Australian guidelines for the clinical care of people with COVID-19
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Summary of recommendations

1 - Reading Guide
2 - Introduction
3 - Methods and processes
4 - Definition of disease severity

4.1 - Definition of disease severity for adults

<table>
<thead>
<tr>
<th>Mild illness</th>
<th>Adults not presenting any clinical features suggestive of moderate or severe disease or a complicated course of illness.</th>
</tr>
</thead>
</table>
| Characteristics: | • no symptoms  
• or mild upper respiratory tract symptoms  
• or cough, new myalgia or asthenia without new shortness of breath or a reduction in oxygen saturation |

<table>
<thead>
<tr>
<th>Moderate illness</th>
<th>Stable adult patient presenting with respiratory and/or systemic symptoms or signs. Able to maintain oxygen saturation above 92% (or above 90% for patients with chronic lung disease) with up to 4 L/min oxygen via nasal prongs.</th>
</tr>
</thead>
</table>
| Characteristics: | • prostration, severe asthenia, fever > 38°C or persistent cough  
• clinical or radiological signs of lung involvement  
• no clinical or laboratory indicators of clinical severity or respiratory impairment |

<table>
<thead>
<tr>
<th>Severe illness</th>
<th>Adult patients meeting any of the following criteria:</th>
</tr>
</thead>
</table>
| • respiratory rate ≥ 30 breaths/min  
• oxygen saturation ≤ 92% at a rest state  
• arterial partial pressure of oxygen (PaO2)/ Inspired oxygen fraction (FiO2) ≤ 300 |

<table>
<thead>
<tr>
<th>Critical illness</th>
<th>Adult patient meeting any of the following criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory failure</td>
<td>• Occurrence of severe respiratory failure (PaO2/FiO2 &lt; 200), respiratory distress or acute respiratory distress syndrome (ARDS). This includes patients deteriorating despite advanced forms of respiratory support (NIV, HFNO) OR patients requiring mechanical ventilation.</td>
</tr>
</tbody>
</table>
| OR other signs of significant deterioration | • hypotension or shock  
• impairment of consciousness  
• other organ failure |
4.2 - Definition of disease severity for children and adolescents
These definitions apply to children under 16 years of age. Depending on the physical size and/or developmental status of the patient, either the paediatric or adult severity grading can be applied.

Cardiorespiratory and vital parameters must be considered within the normal age-appropriate ranges for neonates and children. If criteria fall across different severity classifications, use the more severe classification to manage illness.

<table>
<thead>
<tr>
<th></th>
<th>Feeding / hydration / conscious state</th>
<th>Respiratory / vital signs</th>
<th>Oxygen requirement[1]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild illness</strong></td>
<td>Normal or mildly reduced feeding</td>
<td>No or mild upper respiratory tract symptoms OR No or mild work of breathing</td>
<td>No supplemental oxygen required to maintain SpO$_2$ &gt; 92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate work of breathing OR Abnormal vital signs for age (tachycardia, tachypnoea) but does not persistently breach Early Warning (e.g. MET) Criteria[2] OR Brief self-resolving apnoea (infants)</td>
<td>Requires low-flow oxygen (nasal prongs or mask) to maintain SpO$_2$ &gt; 92%</td>
</tr>
<tr>
<td><strong>Moderate illness</strong></td>
<td>Poor feeding, unable to maintain hydration without nasogastric or IV fluids AND Normal conscious state</td>
<td>Moderate-severe work of breathing OR Abnormal vital signs for age (tachycardia, tachypnoea) with breaches of Early Warning / Medical Emergency Team criteria OR Apnoea needing support / stimulation (infants)</td>
<td>Requires high-flow oxygen at 2 L/kg/min[3] to maintain SpO$_2$ &gt; 92%</td>
</tr>
<tr>
<td><strong>Severe illness</strong></td>
<td>Poor feeding, unable to maintain hydration without nasogastric or IV fluids OR Drowsy / tired but easily rousable</td>
<td>Unable to maintain breathing or prevent apnoea without advanced modes of support OR Abnormal vital signs for age with persistent breaches of Early Warning (e.g. MET) Criteria OR Haemodynamically unstable without inotropic or vasopressor support OR Other organ failure</td>
<td>Requires advanced modes of support to maintain oxygenation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High-flow nasal oxygen at &gt; 2 L/kg/min[3] OR Non-invasive ventilation OR Intubation and mechanical ventilation OR Extracorporeal membrane oxygenation (ECMO)</td>
</tr>
<tr>
<td><strong>Critical illness</strong></td>
<td>Poor feeding, unable to maintain hydration without nasogastric or IV fluids OR Altered conscious state / unconscious</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Oxygen saturation target should be modified for patients with cyanotic heart disease.

Temperature instability should be considered an abnormal vital sign in infants. Fever is common in children and does not contribute to determination of illness severity in isolation.

Preterm infants and neonates < 4 kg may be managed on high-flow nasal cannula oxygen at 2-8 L/min irrespective of weight.

Note: co-morbidities (e.g. preterm infants, oncology, immunosuppressed, etc.) may increase the risk of more severe disease.

5 - Monitoring and markers of clinical deterioration

5.1 - Monitoring and markers of clinical deterioration

Consensus Recommendation
For people with COVID-19, monitor markers of clinical progression, such as rapidly progressive respiratory failure and sepsis, especially on days 5 to 10 after onset of symptoms.

6 - Disease-modifying treatments

6.1 - Dexamethasone

6.1.1 - Dexamethasone for adults

Strong Recommendation
Use dexamethasone 6 mg daily intravenously or orally for up to 10 days in adults with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

Weak Recommendation Against
Do not routinely use dexamethasone to treat COVID-19 in adults who do not require oxygen.

Dexamethasone may still be considered for other evidence-based indications in people who have COVID-19.

6.1.2 - Dexamethasone for pregnant or breastfeeding women

Strong Recommendation
Use dexamethasone 6 mg daily intravenously or orally for up to 10 days in pregnant or breastfeeding women with COVID-19 who are receiving oxygen (including mechanically ventilated patients).
Do not routinely use dexamethasone to treat COVID-19 in pregnant or breastfeeding women who do not require oxygen. Antenatal corticosteroids should still be used for fetal lung maturation in pregnant women at risk of preterm birth who also have COVID-19. Dexamethasone should still be used for other evidence-based indications in pregnant and breastfeeding women who have COVID-19.

6.1.3 - Dexamethasone for children or adolescents

Weak Recommendation
Consider using dexamethasone daily intravenously or orally for up to 10 days in children and adolescents with COVID-19 who are receiving oxygen (including mechanically ventilated).

A dose of 6 mg daily was used for adults. The protocol stated a dose of 0.15 mg/kg/day to a maximum of 6 mg/day for children but it is unclear how many children were included in the trial.

Weak Recommendation Against
Do not routinely use dexamethasone to treat COVID-19 in children or adolescents who do not require oxygen.

Dexamethasone should still be used for other evidence-based indications in children or adolescents who have COVID-19.

6.2 - Remdesivir

6.2.1 - Remdesivir for adults

Weak Recommendation
Whenever possible remdesivir should be administered in the context of a randomised trial with appropriate ethical approval. Use of remdesivir for adults with moderate, severe or critical COVID-19 outside of a trial setting may be considered.

The inclusion in these studies of older people or those requiring palliative care is uncertain. Until further evidence in these populations is available, the Taskforce does not believe a different recommendation should apply, unless contraindicated.

Due to antagonism observed in vitro, concomitant use of remdesivir with chloroquine or hydroxychloroquine is not recommended [22].

For information on dosages, length of treatment and characteristics of the patients in the trials used for this recommendation, see the Practical info tab below.
6.2.2 - Remdesivir for pregnant or breastfeeding women

**Weak Recommendation Against**

Use of remdesivir for pregnant or breastfeeding women with COVID-19 outside of a trial setting should not be considered routinely.

As pregnant and breastfeeding women are often excluded from clinical trials, use of remdesivir in this population would be outside a clinical trial setting. Pregnant and breastfeeding women receiving remdesivir should nonetheless be enrolled in national COVID-19 registries. Currently, there is no direct evidence of the effects of remdesivir in pregnant and breastfeeding women. Information about the patients and the intervention (dosages, duration) in the trials used for this recommendation can be found in the Practical info tab.

Due to antagonism observed in vitro, concomitant use of remdesivir with chloroquine or hydroxychloroquine is not recommended [22].

6.2.3 - Remdesivir for children or adolescents

**Weak Recommendation Against**

Use of remdesivir for children or adolescents with COVID-19 outside of a trial setting should not be considered routinely.

If treatment is considered—in exceptional circumstances—it should be in consultation with a clinical reference group, such as the ANZPID COVID-19 Clinical Reference Group. Informed consent from parents/caregivers should also be obtained. Currently, there is no direct evidence for the use of remdesivir in children or adolescents. Information about the patients and the intervention (dosages, duration) in the trials used for this recommendation can be found in the Practical info tab.

Due to antagonism observed in vitro, concomitant use of remdesivir with chloroquine or hydroxychloroquine is not recommended [22].

6.3 - Hydroxychloroquine

**Strong Recommendation Against**

For people with COVID-19, do not use hydroxychloroquine outside of randomised trials with appropriate ethical approval.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use hydroxychloroquine in these populations unless they are eligible to be enrolled in trials.

6.4 - Baloxavir marboxil

**Strong Recommendation Against**

For people with COVID-19, do not use baloxavir marboxil outside of randomised trials with appropriate ethical approval.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use baloxavir marboxil in these populations unless they are eligible to be enrolled in trials.
6.5 - Chloroquine

- **Strong Recommendation Against**

For people with COVID-19, do not use chloroquine outside of randomised trials with appropriate ethical approval.

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use chloroquine in these populations unless they are eligible to be enrolled in trials.*

6.6 - Colchicine

- **Strong Recommendation Against**

For people with COVID-19, do not use colchicine outside of randomised trials with appropriate ethical approval.

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use colchicine in these populations unless they are eligible to be enrolled in trials.*

6.7 - Convalescent plasma

- **Strong Recommendation Against**

For people with COVID-19, do not use convalescent plasma outside of randomised trials with appropriate ethical approval.

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use convalescent plasma in these populations unless they are eligible to be enrolled in trials.*

6.8 - Darunavir-cobicistat

- **Strong Recommendation Against**

For people with COVID-19, do not use darunavir-cobicistat outside of randomised trials with appropriate ethical approval.

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use darunavir-cobicistat in these populations unless they are eligible to be enrolled in trials.*
6.9 - Favipiravir

**Strong Recommendation Against**

For people with COVID-19, do not use favipiravir outside of randomised trials with appropriate ethical approval.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use favipiravir in these populations unless they are eligible to be enrolled in trials.

6.10 - Interferon β-1a

**Strong Recommendation Against**

For people with COVID-19, do not use interferon β-1a outside of randomised trials with appropriate ethical approval.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use interferon β-1a in these populations unless they are eligible to be enrolled in trials.

6.11 - Lopinavir-ritonavir

**Strong Recommendation Against**

For people with COVID-19, do not use lopinavir-ritonavir outside of randomised trials with appropriate ethical approval.

The Taskforce notes the release of the press statement from the chief investigators of the RECOVERY trial on 29 June that found no clinical benefit from using lopinavir-ritonavir in hospitalised patients with COVID-19. On 4 July WHO announced the lopinavir-ritonavir treatment arm of the Solidarity Trial had been discontinued with immediate effect. We await publication of the results of both trials.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use lopinavir-ritonavir in these populations unless they are eligible to be enrolled in trials.

