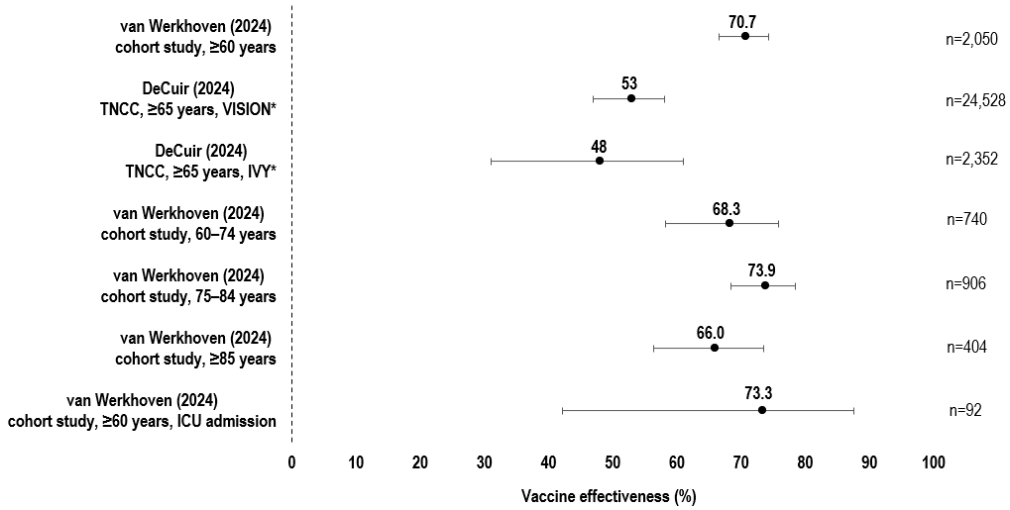
A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months compared with no dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months in people aged 6 months and over

Patient or population: People aged 6 months and over
Intervention: A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months
Comparison: No dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
(continued) **VE against COVID-19-related hospitalisation [mRNA COVID-19 vaccine]** Assessed with: patients who were admitted to hospital with CLI or ARI and were tested for SARS-CoV-2 using PCR and/or hospitalisations where COVID-19 was the primary reason for hospital admission Follow-up: ≥7 days	**VE of a single dose of the most recent COVID-19 vaccine formulation against COVID-19-related hospitalisation in different age subgroups ≥18 years**  * Note: DeCuir (2024) contains a VE estimate from two separate USA datasets, IVY and VISION.	1,105,156 (4 non-randomised studies)[1-4]	⊕⊕⊕◯ Moderate[a]	A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months likely results in a moderate reduction in hospitalisation compared with no dose of the most recent COVID-19 formulation within the past 6–12 months.

A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months compared with no dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months in people aged 6 months and over

Patient or population: People aged 6 months and over
Intervention: A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months
Comparison: No dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
(continued) **VE against COVID-19-related hospitalisation [mRNA COVID-19 vaccine]** Assessed with: patients who were admitted to hospital with CLI or ARI and were tested for SARS-CoV-2 using PCR and/or hospitalisations where COVID-19 was the primary reason for hospital admission Follow-up: ≥7 days	**VE of a single dose of the most recent COVID-19 vaccine formulation against COVID-19-related hospitalisation in different age subgroups ≥60 years**  * Note: DeCuir (2024) contains a VE estimate from two separate USA datasets, IVY and VISION.	1,105,156 (4 non-randomised studies)[1-4]	⊕⊕⊕◯ Moderate[a]	A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months likely results in a moderate reduction in hospitalisation compared with no dose of the most recent COVID-19 formulation within the past 6–12 months.

A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months compared with no dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months in people aged 6 months and over

Patient or population: People aged 6 months and over
Intervention: A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months
Comparison: No dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months

<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): myocarditis (with or without pericarditis) [mRNA COVID-19 vaccine]

Assessed with: strong clinical evidence including the patient's symptoms, and results of tests and imaging indicating a diagnosis of myocarditis; or cases that are probably myocarditis based on a combination of symptoms and routine tests for heart conditions; or cases that are possibly myocarditis based on symptoms and a doctor's report that myocarditis is the most likely diagnosis in the absence of medical tests and investigations

Follow-up: ≤42 days where possible</td>
<td>Table 1. Rates of likely myocarditis cases following Comirnaty (Pfizer),‡ 29 June 2023
<table>
<tr><th rowspan="3">Age (years)</th><th colspan="2">All doses</th><th colspan="2">Second doses</th></tr>
<tr><th colspan="2">Rate* per 100,000 doses</th><th colspan="2">Rate* per 100,000 doses</th></tr>
<tr><th>Male</th><th>Female</th><th>Male</th><th>Female</th></tr>
<tr><td>5–11</td><td>0.3</td><td>0.1</td><td>0.2</td><td>0</td></tr>
<tr><td>12–17</td><td>8.1</td><td>1.7</td><td>13.2</td><td>2.8</td></tr>
<tr><td>18–29</td><td>5.1</td><td>1.6</td><td>9.2</td><td>2.9</td></tr>
<tr><td>30–39</td><td>2.4</td><td>0.9</td><td>3.2</td><td>1.0</td></tr>
<tr><td>40–49</td><td>1.0</td><td>1.0</td><td>1.5</td><td>2.0</td></tr>
<tr><td>50–59</td><td>0.8</td><td>0.4</td><td>0.8</td><td>0.4</td></tr>
<tr><td>60–69</td><td>0.4</td><td>0.3</td><td>0.4</td><td>0.4</td></tr>
<tr><td>≥70</td><td>0.1</td><td>0.3</td><td>0</td><td>0.4</td></tr>
<tr><td>All ages*</td><td>2.4</td><td>0.9</td><td>4.7</td><td>1.6</td></tr>
</table>
Notes for Table 1
* The rate includes cases of myocarditis that occurred after vaccination but may not be vaccine related.
‡ To 25 June 2023, from about 2.4 million vaccine doses given, 4 likely cases of myocarditis have been reported in children aged 5–11 years following vaccination with Comirnaty (Pfizer).</td>
<td>68,047,109 doses (TGA report)[5]</td>
<td>⊕⊕⊕⊕
High[b]</td>
<td>A dose of mRNA COVID-19 vaccine results in an increase in reporting rates of likely myocarditis and pericarditis compared with no dose of mRNA COVID-19 vaccine.

Note: The reporting rates of likely myocarditis and pericarditis following a dose of mRNA COVID-19 vaccines are similar to those reflected in a large multinational Nordic cohort study.[6]</td>
</tr>
</table>

A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months compared with no dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months in people aged 6 months and over

Patient or population: People aged 6 months and over
Intervention: A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months
Comparison: No dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
(*continued*) **AESI: myocarditis (with or without pericarditis) [mRNA COVID-19 vaccine]** Assessed with: strong clinical evidence including the patient's symptoms, and results of tests and imaging indicating a diagnosis of myocarditis; or cases that are probably myocarditis based on a combination of symptoms and routine tests for heart conditions; or cases that are possibly myocarditis based on symptoms and a doctor's report that myocarditis is the most likely diagnosis in the absence of medical tests and investigations Follow-up: ≤42 days where possible	**Table 2. Rates of likely myocarditis cases following Spikevax (Moderna),† 29 June 2023** **Age (years)** / **All doses** / **Second doses** / **Rate* per 100,000 doses** / **Male** / **Female** / **Male** / **Female** 12–17: 12.1 / 2.9 / 23.6 / 5.0 18–29: 9.8 / 1.7 / 20.1 / 4.7 30–39: 3.3 / 0.7 / 5.0 / 0 40–49: 1.7 / 1.1 / 3.2 / 2.0 50–59: 0.9 / 1.5 / 2.0 / 2.5 60–69: 0 / 0.2 / 0 / 0 ≥70: 0.1 / 0.1 / 0 / 0 **All ages*: 3.2 / 1.0 / 11.1 / 2.6** *Notes for Table 2* * The rate includes cases of myocarditis that occurred after vaccination but may not be vaccine related. † The rates for Spikevax (Moderna) are less certain due to low numbers of cases overall and small changes in case number can lead to fluctuations in the rates for different groups.	68,047,109 doses (TGA report)[5]	⊕⊕⊕⊕ High[b]	A dose of mRNA COVID-19 vaccine results in an increase in reporting rates of likely myocarditis and pericarditis compared with no dose of mRNA COVID-19 vaccine. *Note:* The reporting rates of likely myocarditis and pericarditis following a dose of mRNA COVID-19 vaccines are similar to those reflected in a large multinational Nordic cohort study.[6]