6.12 - Ruxolitinib

**Strong Recommendation Against**

For people with COVID-19, do not use ruxolitinib outside of randomised trials with appropriate ethical approval.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use ruxolitinib in these populations unless they are eligible to be enrolled in trials.
6.13 - Other disease-modifying treatments

<table>
<thead>
<tr>
<th>Consensus Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>For people with COVID-19, do not use other disease-modifying treatments outside of randomised trials with appropriate ethical approval.</td>
</tr>
</tbody>
</table>

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use other disease-modifying treatments in these populations unless they are eligible to be enrolled in trials.*

7 - Chemoprophylaxis

7.1 - Hydroxychloroquine for post-exposure prophylaxis

<table>
<thead>
<tr>
<th>Strong Recommendation Against</th>
</tr>
</thead>
<tbody>
<tr>
<td>For people exposed to individuals with COVID-19, only administer hydroxychloroquine for post-exposure prophylaxis in the context of randomised trials with appropriate ethical approval.</td>
</tr>
</tbody>
</table>

*The Taskforce is continually monitoring research on chemoprophylaxis. As evidence accumulates the Taskforce will continue to review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).*

8 - Respiratory support

<table>
<thead>
<tr>
<th>Consensus Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guiding principles of care</strong></td>
</tr>
<tr>
<td>For patients with COVID-19 for whom respiratory support (HFNO/NIV) is being considered, decisions should balance likelihood of patient benefit against the risk of infection for healthcare workers. For patients with COVID-19 receiving respiratory support (HFNO/NIV) or requiring intubation, use single rooms or negative pressure rooms wherever possible and ensure contact, droplet and airborne precautions are in place.</td>
</tr>
</tbody>
</table>

*The relative risk of infection to healthcare workers associated with specific oxygen therapies remains uncertain and may vary from site to site.*
8.1 - High-flow nasal oxygen therapy

Recommendation Strength Not Set

High-flow nasal oxygen (HFNO) therapy is a form of respiratory support where oxygen is delivered, often in conjunction with compressed air and humidification. It delivers high flow oxygen via large diameter nasal cannula that is humidified and heated. Flow rates can be given up to 60 L/min in adults and 25 L/min in children with an oxygen/air blender supplying oxygen at 21-100%.

High-flow humidified oxygen should be considered when unable to maintain SaO2 ≥ 92% despite conventional oxygen delivery at > 6 L/min or an FiO2 0.4

Strong Recommendation

In negative pressure rooms, use high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

Use the lowest flow necessary to maintain oxygen saturation ≥ 92%.

Weak Recommendation

In single rooms or shared ward spaces with cohorting of confirmed COVID-19 patients only, consider using high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

Use the lowest flow necessary to maintain oxygen saturation ≥ 92%.

Strong Recommendation Against

In shared wards or emergency department cubicles do not use high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19.

Strong Recommendation Against

During inter-hospital patient transfer/retrieval do not use high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19.
8.2 - Non-invasive ventilation

**Recommendation Strength Not Set**

Non-invasive ventilation (NIV), also known as non-invasive positive pressure ventilation (NIPPV) or bilevel positive pressure support (BiPAP), is a form of respiratory support. Bilevel positive pressure is delivered throughout the respiratory cycle by a firm-fitting nasal-face mask. The patient breathes spontaneously and triggers the device to cycle.

A higher level of pressure is provided during the inspiratory phase to enhance ventilation, while a lower level of continuous positive pressure is delivered during the expiratory phase (also known as positive end-expiratory pressure or PEEP). Supplemental oxygen can also be delivered through the device.

**Consensus Recommendation**

In *negative pressure rooms*, consider using NIV therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

**Consensus Recommendation**

In *single rooms or shared ward spaces with cohorting of confirmed COVID-19 patients only*, consider using NIV therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

**Consensus Recommendation**

In *shared wards or emergency department cubicles*, do not use NIV therapy for patients with hypoxaemia associated with COVID-19.

**Consensus Recommendation**


**Consensus Recommendation**

In patients with COVID-19 for whom NIV is appropriate for an alternate clinical presentation (e.g. concomitant COPD with type 2 respiratory failure and hypercapnoea, APO), ensure airborne and other infection control precautions are optimised.

8.3 - Respiratory management of the deteriorating patient

**Consensus Recommendation**

In patients with COVID-19 who are deteriorating, consider early endotracheal intubation and invasive mechanical ventilation.

*Patients can deteriorate rapidly 5 to 10 days after onset of symptoms.*
8.4 - Videolaryngoscopy

**Weak Recommendation**

In adults with COVID-19 undergoing endotracheal intubation, consider using videolaryngoscopy over direct laryngoscopy if available and the operator is trained in its use.

8.5 - Neuromuscular blockers

**Recommendation Strength Not Set**

Neuromuscular blocking agents (NMBAs) are a pharmaceutical intervention that may facilitate protective lung ventilation in patients who are mechanically ventilated with moderate to severe acute respiratory distress syndrome (ARDS). NMBAs may reduce patient-ventilator dysynchrony and facilitate improved oxygenation by various mechanisms, including reducing the inspiratory muscle effort and the work of breathing, and reducing ventilator-induced lung injury.

**Weak Recommendation Against**

For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, do not routinely use continuous infusions of neuromuscular blocking agents (NMBAs).

*However, if protective lung ventilation cannot be achieved, consider using NMBAs for up to 48 hours. If indicated, consider cisatracurium as first-line agent, if cisatracurium is not available alternatives include atracurium or vecuronium by infusion.*

8.6 - Positive end-expiratory pressure

**Consensus Recommendation**

For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, consider using a higher PEEP strategy (PEEP > 10 cm H2O) over a lower PEEP strategy.

8.7 - Prone positioning

**Recommendation Strength Not Set**

Positioning the patient in a face-down (prone) position may help to open up (recruit) collapsed alveoli and improve oxygen levels in the blood.
8.7.1 - Prone positioning for adults

**Consensus Recommendation**

For mechanically ventilated adults with COVID-19 and hypoxaemia despite optimising ventilation, consider prone positioning for more than 12 hours a day.

*Current reports suggest prone ventilation is effective in improving hypoxia associated with COVID-19. This should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and that minimises the risk of adverse events, e.g. accidental extubation.*

**Consensus Recommendation**

For adults with COVID-19 and respiratory symptoms who are receiving any form of supplemental oxygen therapy and have not yet been intubated, consider prone positioning. When positioning a patient in prone, ensure it is used with caution and close monitoring of the patient. Patients who are deteriorating should be considered for early endotracheal intubation and invasive mechanical ventilation.

8.7.2 - Prone positioning for pregnant and postpartum women

**Consensus Recommendation**

For mechanically ventilated pregnant women with COVID-19 and hypoxaemia despite optimising ventilation, consider prone positioning for more than 12 hours a day.

*Current reports suggest prone ventilation in adult patients is effective in improving hypoxia associated with COVID-19. This should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and that minimises the risk of adverse events, e.g. accidental extubation.*

Proning of a pregnant woman should avoid abdominal compression and ensure a woman's hips and chest are supported. In the absence of specialised equipment, proning can be performed using pillows and blankets.

Proning can be challenging in late gestation and delivery of the baby may be warranted.

**Consensus Recommendation**

For pregnant and postpartum women with COVID-19 and respiratory symptoms who are receiving any form of supplemental oxygen therapy and have not yet been intubated, consider prone positioning. When positioning a pregnant woman in prone, care should be taken to support the gravid uterus to reduce aorta-caval compression. Women who are deteriorating should be considered for early endotracheal intubation and invasive mechanical ventilation. Birth of the baby should be considered when it may enhance maternal resuscitation or be beneficial to the fetus.

*Current reports suggest prone ventilation in adult patients is effective in improving hypoxia associated with COVID-19. This should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events, e.g. accidental extubation.*

Proning of a pregnant woman should avoid abdominal compression and ensure a woman's hips and chest are supported. In the absence of specialised equipment, it can be performed using pillows and blankets.

Proning can be challenging in late gestation and delivery of the baby may be warranted.
8.8 - Recruitment manoeuvres

Recommendation Strength Not Set

Patients receiving respiratory support are at an increased risk of lung injury. Recruitment manoeuvres are used to open up ('recruit') collapsed alveoli and are a common element of an 'open lung approach' to protect the lungs during mechanical ventilation. The manoeuvres use a sustained increase in airway pressure to re-open collapsed alveoli.

Types of manoeuvres include: prolonged high continuous positive airway pressure; progressive incremental increases in positive end-expiratory pressure at a constant driving pressure (incremental PEEP, stepwise or staircase); and high driving pressures.

Consensus Recommendation

For mechanically ventilated adults with COVID-19 and hypoxaemia despite optimising ventilation, consider using recruitment manoeuvres.

If recruitment manoeuvres are used, do not use staircase or stepwise (incremental PEEP) recruitment manoeuvres.

8.9 - Extracorporeal membrane oxygenation

Recommendation Strength Not Set

Extracorporeal membrane oxygenation (ECMO) is a form of life support that removes blood from the body via large cannulae, oxygenates and removes carbon dioxide from the blood external to the patient, and then returns the blood to the body.

Venovenous (VV) ECMO provides oxygenation support for the lungs only, while venoarterial (VA) ECMO supports the heart and lungs.

8.9.1 - ECMO for adults

Consensus Recommendation

In mechanically ventilated adults with COVID-19 and refractory respiratory failure (despite optimising ventilation, including proning), consider using venovenous extracorporeal membrane oxygenation (VV ECMO) if available, or referring the patient to an ECMO centre.

Due to the resource-intensive nature of ECMO and the need for experienced centres, healthcare workers and infrastructure, ECMO should only be considered in selected patients with COVID-19 and severe ARDS.
8.9.2 - ECMO for pregnant and postpartum women

Consensus Recommendation

Consider referral to an ECMO centre for venovenous ECMO in mechanically ventilated pregnant women with COVID-19 and refractory respiratory failure (despite optimising ventilation, including proning). Delivery of the baby prior to ECMO to enhance maternal resuscitation should be considered on a case-by-case basis.

Due to the resource-intensive nature of ECMO and the need for experienced centres, healthcare workers and infrastructure, ECMO should only be considered in selected pregnant women with COVID-19 and severe ARDS.

The decision on whether to use ECMO should be taken in consultation with the woman’s family, as well as obstetric and intensive care specialists. Key considerations include gestational age, fetal viability, fetal well-being and the risks and benefits to mother and baby.

Early referral to an ECMO centre is preferred.

As pregnant and postpartum women may have haemostatic alterations, anticoagulation regimens may need to be modified appropriately.

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9 - Steroids for people with asthma or COPD and COVID-19

9.1 - Steroids for people with asthma or COPD and COVID-19

Consensus Recommendation

Use inhaled or oral steroids for the management of people with co-existing asthma or COPD and COVID-19 as you would normally for viral exacerbation of asthma or COPD. Do not use a nebuliser.

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10 - Anticoagulants

10.1 - Venous thromboembolism (VTE) prophylaxis

Consensus Recommendation

Use prophylactic doses of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) in adults with moderate COVID-19 or other indications, unless there is a contraindication, such as risk for major bleeding. Where severe acute kidney disease is present, unfractionated heparin or renally adjusted doses of LMWH may be used (e.g. enoxaparin 20 mg once daily or dalteparin 2500 IU once daily).
10.2 - Increased-dose venous thromboembolism (VTE) prophylaxis

**Consensus Recommendation**

Consider using increased prophylactic dosing of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg twice daily or dalteparin 5000 IU twice daily) in adults with severe or critical COVID-19 or other indications, unless there is a contraindication, such as risk for major bleeding or platelet count < 30 x 10^9/L. Where severe acute kidney disease is present (creatinine clearance < 30 mL/min), unfractionated heparin or renal adjusted doses of LMWH may be used (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily).

11 - ACEIs/ARBs in patients with COVID-19

11.1 - ACEIs/ARBs in patients with COVID-19

**Strong Recommendation**

In patients with COVID-19 who are receiving ACEIs/ARBs, there is currently no evidence to deviate from usual care and these medications should be continued unless contraindicated.

Stopping these medications abruptly can lead to acute heart failure or unstable blood pressure.

12 - Pregnancy and perinatal care

**Recommendation Strength Not Set**

For recommendations on disease modifying treatments, chemoprophylaxis and respiratory support in pregnant or breastfeeding women please see sections above. We are continuously working on updating all recommendations to reflect special populations, including pregnant and breastfeeding women.

12.1 - Mode of birth

**Weak Recommendation**

For pregnant women with COVID-19, mode of birth should remain as per usual care.

There is currently no evidence to indicate that caesarean section for women with COVID-19 reduces the risk of vertical transmission to the newborn. Mode of birth should continue as per usual care. Respiratory deterioration due to COVID-19 may prompt urgent delivery on an individual basis.
12.2 - Breastfeeding

**Weak Recommendation**

Breastfeeding is supported irrespective of the presence of COVID-19. However, women with COVID-19 who are breastfeeding should use infection prevention and control measures (mask and hand hygiene) while infectious.

*There is currently no evidence to indicate that breastfeeding increases the risk of vertical transmission to the newborn. As there are substantial known benefits for breastfeeding, women should be supported to initiate or continue breastfeeding.*

12.3 - Rooming-in

**Weak Recommendation**

For women with COVID-19 who have given birth, support rooming-in of mother and newborn. However, women with COVID-19 should use infection prevention and control measures (mask and hand hygiene) while infectious.

*There is currently no evidence to indicate that a woman with a known COVID-19 infection should be separated from her newborn to prevent transmission. As there are substantial known benefits for keeping mother and newborn together postpartum, women should be supported to be with their newborn as per usual care.*

*Women should be encouraged and supported in using good hand hygiene before and after handling their baby, and using a mask while in close contact with their baby. To the extent possible, women who are infectious should practice physical distancing when not feeding or caring for the baby.*

13 - Abbreviations and Acronyms
1 - Reading Guide

The treatment of novel coronavirus disease 2019 (COVID-19) is a rapidly expanding area of research, with an unprecedented global effort underway to combat this disease. As a result, recommendations based on current evidence are likely to become outdated quickly as new primary studies are published. The living evidence approach facilitates rapid updating of recommendations. By frequently incorporating the most up-to-date evidence, these methods ensure that the currency of each recommendation remains high.

It is anticipated that these living recommendations will be updated weekly as and when new evidence is available. This will be reflected in the publication of a new version in which changes made to a specific recommendation or supporting information are highlighted to emphasise the update.

The guideline consists of two layers:

1. The Recommendation

   Recommendation for (Green)
   A strong recommendation is given when there is high-certainty evidence showing that the overall benefits of the intervention are clearly greater than the disadvantages. This means that all, or nearly all, patients will want the recommended intervention.

   Recommendation against (Red)
   A strong recommendation against the intervention is given when there is high-certainty evidence showing that the overall disadvantages of the intervention are clearly greater than the benefits. A strong recommendation is also used when the examination of the evidence shows that an intervention is not safe.

   Conditional Recommendation for (Yellow)
   A conditional recommendation is given when it is considered that the benefits of the intervention are greater than the disadvantages, or the available evidence cannot rule out a significant benefit of the intervention while assessing that the adverse effects are few or absent. This recommendation is also used when patient preferences vary.

   Conditional Recommendation against (Orange)
   A conditional recommendation is given against the intervention when it is judged that the disadvantages of the intervention are greater than the benefits, but where this is not substantiated by strong evidence. This recommendation is also used where there is strong evidence of both beneficial and harmful effects, but where the balance between them is difficult to determine. Likewise, it is also used when patient preferences vary.

   Consensus Recommendation (Bluish-Purple)

A consensus recommendation can be given for or against the intervention. This type of recommendation is used when there is not enough evidence to give an evidence-based recommendation, but the panel still regards it as important to give a recommendation.

2. Supporting information

Click on the recommendation to learn more about the basis of the recommendation. Note that early recommendations are primarily adapted from other guidelines and/or based on the consensus of the guideline panel, and supporting information will be limited. Additional information will be added as recommendations are updated in light of new evidence.

Evidence profile: The overall effect estimates and references to the studies.
Summary: Overview and brief review of the underlying evidence.
Certainty of the evidence:
  • High: We are very sure that the true effect is close to the estimated effect.
  • Moderate: We are moderately sure of the estimated effect. The true effect is probably close to this one, but there is a possibility that it is significantly different.
  • Low: We have limited confidence in the estimated effect. The true effect may be significantly different from the estimated effect.
  • Very low: We have very little confidence in the estimated effect. The true effect is likely to be significantly different from that estimated effect.

Key information: Brief description of beneficial and harmful effects, certainty of evidence and considerations of patient preferences.
Rationale: Description of how the above elements were weighted in relation to each other and resulted in the current recommendation direction and strength.
Practical information: Practical information regarding the treatment and information on any special patient considerations.
Adaption: If the recommendation is adapted from another guideline you can find more information here.
Feedback: If you are logged in as a user, you can comment here on specific recommendations. See here for guidance on how to log in.
References: Reference list for the recommendation.

The gradation of evidence quality and recommendation strength used is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE). For a quick and informative introduction to GRADE, the article Understanding GRADE: an introduction by Goldet & Howick is recommended (J Evid Based Med 2013;6(1):50-4). See also http://www.gradeworkinggroup.org.
2 - Introduction

Introduction

Novel coronavirus disease 2019 (COVID-19) is an infectious disease caused by the newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since its identification in December 2019, COVID-19 has spread around the world and was declared a Public Health Emergency of International Concern by the World Health Organization (WHO) on 30 January 2020 [1].

People infected with the COVID-19 virus are most likely to only experience mild symptoms and recover without requiring special treatment. However, some people will experience moderate or severe disease. Older people and those with underlying diseases or medical conditions (such as cardiovascular disease, diabetes, chronic respiratory disease and cancer) are more likely to develop serious illness that require special care and treatment [90].

Clinical guidelines are integral to ensuring that healthcare decisions are based on the best available evidence. Since the emergence of the COVID-19 pandemic, many national and international organisations have released guidelines related to different aspects of the management of people with COVID-19. With the support of the National Health and Medical Research Council (NHMRC), the National COVID-19 Clinical Evidence Taskforce was established to develop (in partnership with a range of national professional societies and organisations) living guidelines for clinical management and care of people with suspected or confirmed COVID-19.

The recommendations within this guideline were developed in collaboration with:

- Australian Living Evidence Consortium (Coordinating Lead)
- Cochrane Australia (Secretariat)
- Australasian Association of Academic Primary Care
- Australasian College for Emergency Medicine
- Australasian College for Infection Prevention and Control
- Australasian Sleep Association
- Australasian Society of Clinical and Experimental Pharmacologists and Toxologists
- Australasian Society for Infectious Diseases
- Australian Association of Gerontology
- Australian College of Critical Care Nurses
- Australian College of Midwives
- Australian College of Nursing
- Australian College of Rural and Remote Medicine
- Australian COVID-19 Palliative Care Working Group
- Australian and New Zealand College of Anaesthetists
- Australian and New Zealand Intensive Care Society
- Australian and New Zealand Society for Geriatric Medicine
- Australian Primary Health Care Nurses Association
- Australian Resuscitation Council
- Australian Society of Anaesthetists
- College of Emergency Nursing Australasia
- CRANAPlus
- National Aboriginal Community Controlled Health Organisation
- Royal Australasian College of Physicians
- Royal Australian College of General Practitioners
- Royal Australian and New Zealand College of Obstetricians and Gynaecologists
- Society of Hospital Pharmacists of Australia
- Thoracic Society of Australia and New Zealand
- Thrombosis and Haemostasis Society of Australia and New Zealand

Updating and public consultation

A considerable volume of research related to the care of people with COVID-19 is ongoing and will potentially impact clinical recommendations. To ensure these guidelines are updated rapidly in response to new and important evidence, the underpinning knowledge syntheses and recommendations will be reviewed and updated on an ongoing basis. It is anticipated that these living recommendations will be updated weekly as and when new evidence is available. This will be reflected in the publication of a new version in which changes made to a specific recommendation or supporting information are highlighted in order to emphasise the update.

The consortium is seeking NHMRC approval of the guideline under section 14A of the National Health and Medical Research Council Act 1992. As part of the approval process (and for the lifetime of the guidelines), public consultation is required. We welcome your feedback and suggestions. Comments can be submitted via the feedback function under each recommendation in MAGIC, see the reading guide in the above section for guidance, or by emailing guidelines@covid19evidence.net.au.

Purpose

The purpose of this guideline is to provide health professionals and patients with up-to-date, evidence-based recommendations to guide shared decision-making in the treatment of COVID-19. The guideline contains specific and actionable recommendations for selected, well-defined clinical problems (i.e. what needs to be done and who it is relevant to). It does not define the individuals responsible for providing care, nor does it consider the social or economic implications of guideline adherence.

Scope

This guideline aims to provide specific, patient-focused recommendations on management and care of people with suspected or confirmed COVID-19. With the exception of chemoprophylaxis for the prevention of infection in people exposed to COVID-19, the guideline does not include other interventions used in the prevention of COVID-19 infection or transmission. Within each recommendation, the patient population of interest is specified.

Note on the language in the pregnancy and perinatal care recommendations

The Taskforce recognises that individuals have diverse gender identities. Terms such as pregnant person, childbearing people and parent can be used to avoid gendering birth, and those who give birth, as feminine. However, because women are also marginalised and oppressed in most places around the world, we have continued to use the terms woman, mother or maternity. When we use these words, it is not meant to exclude those who give birth and do not identify as women.

Note on people requiring palliative care and older people living with frailty or cognitive impairment

The Taskforce recognises the need for specific recommendations and considerations for older people living with frailty or cognitive impairment. These populations are particularly vulnerable and have been reported as having an increased risk of mortality due to COVID-19 [2]. The Taskforce's Palliative and Aged Care Panel provides clinical expertise to ensure these populations are appropriately considered in our guidance. The following definitions have been agreed for these populations:
Older people (> 65 years) with frailty or cognitive impairment and COVID-19
This population includes older people (usually > 65 years) with impairments of physical, cognitive and/or physiological function, or who have frailty. Frailty is a multifaceted syndrome that includes physical impairments and higher susceptibility to disease [3]. Comorbidities are often present, such as cerebrovascular disease, dementia, heart failure and chronic lung disease [3].

People requiring palliative care and COVID-19
This population includes people with COVID-19 whose prognosis due to co-existing advanced progressive disease is limited or uncertain, or people with critical COVID-19 illness where recovery is not expected.

Target audience
These recommendations are applicable to individuals responsible for the care of people with COVID-19. These include health professionals, individuals providing support and education to people with COVID-19, and people with diagnosed or suspected COVID-19 themselves.

Individuals such as policymakers, practice managers, researchers and students may elect to use or adopt these recommendations for purposes other than the treatment of COVID-19; however these individuals do not represent the target audience. Additional considerations not addressed within this guideline are required when using these recommendations for any purpose other than for the treatment or support of individuals with COVID-19.

How to cite this guideline
3 - Methods and processes

**Methods and processes**
Information about the methods and processes used is described in the technical report.
Information about our governance structure and members' details is available here.
Our policy on the use of media statements, preprints and other non-peer-reviewed papers in formulating recommendations is available here.