A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months compared with no dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months in people aged 6 months and over

Patient or population: People aged 6 months and over
Intervention: A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months
Comparison: No dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
(*continued*) **AESI: myocarditis (with or without pericarditis) [mRNA COVID-19 vaccine]** Assessed with: strong clinical evidence including the patient's symptoms, and results of tests and imaging indicating a diagnosis of myocarditis; or cases that are probably myocarditis based on a combination of symptoms and routine tests for heart conditions; or cases that are possibly myocarditis based on symptoms and a doctor's report that myocarditis is the most likely diagnosis in the absence of medical tests and investigations Follow-up: ≤42 days where possible	So far, reports of myocarditis after a further dose are very rare, occurring in less than 1 in every 100,000 doses administered. **Table 3. Rates of likely pericarditis cases following the mRNA vaccines,† 29 June 2023**	68,047,109 doses (TGA report)[5]	⊕⊕⊕⊕ High[b]	A dose of mRNA COVID-19 vaccine results in an increase in reporting rates of likely myocarditis and pericarditis compared with no dose of mRNA COVID-19 vaccine. *Note:* The reporting rates of likely myocarditis and pericarditis following a dose of mRNA COVID-19 vaccines are similar to those reflected in a large multinational Nordic cohort study.[6]

Age (years)	Rate* per 100,000 doses	
	Comirnaty (Pfizer)	Spikevax (Moderna)
5–11‡	0.3	–
12–17	2.4	2.3
18–29	4.4	5.4
30–39	4.6	5.2
40–49	3.0	3.0
50–59	1.7	1.4
60–69	0.8	0.5
≥70	0.2	0.2
All ages*	**2.8**	**2.6**

Notes for Table 3

* The rate includes cases of pericarditis that occurred after vaccination but may not be vaccine related.

‡ To 25 June 2023, from about 2.4 million Comirnaty (Pfizer) vaccine doses given, one probable and 7 possible cases of pericarditis have been reported in children aged 5–11 years. No cases of pericarditis have been reported following Spikevax (Moderna) in this age group.

† The rates are less certain in some age groups due to low numbers of cases overall. This means small changes in case number can lead to fluctuations in the rates.

A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months compared with no dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months in people aged 6 months and over				
Patient or population: People aged 6 months and over **Intervention:** A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months **Comparison:** No dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
AESI: myocarditis (with or without pericarditis) [protein subunit COVID-19 vaccine] Assessed with: strong clinical evidence including the patient's symptoms, and results of tests and imaging indicating a diagnosis of myocarditis; or cases that are probably myocarditis based on a combination of symptoms and routine tests for heart conditions; or cases that are possibly myocarditis based on symptoms and a doctor's report that myocarditis is the most likely diagnosis in the absence of medical tests and investigations Follow-up: ≤42 days where possible	To 25 June 2023, almost 261,000 doses of Nuvaxovid (Novavax) have been administered in Australia. Myocarditis is reported in around 3–4 in every 100,000 doses of Nuvaxovid. Overall, pericarditis is reported in 13 in every 100,000 doses but is more common in men aged 18–49 years (estimated at 27 per 100,000 doses). Noting the reporting rate estimates for pericarditis are less certain for Novavax than for Comirnaty and Spikevax vaccines due to the low number of Nuvaxovid vaccine doses given. To 26 June 2023, there have only been about 2,300 Nuvaxovid doses administered in people aged 12–17 years and no adverse events following immunisation have been reported. To 26 June 2023, reports of myocarditis after a further dose of any type of COVID-19 vaccine are very rare, occurring in <1 in every 100,000 doses administered.	68,047,109 doses (TGA report)[5]	⊕⊕⊕⊕ High[b]	A dose of protein subunit COVID-19 vaccine results in an increase in reporting rates of likely myocarditis and pericarditis compared to no dose of protein subunit COVID-19 vaccine.

A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months compared with no dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months in people aged 6 months and over

Patient or population: People aged 6 months and over
Intervention: A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months
Comparison: No dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months

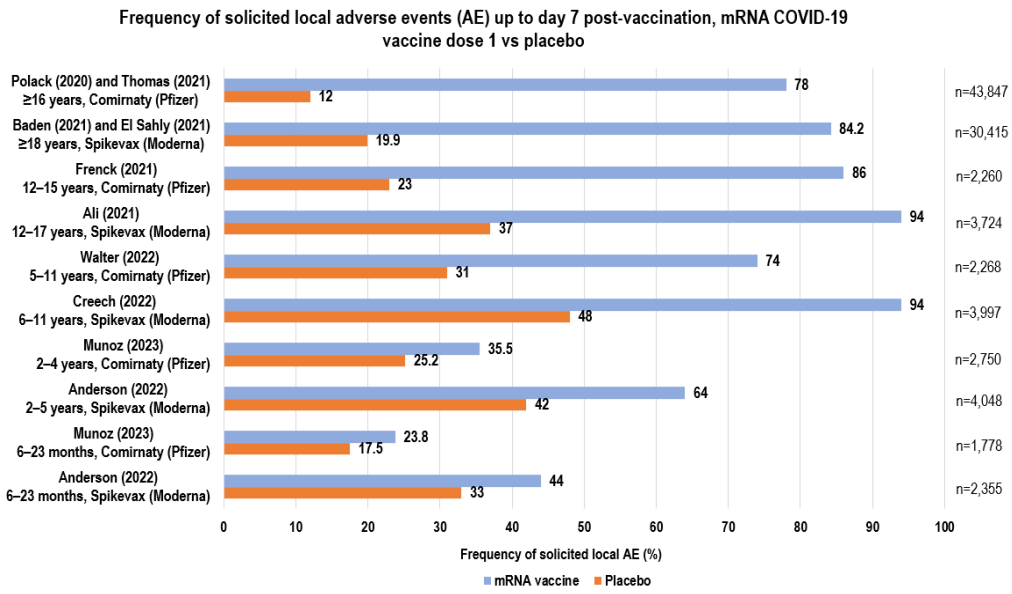
<table>
<tr><th>Outcomes</th><th>Impact</th><th>№ of participants (studies)</th><th>Certainty of the evidence (GRADE)</th><th>Interpretation</th></tr>
<tr>
<td>Serious adverse events (SAE) [protein subunit COVID-19 vaccine]
Assessed with: any adverse event or adverse reaction, at any dose, which results in any of the following outcomes: death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, congenital anomaly or birth defect, or other situations such as medically important events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition

Follow-up: range 1 days to ≥6 months post-final dose</td>
<td>Table 5. Frequency of any SAEs and trial/vaccine-related SAEs reported in COVID-19 protein subunit vaccine clinical trials
<table>
<tr><th rowspan="2">Study and age group</th><th colspan="2">Any SAE (%)</th><th colspan="2">Vaccine-related SAE (%)</th><th rowspan="2">N</th></tr>
<tr><th>Protein subunit vaccine</th><th>Placebo</th><th>Protein subunit vaccine</th><th>Placebo</th></tr>
<tr><td colspan="6">Nuvaxovid (Novavax)</td></tr>
<tr><td>Heath (2021) and Heath (2023), 18–84 years</td><td>0.8</td><td>0.8</td><td><0.1</td><td>0</td><td>15,139</td></tr>
<tr><td>Dunkle (2021), ≥18 years</td><td>0.9</td><td>1.0</td><td>0.1</td><td><0.1</td><td>29,582</td></tr>
<tr><td>Áñez (2023), 12–17 years</td><td>0.5</td><td>0.3</td><td>0</td><td>0</td><td>2,232</td></tr>
</table>
</td>
<td>46,953 (3 randomised control trials [RCTs])</td>
<td>⊕⊕⊕⊕
High[c]</td>
<td>A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months results in little to no difference in overall SAE compared with no dose of the most recent COVID-19 formulation within the past 6–12 months.