**Conflicts of interest**
The policy for management of conflicts of interest and the template used for collecting the declarations of interest can be found on the website here and here.
Declarations of interest will soon be made available on the website.
### 4 - Definition of disease severity

#### 4.1 - Definition of disease severity for adults

<table>
<thead>
<tr>
<th>Consensus Recommendation</th>
<th>Adults not presenting any clinical features suggestive of moderate or severe disease or a complicated course of illness.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild illness</td>
<td></td>
</tr>
<tr>
<td>Characteristics:</td>
<td>• no symptoms</td>
</tr>
<tr>
<td></td>
<td>• or mild upper respiratory tract symptoms</td>
</tr>
<tr>
<td></td>
<td>• or cough, new myalgia or asthenia without new shortness of breath or a reduction in oxygen saturation</td>
</tr>
<tr>
<td>Moderate illness</td>
<td>Stable adult patient presenting with respiratory and/or systemic symptoms or signs. Able to maintain oxygen saturation above 92% (or above 90% for patients with chronic lung disease) with up to 4 L/min oxygen via nasal prongs.</td>
</tr>
<tr>
<td>Characteristics:</td>
<td>• prostration, severe asthenia, fever &gt; 38°C or persistent cough</td>
</tr>
<tr>
<td></td>
<td>• clinical or radiological signs of lung involvement</td>
</tr>
<tr>
<td></td>
<td>• no clinical or laboratory indicators of clinical severity or respiratory impairment</td>
</tr>
<tr>
<td>Severe illness</td>
<td>Adult patients meeting any of the following criteria:</td>
</tr>
<tr>
<td></td>
<td>• respiratory rate ≥ 30 breaths/min</td>
</tr>
<tr>
<td></td>
<td>• oxygen saturation ≤ 92% at a rest state</td>
</tr>
<tr>
<td></td>
<td>• arterial partial pressure of oxygen (PaO2)/ inspired oxygen fraction (FiO2) ≤ 300</td>
</tr>
<tr>
<td>Critical illness</td>
<td>Adult patient meeting any of the following criteria:</td>
</tr>
<tr>
<td></td>
<td>Respiratory failure</td>
</tr>
<tr>
<td></td>
<td>• Occurrence of severe respiratory failure (PaO2/FiO2 &lt; 200), respiratory distress or acute respiratory distress syndrome (ARDS). This includes patients deteriorating despite advanced forms of respiratory support (NIV, HFNO) OR patients requiring mechanical ventilation.</td>
</tr>
<tr>
<td>OR other signs of significant deterioration</td>
<td>• hypotension or shock</td>
</tr>
<tr>
<td></td>
<td>• impairment of consciousness</td>
</tr>
<tr>
<td></td>
<td>• other organ failure</td>
</tr>
</tbody>
</table>

**Adaptation**

The definitions of disease severity are adapted from published definitions from China [4], Italy [5] and Alfred Health (Melbourne) [6].
4.2 - Definition of disease severity for children and adolescents
Consensus Recommendation

These definitions apply to children under 16 years of age. Depending on the physical size and/or developmental status of the patient, either the paediatric or adult severity grading can be applied.

Cardiorespiratory and vital parameters must be considered within the normal age-appropriate ranges for neonates and children. If criteria fall across different severity classifications, use the more severe classification to manage illness.

<table>
<thead>
<tr>
<th>Mild illness</th>
<th>Feeding / hydration / conscious state</th>
<th>Respiratory / vital signs</th>
<th>Oxygen requirement[1]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal or mildly reduced feeding</td>
<td>No or mild upper respiratory tract symptoms OR No or mild work of breathing</td>
<td>No supplemental oxygen required to maintain SpO₂ &gt; 92%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate illness</th>
<th>Feeding / hydration / conscious state</th>
<th>Respiratory / vital signs</th>
<th>Oxygen requirement[1]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Poor feeding, unable to maintain hydration without nasogastric or IV fluids AND Normal conscious state</td>
<td>Moderate work of breathing OR Abnormal vital signs for age (tachycardia, tachypnoea) but does not persistently breach Early Warning (e.g. MET) Criteria[2] OR Brief self-resolving apnoea (infants)</td>
<td>Requires low-flow oxygen (nasal prongs or mask) to maintain SpO₂ &gt; 92%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severe illness</th>
<th>Feeding / hydration / conscious state</th>
<th>Respiratory / vital signs</th>
<th>Oxygen requirement[1]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Poor feeding, unable to maintain hydration without nasogastric or IV fluids OR Drowsy / tired but easily rousable</td>
<td>Moderate-severe work of breathing OR Abnormal vital signs for age (tachycardia, tachypnoea) with breaches of Early Warning / Medical Emergency Team criteria OR Apnoea needing support / stimulation (infants)</td>
<td>Requires high-flow oxygen at 2 L/kg/min[3] to maintain SpO₂ &gt; 92%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Critical illness</th>
<th>Feeding / hydration / conscious state</th>
<th>Respiratory / vital signs</th>
<th>Oxygen requirement[1]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Poor feeding, unable to maintain hydration without nasogastric or IV fluids OR Altered conscious state / unconscious</td>
<td>Unable to maintain breathing or prevent apnoea without advanced modes of support OR Abnormal vital signs for age with persistent breaches of Early Warning (e.g. MET) Criteria OR Haemodynamically unstable without inotropic or vasopressor support OR Other organ failure</td>
<td>Requires advanced modes of support to maintain oxygenation</td>
</tr>
</tbody>
</table>

High-flow nasal oxygen at > 2 L/kg/min[3] OR Non-invasive ventilation OR Intubation and mechanical ventilation OR Extracorporeal membrane
Oxygen saturation target should be modified for patients with cyanotic heart disease.

Temperature instability should be considered an abnormal vital sign in infants. Fever is common in children and does not contribute to determination of illness severity in isolation.

Preterm infants and neonates < 4 kg may be managed on high-flow nasal cannula oxygen at 2-8 L/min irrespective of weight.

Note: co-morbidities (e.g. preterm infants, oncology, immunosuppressed, etc.) may increase the risk of more severe disease.
5 - Monitoring and markers of clinical deterioration

5.1 - Monitoring and markers of clinical deterioration

Consensus Recommendation

For people with COVID-19, monitor markers of clinical progression, such as rapidly progressive respiratory failure and sepsis, especially on days 5 to 10 after onset of symptoms.

Adaptation

The recommendation for monitoring and markers of clinical deterioration is adapted from published recommendations by the World Health Organization [90], National Institute for the Infectious Diseases (Italy) [5] and Surviving Sepsis Campaign [88]. Wording has been adapted for clarity and applicability to the Australian context.
6 - Disease-modifying treatments

Several classes of therapies are currently under investigation to determine their effectiveness in treating COVID-19. These include, but are not limited to, antivirals (remdesivir, lopinavir and ritonavir), antimalarials (hydroxychloroquine and chloroquine), interleukin receptor agonists (tocilizumab and anakinra), corticosteroids and convalescent plasma. The categories of disease-modifying treatments being considered can be seen in the table below. We are continually monitoring new research for randomised trials that evaluate any disease-modifying treatments for COVID-19.

While national and international guidelines published early in the pandemic did not support the use of disease-modifying therapies in treating people with COVID-19 (except in the context of clinical trials), this is now changing as evidence for certain treatments emerges.

<table>
<thead>
<tr>
<th>Category</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agents that may have activity against SARS-CoV-2</td>
<td>Antimalarials</td>
</tr>
<tr>
<td>Agents that may have activity against the associated cytokine-release syndrome</td>
<td>Tocilizumab</td>
</tr>
<tr>
<td>Agents that may have activity against the associated cytokine-release syndrome</td>
<td>Anakinra (IL1RA)</td>
</tr>
<tr>
<td>Agents that may have activity against the associated cytokine-release syndrome</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Other and ancillary agents</td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>Blood purification systems for reducing cytokines in ICU</td>
<td>NSAIDs</td>
</tr>
<tr>
<td>Blood purification systems for reducing cytokines in ICU</td>
<td>Cytokine removal</td>
</tr>
</tbody>
</table>

6.1 - Dexamethasone

6.1.1 - Dexamethasone for adults

**Strong Recommendation**

Use dexamethasone 6 mg daily intravenously or orally for up to 10 days in **adults with COVID-19 who are receiving oxygen** (including mechanically ventilated patients).

Key Info

**Benefits and harms**

In patients receiving oxygen or invasive mechanical ventilation, all-cause mortality is reduced with dexamethasone.

The preliminary report of the trial does not include any data for adverse events or serious adverse events. However, the panel believes that the mortality benefit outweighs any potential harms that may be associated with adverse events despite these not being reported in the trial.

**Older people living with frailty or cognitive impairment**

People aged over 65 years were included in the trial but no details were reported for frailty or cognitive impairment. The proportion of people aged over 70 who were in the subgroup who received invasive mechanical ventilation was smaller than the overall proportion of people aged over 70 in the trial.

**People requiring palliative care**

In addition to the concerns in the general adult population, there is uncertainty regarding benefits and harms for people requiring palliative care as no details were reported in the trial for this population. In particular, the benefits of dexamethasone for the management of specific symptoms are uncertain.

**Certainty of the Evidence**

Certainty of the evidence for mortality in patients receiving oxygen or invasive mechanical ventilation is moderate based on the reliance on a single study. Patients, personnel involved in administering treatment and outcome assessors were not blinded.
due to a reduction in all-cause mortality, along with no important resource implications and the likely acceptability of the drug, we recommend dexamethasone for adults with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

however this is unlikely to affect the assessment of outcomes.

people requiring palliative care and older people living with frailty or cognitive impairment
people aged over 65 years were included in the trial but no details were reported for frailty or cognitive impairment. it is unclear whether people requiring palliative care were included in the trial.

preference and values
we have no systematically collected information regarding patients’ preferences and values. the panel believes that since there are mortality benefits most patients would opt for dexamethasone.

people requiring palliative care and older people living with frailty or cognitive impairment
additional variability may be expected in these populations given the potentially different preferences and values placed on outcomes and goals of care, such as symptom relief.

resources and other considerations

Dexamethasone is widely available and affordable. Use of dexamethasone in adults with COVID-19 who are receiving supplementary oxygen or invasive ventilation is unlikely to have an impact on availability of this drug for other indications.

equity
we have no systematically collected direct evidence regarding impact on equity. Since dexamethasone is widely available and affordable, no negative impact is expected.

acceptability
although we have no systematically collected evidence regarding acceptability, dexamethasone is likely to be acceptable to both patients and clinicians.

people requiring palliative care and older people living with frailty or cognitive impairment
acceptability may vary in these populations due to individual decision-making around goals of care.

feasibility
Dexamethasone is likely to be feasible because it is already widely used for other indications. There are no known issues with availability of this drug.

Rationale
Due to a reduction in all-cause mortality, along with no important resource implications and the likely acceptability of the drug, we recommend dexamethasone for adults with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

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Summary
Evidence indicates that dexamethasone probably decreases all-cause mortality in patients with COVID-19 who require oxygen or invasive mechanical ventilation. In contrast, dexamethasone in patients who do not require oxygen may lead to increased mortality.

Evidence informing this recommendation comes from a single, open-label randomised trial that compared dexamethasone plus usual care to usual care alone in 6425 hospitalised patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection [12]. Patients were originally restricted to adults 18 years of age or older, however this restriction was removed during recruitment. The mean age of patients was 67 years in the dexamethasone group and 66 years in the usual care group—the proportion of women was 36% in both groups.

Outcomes reported include 28-day mortality, duration of hospital stay, number discharged from hospital after 28 days, and number of patients requiring mechanical ventilation. The study has not yet reported on adverse events, serious adverse events or discontinuation of treatment due to adverse events.

Certainty of the evidence for all-cause mortality for patients not receiving oxygen is low. This judgement is based on serious imprecision due to the reliance on a single study and non-significant findings when the data were adjusted for age. Patients, personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect the assessment of this outcome.

Certainty of the evidence for all-cause mortality for patients receiving oxygen or receiving invasive mechanical ventilation is moderate. This judgement is based on reliance on a single study. Patients, personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect the assessment of this outcome. Certainty of the evidence for other outcomes (mechanical ventilation requirement, discharge from hospital, duration of hospital stay) is moderate.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality (patients who received no oxygen)</strong></td>
<td>Relative risk 1.27 (CI 95% 1 - 1.61) Based on data from 1,535 patients in 1 studies.</td>
<td><strong>140</strong> per 1000</td>
<td>Low Due to very serious imprecision</td>
<td>Dexamethasone may increase all-cause mortality in patients who receive no oxygen (total no of events = 234)</td>
</tr>
<tr>
<td>Within 28 days after commencing treatment</td>
<td></td>
<td><strong>178</strong> per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Critical</td>
<td></td>
<td>Difference: 38 more per 1000 ( CI 95% 0 fewer - 85 more )</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality (patients who received oxygen only)</strong></td>
<td>Relative risk 0.89 (CI 95% 0.76 - 1) Based on data from 3,883 patients in 1 studies.</td>
<td><strong>262</strong> per 1000</td>
<td>Moderate Due to only one study</td>
<td>Dexamethasone probably decreases all-cause mortality in patients who receive oxygen only (total no of events = 980)</td>
</tr>
<tr>
<td>Within 28 days after commencing treatment</td>
<td></td>
<td><strong>233</strong> per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Critical</td>
<td></td>
<td>Difference: 29 fewer per 1000 ( CI 95% 63 fewer - 0 fewer )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### All-cause mortality

**Patients who received invasive mechanical ventilation**

Within 28 days after commencing treatment

- **Relative risk:** 0.71 (CI 95% 0.58 - 0.86)
- **Based on data from:** 1,007 patients in 1 studies. (Randomized controlled)

<table>
<thead>
<tr>
<th>None</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>414</td>
<td>294</td>
</tr>
<tr>
<td>(per 1000)</td>
<td>(per 1000)</td>
</tr>
</tbody>
</table>

**Difference:** 120 fewer per 1000 (CI 95% 174 fewer - 58 fewer)

**Critical**

**Moderate**

**Due to only one study**

Dexamethasone probably decreases all-cause mortality in patients who receive invasive mechanical ventilation (total no of events = 378)

---

### Mechanical ventilation requirement or death

**Patients who received no oxygen**

Within 28 days after commencing treatment

- **Relative risk:** 1.19 (CI 95% 0.95 - 1.49)
- **Based on data from:** 1,535 patients in 1 studies. (Randomized controlled)

<table>
<thead>
<tr>
<th>None</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>155</td>
<td>184</td>
</tr>
<tr>
<td>(per 1000)</td>
<td>(per 1000)</td>
</tr>
</tbody>
</table>

**Difference:** 29 more per 1000 (CI 95% 8 fewer - 76 more)

**Critical**

**Low**

**Due to very serious imprecision**

Dexamethasone may have little or no difference on mechanical ventilation requirement or death in patients who receive no oxygen

---

### Mechanical ventilation requirement or death

**Patients who received oxygen only**

Within 28 days after commencing treatment

- **Relative risk:** 0.87 (CI 95% 0.79 - 0.96)
- **Based on data from:** 3,883 patients in 1 studies. (Randomized controlled)

<table>
<thead>
<tr>
<th>None</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>320</td>
<td>278</td>
</tr>
<tr>
<td>(per 1000)</td>
<td>(per 1000)</td>
</tr>
</tbody>
</table>

**Difference:** 42 fewer per 1000 (CI 95% 67 fewer - 13 fewer)

**Critical**

**Moderate**

**Due to only one study**

Dexamethasone probably decreases need for mechanical ventilation requirement

---

### Discharge from hospital

**Patients who received no oxygen**

Within 28 days after commencing treatment

- **Relative risk:** 0.96 (CI 95% 0.85 - 1.08)
- **Based on data from:** 1,007 patients in 1 studies. (Randomized controlled)

<table>
<thead>
<tr>
<th>None</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>804</td>
<td>772</td>
</tr>
<tr>
<td>(per 1000)</td>
<td>(per 1000)</td>
</tr>
</tbody>
</table>

**Difference:** 32 fewer per 1000 (CI 95% 121 fewer - 64 more)

**Low**

**Due to very serious imprecision**

Dexamethasone probably has little or no difference on discharge from hospital in patients who receive no oxygen

---

### Discharge from hospital

**Patients who**

Within 28 days after commencing treatment

- **Relative risk:** 1.15 (CI 95% 1.06 - 1.24)
- **Based on data from:** 3,883 patients in 1

<table>
<thead>
<tr>
<th>None</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>674</td>
<td>775</td>
</tr>
<tr>
<td>(per 1000)</td>
<td>(per 1000)</td>
</tr>
</tbody>
</table>

**Difference:** 101 fewer per 1000 (CI 95% 123 fewer - 69 more)

**Moderate**

**Due to only one study**

Dexamethasone probably increases discharge from hospital in patients who receive oxygen
### received oxygen only
Within 28 days after commencing treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline/comparator</th>
<th>Risk of bias</th>
<th>Imprecision</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Control arm of reference used for intervention</td>
<td>No serious</td>
<td>Very Serious</td>
<td>Only data from one study, Wide confidence intervals.</td>
</tr>
<tr>
<td>2.</td>
<td>Control arm of reference used for intervention</td>
<td>No serious</td>
<td>Serious</td>
<td>Only data from one study.</td>
</tr>
</tbody>
</table>

#### Imprecision: Very Serious.

#### Imprecision: Serious.

#### Imprecision: Serious.

#### Imprecision: Very Serious.

#### Imprecision: Serious.

#### Imprecision: Very Serious.

#### Imprecision: Serious.

### Discharge from hospital (patients who received invasive mechanical ventilation)
Within 28 days after commencing treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline/comparator</th>
<th>Risk of bias</th>
<th>Imprecision</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Control arm of reference used for intervention</td>
<td>No serious</td>
<td>Serious</td>
<td>Only data from one study.</td>
</tr>
</tbody>
</table>

#### Imprecision: Very Serious.

#### Imprecision: Serious.

#### Imprecision: Serious.

#### Imprecision: Very Serious.

#### Imprecision: Serious.

### Duration of hospital stay
Time to discharge after commencing treatment (Days)

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline/comparator</th>
<th>Risk of bias</th>
<th>Imprecision</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Control arm of reference used for intervention</td>
<td>No serious</td>
<td>Moderate</td>
<td>Due to only one study.</td>
</tr>
</tbody>
</table>

#### Imprecision: Moderate.

#### Imprecision: Moderate.

#### Imprecision: Moderate.

#### Imprecision: Moderate.

#### Imprecision: Moderate.

#### Imprecision: Moderate.

#### Imprecision: Moderate.

### Important

<table>
<thead>
<tr>
<th>Event</th>
<th>Difference</th>
<th>CI 95%</th>
<th>Reference</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 28 days after commencing treatment</td>
<td><strong>101 more</strong> per 1000 (CI 95% 40 more - 162 more)</td>
<td></td>
<td>oxygen only</td>
<td></td>
</tr>
</tbody>
</table>
Weak Recommendation Against

Do not routinely use dexamethasone to treat COVID-19 in adults who do not require oxygen.

Dexamethasone may still be considered for other evidence-based indications in people who have COVID-19.

Key Info

Benefits and harms

In patients who do not require oxygen, all-cause mortality may be higher with dexamethasone. The published preliminary report of the trial does not include any data for adverse events or serious adverse events.

Certainty of the Evidence

Certainty of the evidence for mortality in patients who do not require oxygen is low based on very serious imprecision due to the reliance on a single study and the difference in the relative risk when using adjusted versus non-adjusted analysis. Patients, personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect the assessment of outcomes.

Preference and values

We have no systematically collected information regarding patients’ preferences and values.

Resources and other considerations

There are no identified resource issues as the recommendation reflects usual care.

Equity

There are no identified equity issues as the recommendation reflects usual care.

Acceptability

We have no systematically collected evidence regarding acceptability.
Rationale
Evidence suggests that dexamethasone in patients with COVID-19 who do not require oxygen may increase the risk of all-cause mortality. We therefore recommend against dexamethasone in this population unless there is an alternative evidence-based indication for its use.

Clinical Question/ PICO
Population: Patients with COVID-19 who do not require oxygen
Intervention: Dexamethasone
Comparator: Standard Care

Summary
See summary for 'Patients with COVID-19 - Dexamethasone vs Standard care'.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Standard care</td>
<td>Dexamethasone</td>
<td></td>
</tr>
<tr>
<td>See evidence profile for 'Patients with COVID-19 - Dexamethasone vs Standard care'</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.1.2 - Dexamethasone for pregnant or breastfeeding women

**Strong Recommendation**

Use dexamethasone 6 mg daily intravenously or orally for up to 10 days in pregnant or breastfeeding women with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

Key Info

**Benefits and harms**

Substantial net benefits of the recommended alternative

In pregnant or breastfeeding women receiving oxygen or invasive mechanical ventilation, all-cause mortality may be reduced.
with dexamethasone.

The preliminary report of the trial does not include any data for adverse events or serious adverse events. However, the panel believes that the mortality benefit outweighs any potential harms that may be associated with adverse events despite these not being reported in the trial.

Dexamethasone is used for other clinical indications during pregnancy and is considered safe to use [14].

### Certainty of the Evidence

Certainty of the evidence for mortality in patients receiving oxygen or invasive mechanical ventilation is low based on the reliance on a single study and the fact that results are based on the general adult population. Patients, personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect the assessment of outcomes.

### Preference and values

We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women. The panel believes that since there are mortality benefits most women would opt for dexamethasone.

### Resources and other considerations

Dexamethasone is widely available and affordable. Use of dexamethasone in pregnant or breastfeeding women with COVID-19 who are receiving supplementary oxygen or invasive ventilation is unlikely to have an impact on availability of this drug for other indications.

### Equity

We have no systematically collected direct evidence regarding impact on equity. Since dexamethasone is widely available and affordable, no negative impact is expected.

### Acceptability

Although we have no systematically collected evidence regarding acceptability, dexamethasone is likely to be acceptable to both patients and clinicians.

### Feasibility

Dexamethasone is likely to be feasible because it is already widely used for other indications. There are no known issues with availability of this drug.

### Rationale

Due to a reduction in all-cause mortality, along with no important resource implications, the likely acceptability of the drug and that the evidence was judged to be applicable to pregnant and breastfeeding women, we recommend dexamethasone for pregnant and breastfeeding women with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

### Clinical Question/ PICO

- **Population:** Special populations with COVID-19 [adapted from general adult population]
- **Intervention:** Dexamethasone
Comparator: Standard care

Summary
Evidence informing this recommendation comes from a single open-label randomised trial that compared dexamethasone plus usual care with usual care alone in 6425 hospitalised patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection [12]. Trial participants were originally restricted to adults 18 years of age or older, although this restriction was removed during recruitment.

The mean age of patients was 67 years in the dexamethasone group and 66 years in the usual care group—the proportion of women was 36% in both groups. Pregnant and breastfeeding women were eligible and six were included in the analyses, however it is unclear to which treatment arm they were assigned. The evidence is judged to be applicable to pregnant and breastfeeding women, with consideration that dexamethasone is used in pregnancy for other indications.

Outcomes reported include 28-day mortality, duration of hospital stay, number discharged from hospital after 28 days, and number of patients requiring mechanical ventilation. The study has not yet reported on adverse events, serious adverse events or discontinuation of treatment due to adverse events.

Certainty of the evidence for all-cause mortality for special populations not receiving oxygen is very low. This judgement is based on serious imprecision due to the reliance on a single study, non-significant findings when the data were adjusted for age, and indirectness as the study involved general adult patients. Patients, personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect the assessment of this outcome.

Certainty of the evidence for special populations receiving oxygen or receiving invasive mechanical ventilation is low. This judgement is based on reliance on a single study and the fact that the study involved general adult patients. Patients, personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect the assessment of these outcomes.

Pregnant or breastfeeding women
The intervention regimen was oral or intravenous dexamethasone 6 mg once daily for 10 days. However, for pregnant or breastfeeding women the intervention regimen was oral prednisolone 40 mg or intravenous hydrocortisone 80 mg twice daily (it was permitted to switch between the two routes of administration according to clinical circumstances).

Dexamethasone is used for other clinical indications during pregnancy and is considered safe to use [14].