Note: There are no large phase 3 trials in humans which evaluate the safety and reactogenicity of XBB/updated formulation COVID-19 vaccines. The updated formulation (XBB) COVID-19 vaccines were approved by regulatory agencies, such as the TGA, by extrapolating safety data from large phase 3 clinical trials of the original and earlier formula COVID-19 vaccines which were compared with placebo.</td>
</tr>
</table>

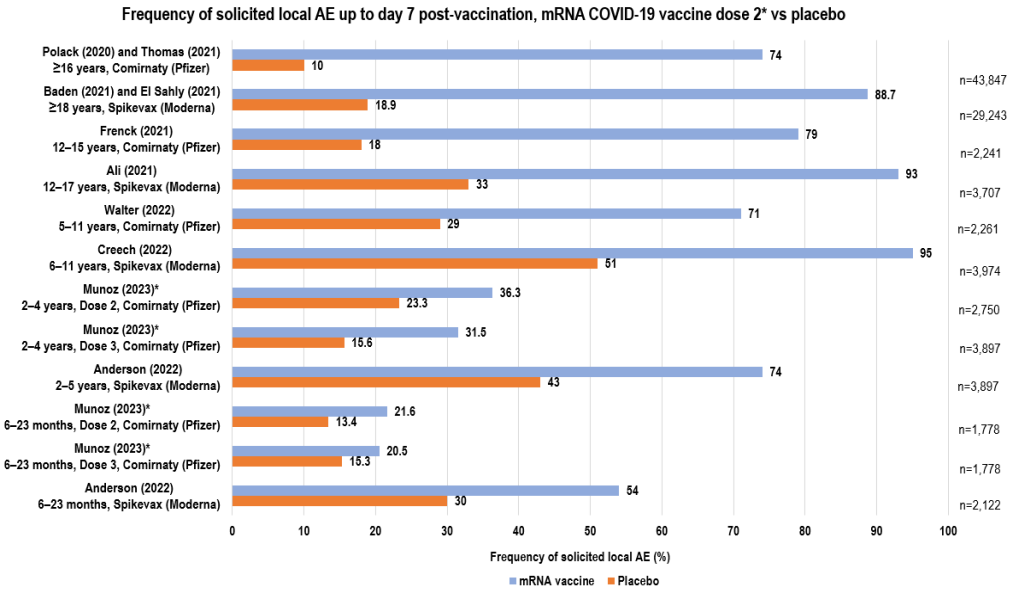
A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months compared with no dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months in people aged 6 months and over

Patient or population: People aged 6 months and over
Intervention: A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months
Comparison: No dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
IMPORTANT OUTCOMES				
Solicited local adverse events (AE) [mRNA COVID-19 vaccine] Assessed with: patient or carer self-report with diary Follow-up: 7 days		(8 RCTs)[7-15]	⨁⨁⨁⨁ High[c]	A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months results in a large increase in solicited local AEs compared with no dose of the most recent COVID-19 formulation within the past 6–12 months. *Note:* There are no large phase 3 trials in humans which evaluate the safety and reactogenicity of XBB/updated formulation COVID-19 vaccines. The updated formulation (XBB) COVID-19 vaccines were approved by regulatory agencies, such as the TGA, by extrapolating safety data from large phase 3 clinical trials of the original and earlier formula COVID-19 vaccines which were compared with placebo.

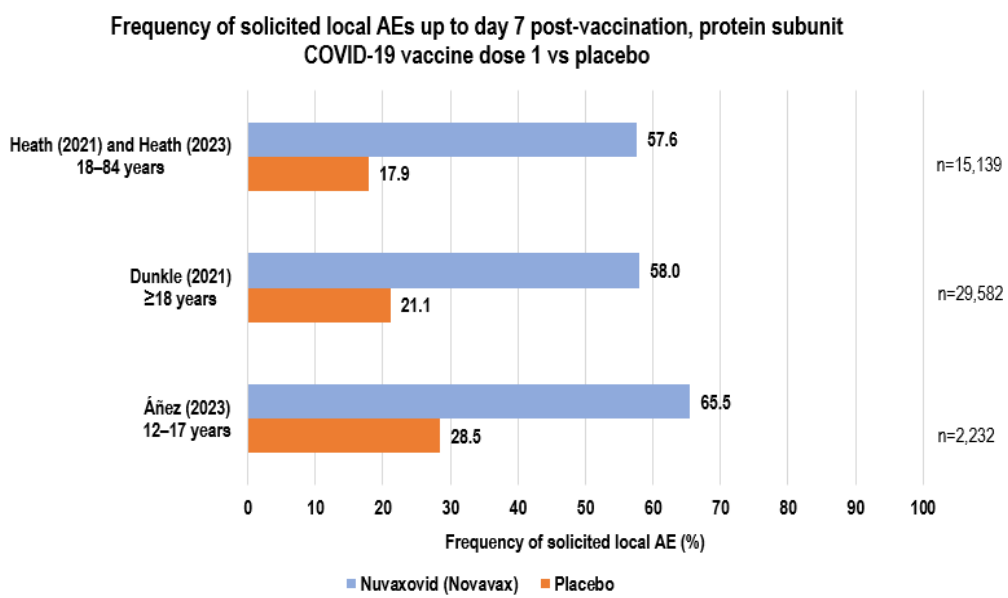
A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months compared with no dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months in people aged 6 months and over

Patient or population: People aged 6 months and over
Intervention: A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months
Comparison: No dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
(*continued*) **Solicited local AE [mRNA COVID-19 vaccine]** Assessed with: patient or carer self-report with diary Follow-up: 7 days	 * Note: Data from Munoz (2023) for Comirnaty (Pfizer) data for the 6 month to 4 year age group also includes data from a third dose, as the primary course in this age group is made up of 3 doses.	(8 RCTs)[7-15]	⨁⨁⨁⨁ High[c]	A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months results in a large increase in solicited local AEs compared with no dose of the most recent COVID-19 formulation within the past 6–12 months. *Note:* There are no large phase 3 trials in humans which evaluate the safety and reactogenicity of XBB/updated formulation COVID-19 vaccines. The updated formulation (XBB) COVID-19 vaccines were approved by regulatory agencies, such as the TGA, by extrapolating safety data from large phase 3 clinical trials of the original and earlier formula COVID-19 vaccines which were compared with placebo.

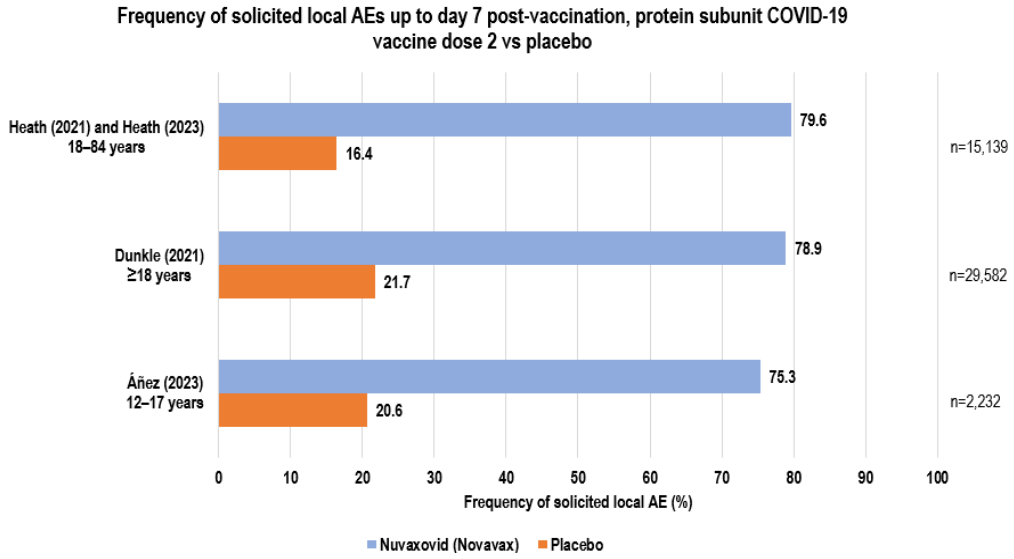
A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months compared with no dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months in people aged 6 months and over

Patient or population: People aged 6 months and over
Intervention: A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months
Comparison: No dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Solicited local AEs [protein subunit COVID-19 vaccine] Assessed with: patient or carer self-report with diary Follow-up: 7 days		(3 RCTs)	⨁⨁⨁⨁ High[c]	A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months results in a large increase in solicited local AEs compared with no dose of the most recent COVID-19 formulation within the past 6–12 months. *Note:* There are no large phase 3 trials in humans which evaluate the safety and reactogenicity of XBB/updated formulation COVID-19 vaccines. The updated formulation (XBB) COVID-19 vaccines were approved by regulatory agencies, such as the TGA, by extrapolating safety data from large phase 3 clinical trials of the original and earlier formula COVID-19 vaccines which were compared with placebo.