Children
The intervention regimen was oral or intravenous dexamethasone 6 mg once daily for 10 days for adults. However, the protocol stated a dose of 0.15 mg/kg/day to a maximum of 6 mg/day for children. Dexamethasone is well-established in children and adolescents for other indications.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality (patients who received no oxygen) Within 28 days after commencing treatment</td>
<td>Relative risk 1.27 (CI 95% 1 - 1.61) Based on data from 1,535 patients in 1 studies. ^1 (Randomized controlled)</td>
<td>140 per 1000</td>
<td>178 per 1000</td>
<td>Very Low Due to very serious imprecision and indirectness <strong>2</strong> Dexamethasone may increase all-cause mortality in patients who receive no oxygen (total no of events = 234)</td>
</tr>
</tbody>
</table>

9 Critical
<table>
<thead>
<tr>
<th>All-cause mortality (patients who received oxygen only)</th>
<th>Relative risk 0.89 (CI 95% 0.76 - 1) Based on data from 3,883 patients in 1 studies. (Randomized controlled)</th>
<th>262 per 1000</th>
<th>233 per 1000</th>
<th>Low</th>
<th>Due to only one study and serious indirectness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference: 29 fewer per 1000 (CI 95% 63 fewer - 0 fewer)</td>
<td></td>
<td></td>
<td></td>
<td>Dexamethasone probably decreases all-cause mortality in patients who receive oxygen only (total no of events = 980)</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Due to very serious imprecision. Due to serious indirectness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very Low</td>
<td>Due to very serious imprecision, Due to serious indirectness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Due to very serious imprecision, Due to serious indirectness</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Very Low</td>
<td>Due to very serious imprecision, Due to serious indirectness</td>
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<tr>
<td></td>
<td>Low</td>
<td>Due to very serious imprecision, Due to serious indirectness</td>
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<td></td>
<td>Very Low</td>
<td>Due to very serious imprecision, Due to serious indirectness</td>
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<tr>
<td></td>
<td>Low</td>
<td>Due to very serious imprecision, Due to serious indirectness</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Very Low</td>
<td>Due to very serious imprecision, Due to serious indirectness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Due to very serious imprecision, Due to serious indirectness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge from hospital (patients who received oxygen only)</td>
<td>Relative risk 0.96 (CI 95% 0.85 - 1.08) Based on data from 1,007 patients in 1 studies.</td>
<td>804 per 1000</td>
<td>772 per 1000</td>
<td>Very Low</td>
<td>Due to very serious imprecision, Due to serious indirectness</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Due to very serious imprecision, Due to serious indirectness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very Low</td>
<td>Due to very serious imprecision, Due to serious indirectness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Due to very serious imprecision, Due to serious indirectness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very Low</td>
<td>Due to very serious imprecision, Due to serious indirectness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Due to very serious imprecision, Due to serious indirectness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very Low</td>
<td>Due to very serious imprecision, Due to serious indirectness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scenario</td>
<td>Relative Risk</td>
<td>Difference</td>
<td>CI 95%</td>
<td>Significance</td>
<td>Indirectness</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>---------------</td>
<td>------------</td>
<td>--------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Discharge from hospital (patients who received oxygen only) Within 28 days after commencing treatment</td>
<td>Relative risk 1.15 (CI 95% 1.06 - 1.24) Based on data from 3,883 patients in 3 studies</td>
<td>Difference: 32 fewer per 1000 (CI 95% 121 fewer - 64 more)</td>
<td>Low Due to only one study and serious indirectness</td>
<td>Dexamethasone probably increases discharge from hospital in patients who receive oxygen only</td>
<td></td>
</tr>
<tr>
<td>Discharge from hospital (patients who received invasive mechanical ventilation) Within 28 days after commencing treatment</td>
<td>Relative risk 1.48 (CI 95% 1.16 - 1.9) Based on data from 1,535 patients in 1 studies</td>
<td>Difference: 101 more per 1000 (CI 95% 40 more - 162 more)</td>
<td>Low Due to only one study and serious indirectness</td>
<td>Dexamethasone probably increases discharge from hospital in patients who receive invasive mechanical ventilation</td>
<td></td>
</tr>
<tr>
<td>Duration of hospital stay Time to discharge after commencing treatment (Days)</td>
<td>13 (Median)</td>
<td>12 (Median)</td>
<td>Low Due to only one study and serious indirectness</td>
<td>Dexamethasone probably makes no difference to duration of hospital stay</td>
<td></td>
</tr>
</tbody>
</table>

2. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Very Serious.** Only data from one study, Wide confidence intervals.
4. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study.
Weak Recommendation Against

Do not routinely use dexamethasone to treat COVID-19 in pregnant or breastfeeding women who do not require oxygen.

Antenatal corticosteroids should still be used for fetal lung maturation in pregnant women at risk of preterm birth who also have COVID-19. Dexamethasone should still be used for other evidence-based indications in pregnant and breastfeeding women who have COVID-19.

Key Info

Benefits and harms

In pregnant or breastfeeding women who do not require oxygen, all-cause mortality may be increased with dexamethasone. The preliminary report of the trial does not include any data for adverse events or serious adverse events.

Certainty of the Evidence

Certainty of the evidence for mortality in patients who do not require oxygen is low based on very serious imprecision due to the reliance on a single study, the difference in the relative risk when using adjusted versus non-adjusted analysis, and indirectness due to the results being based on the general adult population. Patients, personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect the assessment of outcomes.
Evidence suggests that dexamethasone in pregnant and breastfeeding women with COVID-19 who do not require oxygen may increase the risk of all-cause mortality. We therefore recommend against dexamethasone in this population unless there is an alternative evidence-based indication for its use.

### Preference and values
We have no systematically collected information regarding preferences and values of pregnant or breastfeeding women.

### Resources and other considerations
There are no identified resource issues as the recommendation reflects usual care.

### Equity
There are no identified equity issues as the recommendation reflects usual care.

### Acceptability
We have no systematically collected evidence regarding acceptability.

### Feasibility
There are no identified feasibility issues as the recommendation reflects usual care.

### Rationale
Evidence suggests that dexamethasone in pregnant and breastfeeding women with COVID-19 who do not require oxygen may increase the risk of all-cause mortality. We therefore recommend against dexamethasone in this population unless there is an alternative evidence-based indication for its use.

### Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women with COVID-19 who do not require oxygen [adapted from general adult population]</td>
<td>Dexamethasone</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

### Summary
See summary for ‘Special populations with COVID-19 [adapted from general population] - Dexamethasone vs Standard care’.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Standard care</td>
<td>Dexamethasone</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

See summary
6.1.3 - Dexamethasone for children or adolescents

**Weak Recommendation**

Consider using dexamethasone daily intravenously or orally for up to 10 days in children and adolescents with COVID-19 who are receiving oxygen (including mechanically ventilated).

*A dose of 6 mg daily was used for adults. The protocol stated a dose of 0.15 mg/kg/day to a maximum of 6 mg/day for children but it is unclear how many children were included in the trial.*

**Key Info**

<table>
<thead>
<tr>
<th>Benefits and harms</th>
<th>Substantial net benefits of the recommended alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>In adult patients receiving oxygen or invasive mechanical ventilation, all-cause mortality is reduced with dexamethasone. It is unclear if any children were included in the trial, therefore there is uncertainty regarding the benefits and harms in this population. The drug is well established in children and adolescents for other indications.</td>
<td></td>
</tr>
<tr>
<td>The preliminary report of the trial does not include any data for adverse events or serious adverse events. However, the panel believes that the mortality benefit outweighs any potential harms that may be associated with adverse events despite these not being reported in the trial.</td>
<td></td>
</tr>
</tbody>
</table>

**Certainty of the Evidence**

Certainty of the evidence for reduction of mortality in children or adolescents receiving oxygen or invasive mechanical ventilation is low based on the reliance on a single study and the uncertainty regarding the inclusion of children and adolescents. The mean age of study participants was 66 years. Patients, personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect the assessment of outcomes.

**Preference and values**

We have no systematically collected information regarding the preferences and values of parents, carers or patients. The panel believes that since there are mortality benefits and well-known safety and adverse effects profiles in children, most parents, carers or patients would opt for dexamethasone.

**Resources and other considerations**

Dexamethasone is widely available and affordable. Use of dexamethasone in children and adolescents with COVID-19 who are receiving supplementary oxygen or invasive ventilation is unlikely to have an impact on availability of this drug for other indications.

**Equity**

We have no systematically collected direct evidence regarding impact on equity. Since dexamethasone is widely available and affordable, no negative impact is expected.

**Acceptability**

Although we have no systematically collected evidence regarding acceptability, dexamethasone is likely to be acceptable to parents, carers, patients and clinicians.
Due to a reduction in all-cause mortality, along with no important resource implications and the likely acceptability of the drug, we recommend dexamethasone be considered for children and adolescents with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

Given it is unclear if any children were included in the dexamethasone arm, and given the different phenotype of COVID-19 in children and adolescents compared to adults, the panel decided not to upgrade to a strong recommendation for dexamethasone use in this population until further evidence becomes available.

Clinical Question/ PICO

**Population:** Special populations with COVID-19 [adapted from general adult population]

**Intervention:** Dexamethasone

**Comparator:** Standard care

**Summary**

Evidence informing this recommendation comes from a single open-label randomised trial that compared dexamethasone plus usual care with usual care alone in 6425 hospitalised patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection [12]. Trial participants were originally restricted to adults 18 years of age or older, although this restriction was removed during recruitment.

The mean age of patients was 67 years in the dexamethasone group and 66 years in the usual care group—the proportion of women was 36% in both groups. Pregnant and breastfeeding women were eligible and six were included in the analyses, however it is unclear to which treatment arm they were assigned. The evidence is judged to be applicable to pregnant and breastfeeding women, with consideration that dexamethasone is used in pregnancy for other indications.

Outcomes reported include 28-day mortality, duration of hospital stay, number discharged from hospital after 28 days, and number of patients requiring mechanical ventilation. The study has not yet reported on adverse events, serious adverse events or discontinuation of treatment due to adverse events.

Certainty of the evidence for all-cause mortality for special populations not receiving oxygen is very low. This judgement is based on serious imprecision due to the reliance on a single study, non-significant findings when the data were adjusted for age, and indirectness as the study involved general adult patients. Patients, personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect the assessment of this outcome.

Certainty of the evidence for special populations receiving oxygen or receiving invasive mechanical ventilation is low. This judgement is based on reliance on a single study and the fact that the study involved general adult patients. Patients, personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect the assessment of these outcomes.

**Pregnant or breastfeeding women**

The intervention regimen was oral or intravenous dexamethasone 6 mg once daily for 10 days. However, for pregnant or breastfeeding women the intervention regimen was oral prednisolone 40 mg or intravenous hydrocortisone 80 mg twice daily (it was permitted to switch between the two routes of administration according to clinical circumstances).

Dexamethasone is used for other clinical indications during pregnancy and is considered safe to use [14].

**Children**

The intervention regimen was oral or intravenous dexamethasone 6 mg once daily for 10 days for adults. However, the protocol stated a dose of 0.15 mg/kg/day to a maximum of 6 mg/day for children. Dexamethasone is well-established in the clinical care of children with COVID-19.
children and adolescents for other indications.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality (patients who received no oxygen)</strong> Within 28 days after commencing treatment</td>
<td>Relative risk 1.27 (CI 95% 1 - 1.61) Based on data from 1,535 patients in 1 studies. (Randomized controlled)</td>
<td>140 per 1000</td>
<td>Very Low Due to very serious imprecision and indirectness</td>
<td>Dexamethasone may increase all-cause mortality in patients who receive no oxygen (total no of events = 234)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>178 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difference: 38 more per 1000 (CI 95% 0 fewer - 85 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality (patients who received oxygen only)</strong> Within 28 days after commencing treatment</td>
<td>Relative risk 0.89 (CI 95% 0.76 - 1) Based on data from 3,883 patients in 1 studies. (Randomized controlled)</td>
<td>262 per 1000</td>
<td>Low Due to only one study and serious indirectness</td>
<td>Dexamethasone probably decreases all-cause mortality in patients who receive oxygen only (total no of events = 980)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>233 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difference: 29 fewer per 1000 (CI 95% 63 fewer - 0 fewer)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality (patients who received invasive mechanical ventilation)</strong> Within 28 days after commencing treatment</td>
<td>Relative risk 0.71 (CI 95% 0.58 - 0.86) Based on data from 1,007 patients in 1 studies. (Randomized controlled)</td>
<td>414 per 1000</td>
<td>Low Due to only one study and serious indirectness</td>
<td>Dexamethasone probably decreases all-cause mortality in patients who receive invasive mechanical ventilation (total no of events = 378)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>294 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difference: 120 fewer per 1000 (CI 95% 174 fewer - 58 fewer)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mechanical ventilation requirement or death (patients who received no oxygen)</strong> Within 28 days after commencing</td>
<td>Relative risk 1.19 (CI 95% 0.95 - 1.49) Based on data from 1,535 patients in 1 studies. (Randomized controlled)</td>
<td>155 per 1000</td>
<td>Very Low Due to very serious imprecision. Due to serious indirectness</td>
<td>Dexamethasone may have little or no difference on mechanical ventilation requirement or death in patients who receive no oxygen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>184 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difference: 29 more per 1000 (CI 95% 8 fewer - 76 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Relative Risk</td>
<td>Difference</td>
<td>Level</td>
<td>Imprecision/Indirectness</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>---------------</td>
<td>------------</td>
<td>---------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Mechanical ventilation requirement or death (patients who received oxygen only) Within 28 days after commencing treatment</td>
<td>0.87 (CI 0.79 - 0.96)</td>
<td>42 fewer per 1000</td>
<td>Low</td>
<td>Due to only one study and serious indirectness</td>
</tr>
<tr>
<td>Discharge from hospital (patients who received no oxygen) Within 28 days after commencing treatment</td>
<td>0.96 (CI 0.85 - 1.08)</td>
<td>32 fewer per 1000</td>
<td>Very Low</td>
<td>Due to very serious imprecision, Due to serious indirectness</td>
</tr>
<tr>
<td>Discharge from hospital (patients who received oxygen only) Within 28 days after commencing treatment</td>
<td>1.15 (CI 1.06 - 1.24)</td>
<td>101 more per 1000</td>
<td>Low</td>
<td>Due to only one study and serious indirectness</td>
</tr>
<tr>
<td>Discharge from hospital (patients who received invasive mechanical ventilation) Within 28 days after commencing treatment</td>
<td>1.48 (CI 1.16 - 1.9)</td>
<td>112 more per 1000</td>
<td>Low</td>
<td>Due to only one study and serious indirectness</td>
</tr>
</tbody>
</table>
### Duration of Hospital Stay

**Time to discharge after commencing treatment (Days)**

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Median</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>13</td>
<td>12</td>
<td>Due to only one study and serious indirectness</td>
</tr>
<tr>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Low due to only one study and serious indirectness.