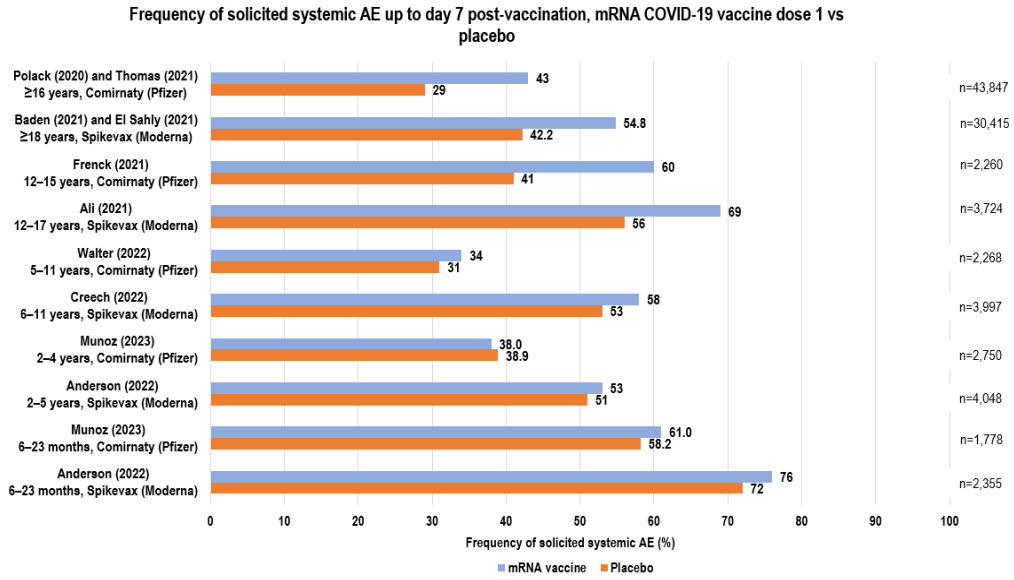
A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months compared with no dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months in people aged 6 months and over

Patient or population: People aged 6 months and over
Intervention: A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months
Comparison: No dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
(*continued*) **Solicited local AEs [protein subunit COVID-19 vaccine]** Assessed with: patient or carer self-report with diary Follow-up: 7 days		(3 RCTs)	⊕⊕⊕⊕ High[c]	A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months results in a large increase in solicited local AEs compared with no dose of the most recent COVID-19 formulation within the past 6–12 months. *Note:* There are no large phase 3 trials in humans which evaluate the safety and reactogenicity of XBB/updated formulation COVID-19 vaccines. The updated formulation (XBB) COVID-19 vaccines were approved by regulatory agencies, such as the TGA, by extrapolating safety data from large phase 3 clinical trials of the original and earlier formula COVID-19 vaccines which were compared with placebo.

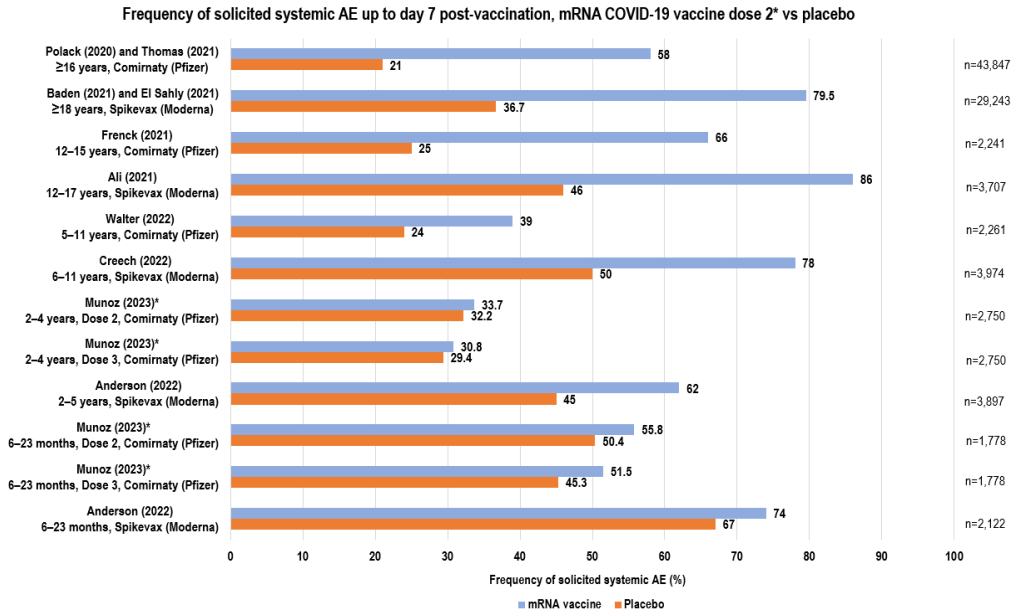
A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months compared with no dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months in people aged 6 months and over

Patient or population: People aged 6 months and over
Intervention: A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months
Comparison: No dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Solicited systemic AEs [mRNA COVID-19 vaccine] Assessed with: patient or carer self-report with diary Follow-up: 7 days		(8 RCTs)[7-15]	⊕⊕⊕⊕ High[c]	mRNA COVID-19 vaccines result in a moderate increase in solicited systemic AEs compared with placebo. *Note:* There are no large phase 3 trials in humans which evaluate the safety and reactogenicity of XBB/updated formulation COVID-19 vaccines. The updated formulation (XBB) COVID-19 vaccines were approved by regulatory agencies, such as the TGA, by extrapolating safety data from large phase 3 clinical trials of the original and earlier formula COVID-19 vaccines which were compared with placebo.

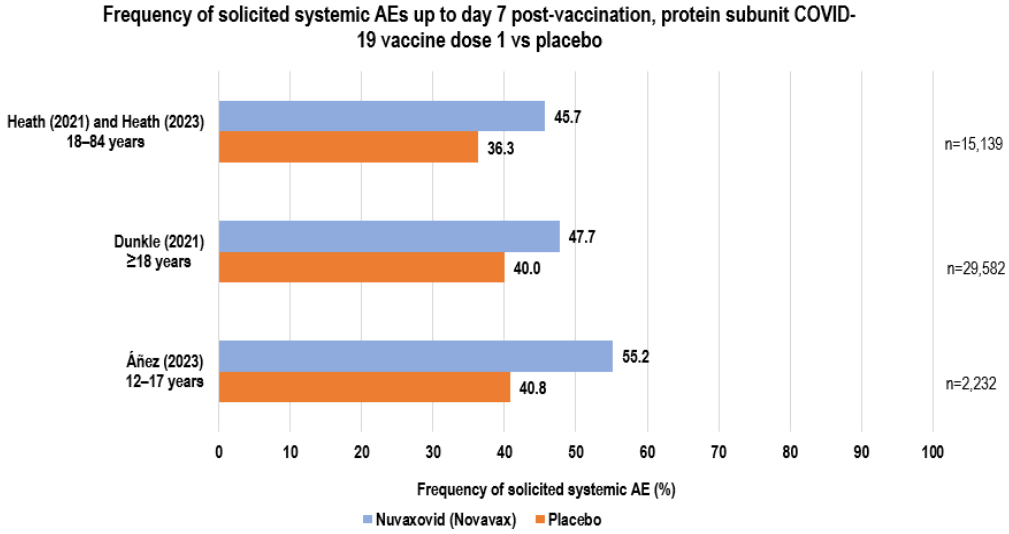
A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months compared with no dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months in people aged 6 months and over

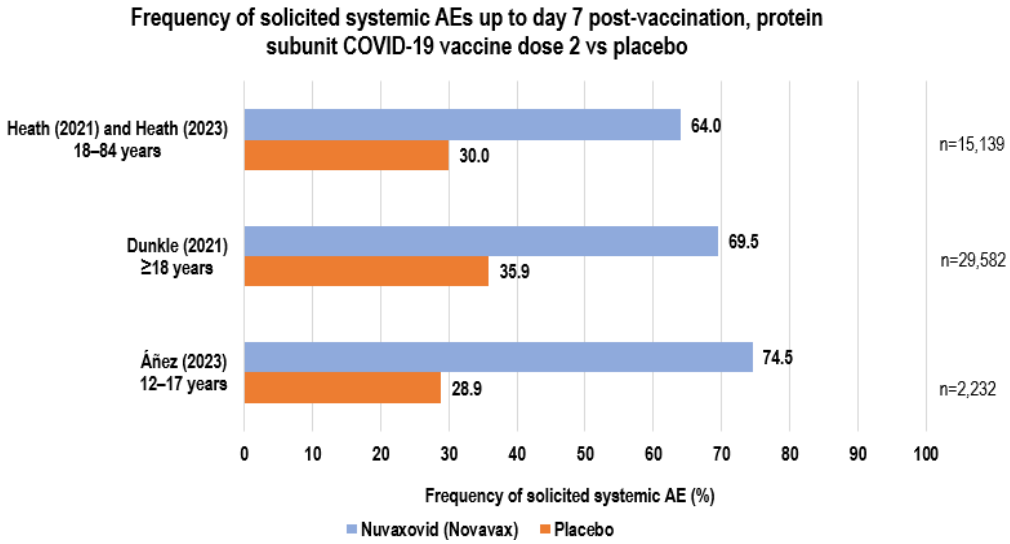
Patient or population: People aged 6 months and over
Intervention: A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months
Comparison: No dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
(*continued*) **Solicited systemic AEs [mRNA COVID-19 vaccine]** Assessed with: patient or carer self-report with diary Follow-up: 7 days	 * Note: Data from Munoz (2023) for Comirnaty (Pfizer) data for the 6 month to 4 year age group also includes data from a third dose, as the primary course in this age group is made up of 3 doses.	(8 RCTs)[7-15]	⨁⨁⨁⨁ High[c]	mRNA COVID-19 vaccines result in a moderate increase in solicited systemic AEs compared with placebo. *Note:* There are no large phase 3 trials in humans which evaluate the safety and reactogenicity of XBB/updated formulation COVID-19 vaccines. The updated formulation (XBB) COVID-19 vaccines were approved by regulatory agencies, such as the TGA, by extrapolating safety data from large phase 3 clinical trials of the original and earlier formula COVID-19 vaccines which were compared with placebo.

A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months compared with no dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months in people aged 6 months and over

Patient or population: People aged 6 months and over
Intervention: A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months
Comparison: No dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Solicited systemic AEs [protein subunit COVID-19 vaccine] Assessed with: patient or carer self-report with diary Follow-up: 7 days		(3 RCTs)	⊕⊕⊕⊕ High[c]	Protein subunit COVID-19 vaccines result in a moderate increase in solicited systemic AEs compared with placebo. *Note:* There are no large phase 3 trials in humans which evaluate the safety and reactogenicity of XBB/updated formulation COVID-19 vaccines. The updated formulation (XBB) COVID-19 vaccines were approved by regulatory agencies, such as the TGA, by extrapolating safety data from large phase 3 clinical trials of the original and earlier formula COVID-19 vaccines which were compared with placebo.

A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months compared with no dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months in people aged 6 months and over				
Patient or population: People aged 6 months and over **Intervention:** A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months **Comparison:** No dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months				
Outcomes	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
(***continued***) **Solicited systemic AEs [protein subunit COVID-19 vaccine]** Assessed with: patient or carer self-report with diary Follow-up: 7 days		(3 RCTs)	⨁⨁⨁⨁ High[c]	Protein subunit COVID-19 vaccines result in a moderate increase in solicited systemic AEs compared with placebo. *Note:* There are no large phase 3 trials in humans which evaluate the safety and reactogenicity of XBB/updated formulation COVID-19 vaccines. The updated formulation (XBB) COVID-19 vaccines were approved by regulatory agencies, such as the TGA, by extrapolating safety data from large phase 3 clinical trials of the original and earlier formula COVID-19 vaccines which were compared with placebo.

A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months compared with no dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months in people aged 6 months and over

Patient or population: People aged 6 months and over
Intervention: A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months
Comparison: No dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 6–12 months

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation

Explanations

a. One study was rated as low risk of bias, and the other three studies were rated as moderate risk of bias. Potential risk of bias was identified in one or more domains of: selection, missing data, measurement of outcomes, and selection of the reported results. The largest study was low risk of bias in all domains except selection, where risk of bias was moderate.

b. The TGA report was rated as moderate risk of bias from the ROBINS-I risk of bias assessment, due to potential risk of bias in the domain of selection. This domain was not downgraded as the TGA report included nationwide data and is the largest and most appropriate study to use to evaluate this outcome.

c. There are no large phase 3 trials in humans which evaluate the safety and reactogenicity of XBB/updated formulation COVID-19 vaccines. The updated formulation (XBB) COVID-19 vaccines were approved by regulatory agencies, such as the TGA, by extrapolating safety data from large phase 3 clinical trials of the original and earlier formula COVID-19 vaccines which were compared with placebo.

Abbreviations: AE=adverse event; AESI=adverse event of special interest; CI=confidence interval; N=number of participants; SAE=serious adverse event; TGA=Therapeutic Goods Administration; TNCC=test-negative case-control; VE=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.

GRADE evidence profile

Evidence profile: A dose of the most recent COVID-19 vaccine formulation after receiving a dose within the past 12 months compared with no dose of the most recent COVID-19 vaccine formulation within the past 12 months in people aged 6 months and over