Dexamethasone probably makes no difference to duration of hospital stay.

---

2. **Indirectness**: Serious. Differences between the population of interest and those studied. **Imprecision**: Very Serious. Only data from one study. Wide confidence intervals.
4. **Indirectness**: Serious. Differences between the population of interest and those studied. **Imprecision**: Serious. Only data from one study.
6. **Risk of bias**: No serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness**: Serious. Differences between the population of interest and those studied. **Imprecision**: Serious. Only data from one study.
7. Primary study[12]. **Baseline/comparator**: Control arm of reference used for intervention.
8. **Risk of bias**: No serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness**: Serious. Differences between the population of interest and those studied. **Imprecision**: Very Serious. Only data from one study.
10. **Risk of bias**: No serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness**: Serious. Differences between the population of interest and those studied. **Imprecision**: Serious. Only data from one study.
11. Primary study[12]. **Baseline/comparator**: Control arm of reference used for intervention.
12. **Indirectness**: Serious. Differences between the population of interest and those studied. **Imprecision**: Very Serious. Only data from one study.
13. Primary study[12]. **Baseline/comparator**: Control arm of reference used for intervention.
14. **Indirectness**: Serious. Differences between the population of interest and those studied. **Imprecision**: Serious. Only data from one study.
15. Primary study[12]. **Baseline/comparator**: Control arm of reference used for intervention.
16. **Indirectness**: Serious. Differences between the population of interest and those studied. **Imprecision**: Serious. Only data from one study.
17. **Risk of bias**: No serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness**: Serious. Differences between the population of interest and those studied. **Imprecision**: Serious. Only data from one study.
Weak Recommendation Against

Do not routinely use dexamethasone to treat COVID-19 in **children or adolescents who do not require oxygen**.

*Dexamethasone should still be used for other evidence-based indications in children or adolescents who have COVID-19.*

---

**Key Info**

**Benefits and harms**

In adult patients who do not require oxygen, all-cause mortality may be higher with dexamethasone. The preliminary report of the trial does not include any data for adverse events or serious adverse events. It is unclear if any children were included in the trial, therefore there is uncertainty regarding the benefits in this population but there are known potential adverse effects.

**Certainty of the Evidence**

Certainty of the evidence for mortality in patients who do not require oxygen is low based on very serious imprecision due to the reliance on a single study, the difference in the relative risk when using adjusted versus non-adjusted analysis, and indirectness due to the results being based on the general adult population. Patients, personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect the assessment of outcomes.

**Preference and values**

We have no systematically collected information regarding the preferences and values of parents, carers or patients.

**Resources and other considerations**

There are no identified resource issues as the recommendation reflects usual care.

**Equity**

There are no identified equity issues as the recommendation reflects usual care.

**Acceptability**

We have no systematically collected evidence regarding acceptability.

**Feasibility**

There are no identified feasibility issues as the recommendation reflects usual care.

**Rationale**

Evidence from an adult population suggests that dexamethasone in people with COVID-19 who do not require oxygen may increase the risk of all-cause mortality. We therefore recommend against dexamethasone in children or adolescents unless there is an alternative evidence-based indication for its use.
6.2 - Remdesivir

6.2.1 - Remdesivir for adults

**Weak Recommendation**

Whenever possible remdesivir should be administered in the context of a randomised trial with appropriate ethical approval. Use of remdesivir for adults with moderate, severe or critical COVID-19 outside of a trial setting may be considered.

The inclusion in these studies of older people or those requiring palliative care is uncertain. Until further evidence in these populations is available, the Taskforce does not believe a different recommendation should apply, unless contraindicated.

Due to antagonism observed in vitro, concomitant use of remdesivir with chloroquine or hydroxychloroquine is not recommended [22].

For information on dosages, length of treatment and characteristics of the patients in the trials used for this recommendation, see the Practical info tab below.

**Practical Info**

**Treatment**

In the two trials where remdesivir was compared to placebo (Beigel 2020, Wang 2020), it was given as a daily intravenous infusion (200 mg initial dose, 100 mg maintenance) for 10 days. A third trial (Goldman 2020) compared a 10-day to a 5-day course of remdesivir but the magnitude of benefit remains uncertain for this treatment strategy. Given that the positive signal for benefit is only apparent in one trial with a 10-day course (Beigel 2020), we suggest considering this length of treatment until further evidence...
becomes available.

**Key inclusion criteria**
- >18 years of age (Beigel 2020, Wang 2020), >12 years of age (Goldman 2020)
- Laboratory-confirmed SARS-CoV-2 infection (positive RT-PCR)
- Clinical
  - Beigel 2020 [18]
    - Hospitalised with symptoms suggestive of COVID-19 AND one of the following criteria suggestive of lower respiratory tract infection:
      - Radiographic infiltrates by imaging study
      - Peripheral oxygen saturation (SpO2) ≤ 94% on room air
      - Requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)
  - Goldman 2020 [21]
    - Radiographic infiltrates by imaging study
    - Peripheral oxygen saturation (SpO2) ≤ 94% on room air or receiving supplemental oxygen
  - Wang 2020 [72]
    - Pneumonia confirmed by chest imaging AND
    - Oxygen saturation of ≤ 94% on room air OR a ratio of arterial oxygen partial pressure to fractional inspired oxygen of ≤ 300 mm Hg
- Duration of symptoms
  - Beigel 2020: no limit to the duration of symptoms before enrolment
  - Wang 2020: within 12 days of symptom onset
  - Goldman 2020: not specified, confirmed SARS-CoV-2 (positive RT-PCR) within 4 days of randomisation

**Key exclusion criteria**
- Pregnancy or breastfeeding
- An alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) > 5 times the upper limit of the normal range (Beigel 2020, Goldman 2020)
- Hepatic cirrhosis (Wang 2020 only)
- Impaired renal function (estimated glomerular filtration rate < 30 mL/min per 1.73 m²) or receipt of continuous renal replacement therapy, haemodialysis (Goldman 2020, Wang 2020) or peritoneal dialysis (Wang 2020).
- Allergy to study drug (Beigel 2020)
- Patients who were receiving mechanical ventilation and extracorporeal membrane oxygenation (ECMO) at screening (Goldman 2020)
- Patients with signs of multiorgan failure (Goldman 2020)
- Patients receiving concurrent treatment (within 24 hours before the start of trial treatment) with other agents with putative activity against COVID-19 (Goldman 2020)

**Severity at baseline**

**Beigel 2020**

1063 patients

Baseline score on 8-category scale
1. Not hospitalised, no limitations of activities: n=0 (0%)
2. Not hospitalised, limitation of activities, home oxygen requirement, or both: n=0 (0%)
3. Hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalisation was extended for infection-control reasons): n=0 (0%)
4. Hospitalised, not requiring supplemental oxygen, requiring ongoing medical care (COVID-19-related or otherwise): n=127 (12%)
5. Hospitalised, requiring supplemental oxygen: n=421 (40%)
6. Hospitalised, receiving noninvasive ventilation or high-flow oxygen devices: n=197 (19%)
7. Hospitalised, receiving invasive mechanical ventilation or ECMO: n=272 (26%)
8. Death: n=0 (0%)

Baseline score missing n=46 (4%)

**Wang 2020**

236 patients

Day 1 score on 6-category scale
1. Discharged or having reached discharge criteria (defined as clinical recovery—i.e. normalisation of pyrexia, respiratory rate < 24
breaths per minute, saturation of peripheral oxygen > 94% on room air, and relief of cough, all maintained for at least 72 hrs; n=0 (0%)
2. Hospital admission, not requiring supplemental oxygen: n=3 (1%)
3. Hospital admission, requiring supplemental oxygen: n=194 (82%)
4. Hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation: n=37 (16%)
5. Hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation: n=1 (< 1%)
6. Death: n=1 (< 1%)

Goldman 2020
397 patients
Baseline score on a 7-category scale
1. Death: n=0 (0%) for both groups
2. Receiving invasive mechanical ventilation or ECMO: 5-day group n=4 (2%); 10-day group n=9 (5%)
3. Receiving noninvasive ventilation or high-flow oxygen: 5-day group n=49 (24%); 10-day group n=60 (30%)
4. Receiving low-flow supplemental oxygen: 5-day group n=113 (56%); 10-day group n=107 (54%)
5. Not receiving supplemental oxygen but requiring medical care: 5-day group n=34 (17%); 10-day group n=21 (11%)
6. Hospitalised, requiring neither supplemental oxygen nor ongoing medical care: n=0 (0%) for both groups
7. Not hospitalised: n=0 (0%) for both groups

Key Info

Benefits and harms
The two trials of remdesivir versus standard care provide preliminary evidence suggesting that remdesivir as a 10-day treatment has an acceptable safety profile. However, there remains uncertainty around the benefits and harms of remdesivir for patients with COVID-19. A third trial that compared a 10-day course to a 5-day course was too uncertain to inform decisions regarding length of treatment at this point.

Older people living with frailty or cognitive impairment
People aged over 65 years were included in the trials but no details were reported for frailty or cognitive impairment.

People requiring palliative care
In addition to the concerns in the general adult population, there is uncertainty regarding benefits and harms for people requiring palliative care as no details were reported in the trials for this population. In particular, the benefits for symptom management are uncertain.

Certainty of the Evidence
Certainty of the evidence for most reported outcomes is low or very low due to serious risk of bias and either serious imprecision or inconsistency in the direction of effect between studies. The exception is serious adverse events, which is considered to be of moderate certainty.

People requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, there is more uncertainty due to lack of information on whether these populations were included in the trials.

Preference and values
We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients may prefer to wait while other patients may be more willing to opt for remdesivir.

People requiring palliative care and older people living with frailty or cognitive impairment
Additional variability may be expected in these populations given the potentially different preferences and values placed on outcomes and goals for care, such as symptom relief.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. At this point, remdesivir remains an experimental therapy.
The effect of remdesivir on mortality is uncertain but it may decrease the time to recovery. Because of this the Taskforce gives a conditional recommendation for the use of remdesivir both within and outside the context of a randomised trial.

The populations in the three studies published to date approximate to the moderate, severe and critical illness categories outlined in these guidelines [18][21][72]. The studies had insufficient power to perform adequate subgroup analyses. Beigel 2020, however, reported small numerical differences between study arms in the outcomes of patients with critical COVID-19, but no statistically significant difference in the primary outcome (time to recovery) by baseline disease severity. The Taskforce recommendation to consider use of remdesivir outside of a randomised trial therefore applies to adult patients with moderate, severe or critical COVID-19.