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Vaccine effectiveness against COVID-19-related hospitalisation [mRNA COVID-19 vaccine] (follow-up: ≥7 days; assessed with: patients who were admitted to hospital with COVID-19-like illness (CLI) or acute respiratory infection (ARI) and were tested for SARS-CoV-2 using polymerase chain reaction (PCR) and/or hospitalisations where COVID-19 was the primary reason for hospital admission)									
4	Non-randomised studies	Serious[a]	Not serious	Not serious	Not serious	None	Vaccine effectiveness (VE) against COVID-19-related hospitalisation ranged from 52.0 to 76.1% for XBB.1.5 based mRNA COVID-19 vaccines among individuals aged 18 years and above.[1-4] VE amongst the different age subgroups was: • ≥18 years (VISION): 52% (95% confidence interval [CI]: 47–57) • ≥18 years (IVY): 43% (95% CI: 27–56) • ≥18 years (preprint): 63% (95% CI: 33–80) • 18–64 years: 43% (95% CI: 20–59) • ≥60 years: 70.7% (95% CI: 66.6–74.3) • ≥65 years (VISION): 53% (95% CI: 47–58) • ≥65 years (IVY): 48% (95% CI: 31–61) • ≥65 years (Denmark): 76.1% (95% CI: 62.3–84.8) • 60–74 years: 68.3% (95% CI: 58.3–75.9) • 75–84 years: 73.9% (95% CI: 68.5–78.4) • ≥85 years: 66.0% (95% CI: 56.4–73.5) Only 1 study reported VE against ICU admission in people aged ≥60 years (73.3%; 95% CI: 42.2–87.6).[1,3]	⊕⊕⊕◯ Moderate	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Adverse event of special interest (AESI): myocarditis (with or without pericarditis) [mRNA COVID-19 vaccine] (follow-up: ≤42 days; assessed with: strong clinical evidence including the patient's symptoms, and results of tests and imaging indicating a diagnosis of myocarditis; or cases that are probably myocarditis based on a combination of symptoms and routine tests for heart conditions; or cases that are possibly myocarditis based on symptoms and a doctor's report that myocarditis is the most likely diagnosis in the absence of medical tests and investigations)									
1	TGA report	Not serious[b]	N/A	Not serious	Not serious	None	Findings from the TGA report were used to report Australian data.[5] Myocarditis (MI) is reported in around 1–2 in every 100,000 people who receive Comirnaty (Pfizer) and around 2 in every 100,000 of those who receive Spikevax (Moderna). It occurs in males and females but is more common after the second dose in boys aged 12–17 years (13 cases per 100,000 Comirnaty doses and 24 cases per 100,000 Spikevax doses) and men under 30 (9 cases per 100,000 Comirnaty doses and 20 cases per 100,000 Spikevax doses). Rates of MI are 2.4 cases per 100,000 doses for all doses for males and 0.9 cases per 100,000 doses for females for all doses of Pfizer. For Moderna, rates of MI across all doses are 3.2 cases per 100,000 doses and 1.0 cases per 100,000 doses for males and females, respectively. So far, reports of myocarditis after a further dose are very rare, occurring in <1 in every 100,000 doses administered. Rates of likely pericarditis cases following the mRNA vaccines across all ages are 2.8 cases per 100,000 doses for Comirnaty (Pfizer) and 2.6 cases per 100,000 doses for Spikevax (Moderna). Rates are highest in people aged 18–29 years (4.4 cases per 100,000 Comirnaty doses and 5.4 cases per 100,000 Spikevax doses) and 30–39 years (4.6 cases per 100,000 Comirnaty doses and 5.2 cases per 100,000 Spikevax doses). *Note:* The reporting rates of likely MI and pericarditis following a dose of mRNA COVID-19 vaccines are similar to those reflected in a large multinational Nordic cohort study.[6]	⊕⊕⊕⊕ High	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
AESI: MI (with or without pericarditis) [protein subunit COVID-19 vaccine] (follow-up: ≤42 days; assessed with: strong clinical evidence including the patient's symptoms, and results of tests and imaging indicating a diagnosis of MI; or cases that are probably myocarditis based on a combination of symptoms and routine tests for heart conditions; or cases that are possibly myocarditis based on symptoms and a doctor's report that MI is the most likely diagnosis in the absence of medical tests and investigations)									
1	TGA report	Not serious[b]	N/A	Not serious	Not serious	None	Findings from the TGA report were used to report Australian data.[5] To 25 June 2023, almost 261,000 doses of Nuvaxovid (Novavax) have been administered in Australia. MI is reported in around 3–4 in every 100,000 doses of Nuvaxovid. Overall, pericarditis is reported in 13 in every 100,000 doses but is more common in men aged 18–49 years (estimated at 27 per 100,000 doses). Noting the reporting rate estimates for pericarditis are less certain for Novavax than for Comirnaty and Spikevax vaccines due to the low number of Nuvaxovid vaccine doses given. To 26 June 2023, there have only been about 2,300 Nuvaxovid doses administered in people aged 12–17 years and no adverse events following immunisation have been reported. To 26 June 2023, reports of MI after a further dose of any type of COVID-19 vaccine are very rare, occurring in <1 in every 100,000 doses administered.	⨁⨁⨁⨁ High	CRITICAL
Serious adverse events (SAE) [mRNA COVID-19 vaccine] (follow-up: range 1 days to ≥6 months post-final dose; assessed with: any adverse event or adverse reaction, at any dose, which results in any of the following outcomes: death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, congenital anomaly or birth defect, or other situations such as medically important events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition)									
8	Randomised trials	Not serious	Not serious	Not serious[c]	Not serious	None	Eight randomised controlled trials (RCTs) reported on SAEs. Any SAE ranged from <0.1 to 1.8% in the vaccine group and ranged from 0 to 2.3% in placebo group. Vaccine-related SAEs ranged from 0 to <1% in vaccine groups and ranged from 0 to 0.2% in placebo group.[7-15]	⨁⨁⨁⨁ High	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
SAE [protein subunit COVID-19 vaccine] (follow-up: range 1 days to ≥6 months post-final dose; assessed with: any adverse event or adverse reaction, at any dose, which results in any of the following outcomes: death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, congenital anomaly or birth defect, or other situations such as medically important events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition)									
3	Randomised trials	Not serious	Not serious	Not serious[c]	Not serious	None	Three RCTs reported on SAEs.[37-40] Any SAE ranged from 0.5 to 0.9% in the vaccine group and ranged from 0.3 to 1.0% in placebo group. Vaccine-related SAEs ranged from 0 to 0.1% in vaccine groups and ranged from 0 to <0.1% in placebo groups.	⨁⨁⨁⨁ High	CRITICAL
Solicited local adverse events (AE) [mRNA COVID-19 vaccine] (follow-up: 7 days; assessed with: patient or carer self-report with diary)									
8	Randomised trials	Not serious	Not serious	Not serious[c]	Not serious	None	Eight RCTs reported on solicited local AEs within 7 days of vaccination.[7-15] The frequency of solicited local AEs ranged from 23.8 to 94% in the vaccine group and 12 to 48% in the placebo group after dose 1. After dose 2, the frequency of solicited local AEs ranged from 20.5 to 95% in the vaccine group and from 10 to 51% in the placebo group. *Note:* Four studies did not report overall local AEs.[12-15] [16] For these studies, the local AE with the highest frequency reported (usually pain) was used. Data from Munoz (2023) for Comirnaty (Pfizer) data for the 6 month–4 year age group also includes data from a third dose, as the primary course in this age group is made up of 3 doses.	⨁⨁⨁⨁ High	IMPORTANT
Solicited local AE [protein subunit COVID-19 vaccine] (follow-up: 7 days; assessed with: patient or carer self-report with diary)									
3	Randomised trials	Not serious	Not serious	Not serious[c]	Not serious	None	Three RCTs reported on local AEs within 7 days of vaccination.[37-40] The frequency of solicited local AEs ranged from 57.6 to 65.5% in the vaccine group and 17.9 to 28.5% in the placebo group after dose 1. After dose 2, the frequency of solicited local AEs ranged from 75.3 to 79.6% in the vaccine group and 16.4 to 21.7% in the placebo group.	⨁⨁⨁⨁ High	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Solicited systemic AE [mRNA COVID-19 vaccine] (follow-up: 7 days; assessed with: patient or carer self-report with diary)									
8	Randomised trials	Not serious	Not serious	Not serious[c]	Not serious	None	Eight RCTs reported on solicited systemic AEs within 7 days of vaccination.[7-15] The frequency of solicited systemic AEs ranged from 34 to 76% in the vaccine group and 29 to 72% in the placebo group after dose 1. After dose 2, the frequency of solicited systemic AEs ranged from 30.8%–86% in the vaccine group and 21 to 67% in the placebo group. *Note:* Four studies did not report overall systemic AEs.[12-15] For these studies, the systemic AE with the highest frequency reported (usually fatigue) was used. Data from Munoz (2023) for Comirnaty (Pfizer) data for the 6 month–4 year age group also includes data from a third dose, as the primary course in this age group is made up of 3 doses.	⊕⊕⊕⊕ High	IMPORTANT
Solicited systemic AE [protein subunit COVID-19 vaccine] (follow-up: 7 days; assessed with: patient or carer self-report with diary)									
3	Randomised trials	Not serious	Not serious	Not serious[c]	Not serious	None	Three RCTs reported on local AEs within 7 days of vaccination.[37-40] The frequency of solicited systemic AEs ranged from 45.7 to 55.2% in the vaccine group and 36.3 to 40.8% in the placebo group after dose 1. After dose 2, the frequency of solicited systemic AEs ranged from 64.0 to 74.5% in the vaccine group and 28.9 to 35.9% in the placebo group.	⊕⊕⊕⊕ High	IMPORTANT

Explanations

a. One study was rated as low risk of bias, and the other three studies were rated as moderate risk of bias. Potential risk of bias was identified in one or more domains of: selection, missing data, measurement of outcomes, and selection of the reported results. The largest study was low risk of bias in all domains except selection, where risk of bias was moderate.

b. The TGA report was rated as moderate risk of bias from the ROBINS-I risk of bias assessment, due to potential risk of bias in the domain of selection. This domain was not downgraded as the TGA included nationwide data, and is the largest and most appropriate study to use to evaluate this outcome.

c. There are no large phase 3 trials in humans which evaluate the safety and reactogenicity of XBB/updated formulation COVID-19 vaccines. The updated formulation (XBB) COVID-19 vaccines were approved by regulatory agencies, such as the TGA, by extrapolating safety data from large phase 3 clinical trials of the original and earlier formula COVID-19 vaccines which were compared with placebo.

Abbreviations: AE=adverse event; AESI=adverse event of special interest; CI= confidence interval; MI= myocarditis; N/A=not applicable; RCT=randomised controlled trial; SAE=serious adverse event; TGA=Therapeutic Goods Administration; VE=vaccine effectiveness

ATAGI Evidence to Decision Framework for a single dose of the updated strain COVID-19 vaccine following a previous dose in the past 6–12 months compared with no updated strain COVID-19 vaccine dose following a previous dose in the past 6–12 months in people aged 6 months and above

PICO Question	
Population	Age 6 months old and over
Intervention	Single dose of an updated strain COVID-19 vaccine following a previous dose between 6 and 12 months prior
Comparison	No dose of an updated strain COVID-19 vaccine following a previous dose between past 6 to 12 months prior
Main outcomes	*Critical* • Vaccine effectiveness (VE) against COVID-19-related hospitalisation • VE against COVID-19-related death • VE against long COVID-19 • Serious adverse events (SAE) (any and vaccine-related) • Adverse event of special interest (AESI): myocarditis (with or without pericarditis) occurring within 42 days of vaccination *Important* • Solicited local adverse events (AEs) • Solicited systemic AEs
Setting	Australia, Argentina, Brazil, Canada, Denmark, Finland, Germany, Mexico, Netherland, Poland, South Africa, Spain Turkey, USA

ASSESSMENT

Problem

Is the problem a priority?

Don't know	Varies	No	Probably no	Probably yes	Yes

- Reducing the risk of severe illness from COVID-19 remains a priority for high-risk groups, i.e. older adults and people with medical risk factors.
- COVID-19 is caused by the severe acute respiratory coronavirus 2 (SARS-CoV-2), a single-stranded RNA betacoronavirus first identified in December 2019. Since its discovery, variant strains have successively become dominant due to advantages in transmissibility or immune escape from immunity acquired from prior infection or vaccination. Since the emergence of the Omicron variant, there has been a consistent decrease in the incidence of severe illness, with a smaller severe-illness peak observed with each subsequent Omicron wave.
- According to the World Health Organization (WHO), monovalent Omicron XBB vaccines provide modestly enhanced protection compared to bivalent variant-containing vaccines and monovalent index virus vaccines. As the virus is expected to continue to evolve from JN.1, the TAG-CO-VAC advises the use of a monovalent JN.1 lineage as the antigen in future formulations of COVID-19 vaccines.[16,17]

- According to the WHO, as of 3 March 2024, over 774 million COVID-19 cases and over 7 million deaths have been reported globally since the start of the pandemic, with a global case fatality rate (CFR) of approximately 0.91%.[18]
- Infection occurs in people of all ages. The risk for severe illness from COVID-19 is low in infants, children, adolescents and healthy younger adults. Rates of severe illness in younger age groups have remained relatively low and stable throughout the Omicron wave, not surpassing 1.3 cases per 100,000 population per week since the start of the fifth Omicron wave.[19]
- According to WHO, healthy children and adolescents aged 6 months to 17 years are a low priority group for vaccination. Primary and booster doses are safe and effective in children and adolescents. However, considering the low incidence of severe illness, the Strategic Advisory Group of Experts on Immunisation (SAGE) advises countries considering vaccination of this age group to base their decisions on contextual factors, such as the disease burden, cost effectiveness, and other health or programmatic priorities and opportunity costs.[20]
- Priority groups such as individuals aged ≥75 years, those with comorbidities and immunocompromised conditions, and those in disability or aged care have an increased risk of severe COVID-19 disease in comparison to the healthy individuals.
- Older age is by far the strongest risk factor associated with morbidity and mortality from COVID-19.[21,22]
- Medical conditions also independently increase the risk of severe disease but to a lesser extent than age.[23]
- Hospitalisation rates are highest in older adults; and despite some recent upticks, hospitalisation rates overall are currently lower than they have been at previous points in the pandemic.[19]

Desirable effects

How substantial are the desirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Vaccination with the updated strain COVID-19 vaccine (XBB.1.5) significantly reduced the risk of severe COVID-19 disease especially in high- risk groups during the period when the XBB variant was the dominate circulating strain (i.e. late September 2023 to early February 2024). Vaccine effectiveness (VE) against hospitalisation ranged from 43 to 76% after receiving the updated strain COVID-19 vaccine.[1-4]
- Protection against hospitalisation was similar across adult groups, with slightly better protection for older adults. VE ranged from 48 to 74% among individuals aged ≥60 years[1,4] (66% for age ≥85 years, 74% for age 75–84 years[4]) compared with VE of 43–63% among individuals aged ≥18 years.[1,3]
- Only one study reported VE against hospitalisation in immunocompromised adults during the period when the XBB variant was the dominant circulating strain, showing a modest benefit from vaccination. In a US study of adults aged ≥18 years with immunocompromising conditions, estimated VE against COVID-19–associated hospitalisation after a dose of updated-strain vaccine was 38% in the subsequent 7–59 days and 34% in the subsequent 60–119 days.[24]
- Recent studies show that emerging subvariants like BA.2.86 and JN.1 were less sensitive to vaccine-induced immune protection from the XBB.1.5 updated COVID-19 vaccine than older subvariants. These emerging subvariants do not appear to confer an increased risk of severe illness. Vaccine effectiveness of XBB.1.5 vaccine against JN.1 related hospitalisation ranged from 26 to 41%.[25-29] WHO Technical Advisory Group for Virus Evolution (TAG-VE) has recommended a JN.1-based antigen for future formulations of COVID-19 vaccines.
- Since the onset of the pandemic, the incidence of severe illness has declined due to high COVID-19 vaccination coverage, hybrid immunity, and with changes in dominant variants. The crude case fatality rate at the start of the Omicron wave to date was 0.19% compared with the lower crude rate during the Delta wave (0.71%).[19]
- Early human immunogenicity data demonstrate Omicron XBB.1.5 vaccine strongly increased anti-spike IgG in all vaccines 8–10 days after a dose and elicited potent neutralising responses against previous and contemporary SARS-CoV-2 lineages, including EG.5.1, and BA.2.86 and JN.1.[30-35]

Undesirable effects

How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- As SARS-CoV-2 has evolved, newer COVID-19 vaccines have been developed to target both the original strain of the virus and newer, more immune-evasive variants. Many updated formulations differ from the original formulation only in the specific spike protein antigen used, and therefore updated formulation (e.g. XBB.1.5) COVID-19 vaccines were approved by regulatory agencies, such as the Therapeutic Goods Administration (TGA), after extrapolating safety data from large phase 3 clinical trials of the original and earlier formulation COVID-19 vaccines.
- These trials reported a moderate incidence of local AEs, and few systemic AEs with original formulation COVID-19 vaccines (mRNA[7-15,35,36] and protein subunit[37-40]) compared with placebo.[7-15,35-40]
- Most post-vaccination AEs are mild to moderate in severity and resolve within 1–2 days.[7-15,35-40]
- No significant differences were seen in total SAEs between vaccine and placebo groups in clinical trials.[7-15,35-40]
- Myocarditis and pericarditis have been identified as adverse events of special interest for mRNA and protein-based vaccines. These conditions have been reported in vaccine recipients very rarely overall, with a higher incidence in males and adolescents.
- As per the June 2024 TGA safety report, myocarditis was reported in around 1–2 in every 100,000 people who receive Comirnaty (Pfizer) and around 2 in every 100,000 of those who receive Spikevax (Moderna). It occurred in males and females but was more common after the second dose in boys aged 12–17 years (13 cases per 100,000 Comirnaty doses and 24 cases per 100,000 Spikevax doses) and men aged under 30 (9 cases per 100,000 Comirnaty doses and 20 cases per 100,000 Spikevax doses).[5]
- Reports of myocarditis after a further dose beyond the primary course of any type of COVID-19 vaccine are very rare, occurring in less than 1 in every 100,000 doses administered.[5]
- Myocarditis and/or pericarditis have also been reported after protein-based vaccines (e.g. Novavax) in Australia and globally, at a similar rate to the mRNA vaccines. As of 20 April 2023, over 250,000 doses of Novavax have been administered in Australia. Based on reports, the incidence of myocarditis is estimated at 40 cases per million doses in Australia. Pericarditis has been reported to occur at an overall rate of 130 per million doses, and more commonly in men aged 18–29 years with a rate of 270 per million doses. The small number of total doses given globally prevents the calculation of a precise risk at this time.[41]
- When the reporting rates of likely myocarditis and pericarditis following a dose of mRNA COVID-19 vaccines in Australia were compared with international reporting rates of myocarditis and pericarditis (e.g. large database study from Nordic countries), similar trends were found.[6]
- Findings of a recent clinical trial of Pfizer monovalent Omicron XBB.1.5 COVID-19 vaccine (single 30 µg dose) among healthy individuals aged ≥12 years did not identify any new safety signals; local AEs and systemic AEs were mostly mild to moderate in severity, AEs were infrequent, and none led to study withdrawal.[35]
- According to AusVaxSafety data, 26% of over 40,000 individuals reported one AE after receiving Pfizer monovalent Omicron XBB.1.5 COVID-19 vaccine. Of those, 21% had local reaction and approximately 16% had systemic reaction, with fewer than 0.2% reporting medical attendance in the days after vaccination.[42]
- With respect to Moderna monovalent Omicron XBB.1.5 COVID-19 vaccine, around 18,000 individuals completed the AusVaxSafety survey and 47% reported at least one AE. Of those, 41% had a local reaction and 33% had systemic reactions, with fewer than 1% reporting medical attendance in the days after vaccination.[43]

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

- The balance of effects probably favours vaccination with updated strain (XBB.1.5) vaccine in the recommended populations (i.e. older age or those with medical conditions associated with increased risk of severe illness).
- The vaccine is efficacious (particularly in the older age groups) and there is a high burden of disease, particularly among the elderly and people with medical conditions.
- The undesirable effects from vaccination are most commonly mild, transient local adverse events. Serious adverse events of special interest are very rare. To date, reports of myocarditis after a further dose (beyond the primary course) of any type of COVID-19 vaccine are very rare, occurring in less than 1 in every 100,000 doses administered.[5]

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 is moderate for two of the GRADED outcomes: VE against COVID-19-related hospitalisation and AESI – myocarditis.
- A significant number of studies reporting rates of myocarditis were identified during the literature search. However, keeping in consideration dose number and generalisability of the findings, TGA safety reports were used to maximise directness.
    - The published TGA report does not include detailed methodology and therefore the risk of bias assessment from the ROBINS-I was completed using information provided by TGA on request. The TGA report was rated as moderate risk of bias from the ROBINS-I risk of bias assessment, due to potential risk of bias in the domain of selection.
- The overall certainty of evidence is high for safety outcomes as all results were identified from robust and large phase 2/3 clinical trials of the original formulation vaccines, and since the updated formulation (XBB) COVID-19 vaccines are identical to older formulations other than updating the specific spike protein antigen. This is the same basis on which these vaccines have been approved by regulatory agencies, such as the TGA.

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

- Medical and health professionals are likely to value COVID-19 vaccination with the updated formulation in the elderly and high-risk populations due to the burden of disease in these populations, and due to the waning of effectiveness of previous doses of (previous formulations of) COVID-19 vaccines against infection and more severe COVID-19 outcomes.
- Older adults and people with risk conditions who are aware that they remain at risk of severe illness are expected to value the option of a more effective vaccine.
- Findings of previous published surveys in Australia have identified factors that increase the perceived value of vaccination, such as older age, concern about contracting COVID-19, and having a chronic medical condition.[44,45] However, as the perceived risk of COVID-19 diminishes with fewer cases and the virus becoming endemic, many Australians may feel less urgency to receive further doses.

Acceptability

Is the intervention acceptable to key stakeholders?

Don't know	Varies	No	Probably no	Probably yes	Yes

- Uptake of recommended further doses has declined over time, but a significant proportion of older adults have received further doses. As of May 2024, more than 71 million total doses of COVID-19 vaccines have been administered in Australia, with around 95,000 weekly increases of COVID-19 doses. Since 1 Jan 2023, 40% of individuals aged ≥75 years have received a further dose in the past 6 months and 25% individuals aged 65–74 years have received a further dose in the past 6 months.[46]
- There will be probably no important uncertainty around acceptability among older adults, high-risk individuals and parents of high-risk kids, as they may be very health-conscious and motivated and would prefer vaccination to prevent severe disease from COVID-19.
- However, Australians' acceptance of COVID-19 vaccines has been shaped by evolving factors over the course of the pandemic. Initially, vaccine uptake was high, driven by the urgency of protecting public health and ending lockdowns. According to findings of a few surveys published earlier in the pandemic (2021–2022), most Australians supported vaccination efforts, leading to high overall vaccination rates, particularly in areas where the perceived risk of the virus was high especially among elderly.[47,48] Factors such as mistrust in government, vaccine fatigue and misinformation have contributed to a decrease in acceptance, but there remains a significant appreciation for the benefits of vaccines among a large segment of the population.[49]

Equity

What would be the impact on health inequities?

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

- There is no expected impact on health inequities of the proposed recommendations. Vaccine supply remains adequate.
- Current recommendations target the sub-populations who have the highest risk of severe illness including older adults.
- Considerations that could impact health inequities are:
  - rollout of newer variant vaccine at the same rate in different providers (e.g. primary care, vaccinator centres, pharmacies, etc.)
  - ensure access to updated strains vaccines in remote areas
  - ensuring access to vulnerable groups, such as those in residential aged care facilities.

Feasibility

Is the intervention feasible to implement?

Don't know	Varies	No	Probably no	Probably yes	Yes

- Updated COVID-19 vaccines should be feasible to implement as the vaccine delivery system is already in use, including through primary care and pharmacist vaccination.
- Receiving multiple vaccines can sometimes be a barrier to vaccination; however, coadministration of COVID-19 vaccines with other routinely recommended vaccines is permitted and should therefore minimise this as a potential barrier to vaccination.

ATAGI recommendation
Primary course vaccination is recommended for all people aged ≥18 years and for children aged 6 months–<18 years with medical conditions that may increase their risk of severe disease or death from COVID-19. Most people require 1 dose for their primary course. People with severe immunocompromise are recommended 2 primary doses and can consider a third dose. Further doses every 6 or 12 months are recommended or can be considered based on an individual's age and presence of risk factors for severe disease. Current recommendations are as follows: • adults aged ≥18 years without severe immunocompromise who have not previously received a COVID-19 vaccine are recommended a single primary dose • all adults aged ≥75 years are recommended further doses of COVID-19 vaccine every 6 months • adults aged 65–74 years without severe immunocompromise are recommended further doses of COVID-19 vaccine every 12 months and can consider further doses every 6 months based on a risk–benefit assessment • adults aged 18–64 years without severe immunocompromise can consider further doses every 12 months based on a risk–benefit assessment, such as the presence of other medical conditions that may increase the risk of severe COVID-19.
Justification and considerations
Additional considerations • To evaluate the certainty of evidence for anticipated benefits and harms from the updated COVID-19 vaccine, NCIRS assessed evidence for the 2023–2024 updated strain (XBB) vaccines for individuals aged ≥6 months. Future updated strains are anticipated to provide protection against emerging and future variants. • Studies reported that a single dose of the updated strain (XBB) COVID-19 vaccine compared with no updated strain COVID-19 vaccine dose prevents hospitalisation in adults aged ≥18 years, especially the elderly. However, no studies have yet reported the outcome of updated strain (XBB) COVID-19 vaccine in infants, children and adolescents. Available recent published and preprints studies from the USA, UK and Nordic countries have been conducted in adults. • Emerging studies report that compared with other SARS-CoV-2 variants, emerging variants like BA.2.86 and the JN.1 sublineage were less sensitive to vaccine-induced immune protection from the XBB.1.5 formulations of COVID-19 vaccine; however, we found no evidence that infection with BA.2.86 or JN.1 resulted in increased disease severity or different symptom profiles. Vaccine effectiveness of XBB.1.5 vaccine against JN.1-related hospitalisation ranged from 26 to 41%.[25-29] • Only one study reported vaccine effectiveness against hospitalisation in immunocompromised adults.[24] Estimated VE against hospitalisation among immunocompromised adults is lower than among immunocompetent adults (ranges 34–38% vs 43–76%)[1-4] after receipt of an updated strain dose. • There are limited data to inform myocarditis risk following an updated strain mRNA dose. The US-based COVID-net data reported that myocarditis rates following booster doses in adolescent and young adult males are lower than rates following primary series, but estimates are limited by fewer numbers of doses for both the bivalent boosters and the previous monovalent boosters administered in the Vaccine Safety Datalink (VSD), which limits the precision for this rare outcome.[50] • As per TGA safety reports to date, reports of myocarditis after a further dose (following the primary course) of any type of COVID-19 vaccine are very rare, occurring in <1 in every 100,000 doses administered.[5] *Justification* • Updated COVID-19 vaccines are safe and effective against severe disease, especially in elderly populations where risk of severe disease is greater. • For people recommended to have COVID-19 vaccination, the benefit of protection against severe disease greatly outweighs the risk of AEs, particularly myocarditis and/or pericarditis.

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