Goldman 2020 compared a 5-day to a 10-day course of treatment, but since there is no established benefit for either approach yet, it remains uncertain that these results can inform the length of treatment.

Equity

There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. Inequity may be further exacerbated in individuals who are eligible for treatment based on compassionate grounds due to factors that may limit access (such as geographic area).

Acceptability

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

People requiring palliative care and older people living with frailty or cognitive impairment

Because the benefit to harm ratio is uncertain, the acceptability may vary in these populations due to individual decision making around goals of care.

Feasibility

On 10 July, the Therapeutic Goods Administration granted provisional approval to use remdesivir in hospitalised adults with severe COVID-19 symptoms (requiring oxygen or high-level support to breathe).

Implementability may be limited by the current arrangements for accessing remdesivir, in terms of the total number of doses available and more general criteria (such as geographic area).

Rationale

The effect of remdesivir on mortality is uncertain but it may decrease the time to recovery. Because of this the Taskforce gives a conditional recommendation for the use of remdesivir both within and outside the context of a randomised trial.

The populations in the three studies published to date approximate to the moderate, severe and critical illness categories outlined in these guidelines [18][21][72]. The studies had insufficient power to perform adequate subgroup analyses. Beigel 2020, however, reported small numerical differences between study arms in the outcomes of patients with critical COVID-19, but no statistically significant difference in the primary outcome (time to recovery) by baseline disease severity. The Taskforce recommendation to consider use of remdesivir outside of a randomised trial therefore applies to adult patients with moderate, severe or critical COVID-19.

Goldman 2020 compared a 5-day to a 10-day course of treatment, but since there is no established benefit for either approach yet, it remains uncertain that these results can inform the length of treatment.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>People with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Remdesivir</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

Summary

Evidence informing this recommendation comes from two randomised trials that compared remdesivir to placebo in patients with COVID-19 [18][72]. One study included 1063 patients with moderate to critical illness [18] and the other included 236 patients with severe to critical illness [72]. In both studies, randomisation was stratified by the level of disease severity, and
in particular whether respiratory support was required.

Certainty of the evidence for most outcomes is low (all-cause mortality at day 14 and 28, respiratory failure or ARDS, time to recovery and adverse events) or very low (septic shock, clinical recovery and adverse events leading to discontinuation). The exception is serious adverse events, which is of moderate certainty. These judgements are based on lack of personnel blinding [18] (which is considered of no relevance in mortality) and either serious imprecision (due to low number of patients and/or observed events, reliance on a single study or wide confidence intervals) or inconsistency in the direction of effect between studies.

It is important to note that Beigel 2020 [18] provides preliminary results only and does not provide data for 28-day mortality. As such, this study will remain under surveillance and additional results will be included when they become available.

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [16].

Based on the available evidence, it remains uncertain as to whether remdesivir is more effective and safer than placebo in treating patients with COVID-19.

### Table: Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality (Day 14)</td>
<td>During treatment (14 days)</td>
<td>Relative risk 0.71 (CI 95% 0.39 - 1.28) Based on data from 1,290 patients in 2 studies. ¹ (Randomized controlled)</td>
<td>Placebo: 102 per 1000</td>
<td>Low Due to serious imprecision and inconsistency ²</td>
<td>Remdesivir may decrease all-cause mortality slightly (day 14; total no of events = 108)</td>
</tr>
<tr>
<td>All-cause mortality (Day 28)</td>
<td>During treatment (28 days)</td>
<td>Relative risk 1.09 (CI 95% 0.54 - 2.18) Based on data from 236 patients in 1 studies. ³ (Randomized controlled)</td>
<td>Placebo: 128 per 1000</td>
<td>Low Due to very serious imprecision ⁴</td>
<td>We are uncertain whether remdesivir increases or decreases all-cause mortality (day 28; total no of events = 32)</td>
</tr>
<tr>
<td>Respiratory failure or ARDS</td>
<td>During treatment (28 days)</td>
<td>Relative risk 0.84 (CI 95% 0.47 - 1.53) Based on data from 1,296 patients in 2 studies. ⁵ (Randomized controlled)</td>
<td>Placebo: 117 per 1000</td>
<td>Low Due to serious imprecision and inconsistency ⁶</td>
<td>We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (total no of events = 132)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>During treatment</td>
<td>Relative risk 1.02 (CI 95% 0.34 - 3.01)</td>
<td>Placebo: 10</td>
<td>Very Low Due to serious</td>
<td>We are uncertain whether remdesivir</td>
</tr>
</tbody>
</table>
### Clinical recovery (Day 28)
**During treatment (28 days)**
- **Relative risk**: 0.86 (CI 95% 0.46 - 1.64)
- **Difference**: 538 fewer per 1000 (CI 95% 291 fewer - 344 more)
- **Risk of bias**: Very Low (Due to serious risk of bias and very serious inconsistency)
- **We are uncertain whether remdesivir improves or worsens clinical recovery (day 28)**

### Serious adverse events
**Number of patients experiencing one or more serious adverse events**
- **Relative risk**: 0.77 (CI 95% 0.63 - 0.94)
- **Difference**: 268 fewer per 1000 (CI 95% 99 fewer - 16 fewer)
- **Risk of bias**: Moderate (Due to serious risk of bias)
- **Remdesivir probably decreases serious adverse events slightly (total no of events = 303)**

### Adverse events
**Number of patients experiencing one or more adverse events**
- **Relative risk**: 0.94 (CI 95% 0.8 - 1.11)
- **Difference**: 370 fewer per 1000 (CI 95% 74 fewer - 41 more)
- **Risk of bias**: Low (Due to serious risk of bias and inconsistency)
- **We are uncertain whether remdesivir increases or decreases adverse events**

### Adverse events leading to discontinuation
**During treatment (28 days)**
- **Relative risk**: 1.29 (CI 95% 0.58 - 2.86)
- **Difference**: 67 more per 1000 (CI 95% 28 fewer - 125 more)
- **Risk of bias**: Very Low (Due to serious risk of bias, imprecision and inconsistency)
- **We are uncertain whether remdesivir increases or decreases adverse events leading to discontinuation**

### Time to recovery (Days)
- **Measured by**: Rate ratio 1.32 (1.12 to 1.55)
- **Based on data from: 607 patients in 1 studies.**
- **Follow up 28 days**
- **Low (Due to serious risk of bias and imprecision)**
- **Remdesivir may decrease time to recovery by a few days**

### Time to improvement (Days)
- **Measured by**: Hazard ratio 1.23 (0.87 to 1.75)
- **Low (Due to serious risk of bias and)**
- **Remdesivir may decrease time to improvement slightly**

2. **Inconsistency**: Serious. The direction of the effect is not consistent between the included studies. **Imprecision**: Serious. Wide confidence intervals.


4. **Imprecision**: Very Serious. Low number of patients, Only data from one study.


6. **Inconsistency**: Serious. The direction of the effect is not consistent between the included studies. **Imprecision**: Serious. Wide confidence intervals.


8. **Risk of bias**: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency**: Serious. The direction of the effect is not consistent between the included studies. **Imprecision**: Serious. Wide confidence intervals.


10. **Risk of bias**: Serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency**: Very Serious. The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies. The direction of the effect is not consistent between the included studies.


12. **Risk of bias**: Serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias.


14. **Risk of bias**: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency**: Serious. The direction of the effect is not consistent between the included studies.


16. **Risk of bias**: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Imprecision**: Serious. Wide confidence intervals.

17. Systematic review with included studies: [18]. **Baseline/comparator**: Control arm of reference used for intervention.

18. **Risk of bias**: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision**: Serious. Only data from one study.

19. Primary study[72]. **Baseline/comparator**: Control arm of reference used for intervention.

20. **Risk of bias**: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision**: Serious. Only data from one study.
Clinical Question/ PICO

**Population:** Special populations with COVID-19  
**Intervention:** Remdesivir  
**Comparator:** Placebo

Summary

Evidence informing this recommendation comes from two randomised trials that compared remdesivir to placebo in patients with COVID-19 [15][51]. One study included 1063 patients with moderate to critical illness [15] and the other included 236 patients with severe to critical illness [51]. In both studies, randomisation was stratified by the level of disease severity, and in particular whether respiratory support was required.

Certainty of the evidence for most outcomes is low (all-cause mortality at day 14 and 28, respiratory failure or ARDS, time to recovery and adverse events) or very low (septic shock, clinical recovery and adverse events leading to discontinuation). The exception is serious adverse events, which is of moderate certainty. These judgements are based on lack of personnel blinding [15] (which is considered of no relevance in mortality) and either serious imprecision (due to low number of patients and/or observed events, reliance on a single study or wide confidence intervals) or inconsistency in the direction of effect between studies.

It is important to note that Beigel 2020 [15] provides preliminary results only and does not provide data for 28-day mortality. As such, this study will remain under surveillance and additional results will be included when they become available.

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [13].

Based on the available evidence, it remains uncertain as to whether remdesivir is more effective and safer than placebo in treating patients with COVID-19.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
</table>
| All-cause mortality (Day 14)  
During treatment (14 days)  
9 Critical | Relative risk 0.71 (CI 95% 0.39 - 1.28)  
Based on data from 1,290 patients in 2 studies.  
(Randomized controlled) | **102**  
per 1000  
**72**  
per 1000  
Difference: **30 fewer**  
per 1000  
( CI 95% 62 fewer - 29 more ) | Very Low  
Due to serious imprecision, indirectness and inconsistency  
(95% CI 59 fewer - 151 more ) | Remdesivir may decrease all-cause mortality slightly (day 14; total no of events = 108) |
| All-cause mortality (Day 28)  
During treatment (28 days)  
9 Critical | Relative risk 1.09 (CI 95% 0.54 - 2.18)  
Based on data from 236 patients in 1 study.  
(Randomized controlled) | **128**  
per 1000  
**140**  
per 1000  
Difference: **12 more**  
per 1000  
( CI 95% 59 fewer - 151 more ) | Very Low  
Due to very serious imprecision and indirectness  
(95% CI 59 fewer - 151 more ) | We are uncertain whether remdesivir increases or decreases all-cause mortality (day 28; total no of events = 32) |
<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
<th>CI 95%</th>
<th>Baseline Events</th>
<th>Randomized Controlled</th>
<th>Difference</th>
<th>Imprecision, Indirectness and Inconsistency</th>
<th>Risk of Bias, Indirectness and Inconsistency</th>
<th>Risk of Bias, Indirectness and Inconsistency</th>
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<tbody>
<tr>
<td><strong>Respiratory failure or ARDS</strong> During treatment (28 days)</td>
<td>0.84</td>
<td>0.47 - 1.53</td>
<td>1,296 patients</td>
<td>2 studies</td>
<td>19 fewer</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (total no of events = 132)</td>
<td></td>
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</tr>
<tr>
<td><strong>Septic shock</strong> During treatment (28 days)</td>
<td>1.02</td>
<td>0.34 - 3.01</td>
<td>1,296 patients</td>
<td>2 studies</td>
<td>0 fewer</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir increases or decreases septic shock (total no of events = 13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical recovery (Day 28)</strong> During treatment (28 days)</td>
<td>0.86</td>
<td>0.46 - 1.64</td>
<td>1,289 patients</td>
<td>2 studies</td>
<td>75 fewer</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir improves or worsens clinical recovery (day 28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serious adverse events</strong> Number of patients experiencing one or more serious adverse events</td>
<td>0.77</td>
<td>0.63 - 0.94</td>
<td>1,296 patients</td>
<td>2 studies</td>
<td>62 fewer</td>
<td>Low</td>
<td>Remdesivir probably decreases serious adverse events slightly (total no of events = 303)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong> Number of patients experiencing one or more adverse events</td>
<td>0.94</td>
<td>0.8 - 1.11</td>
<td>1,296 patients</td>
<td>2 studies</td>
<td>22 fewer</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir increases or decreases adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events leading to discontinuation</strong></td>
<td>1.29</td>
<td>0.58 - 2.86</td>
<td>1,296 patients</td>
<td>2 studies</td>
<td>19 more</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir increases or decreases adverse events leading to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During treatment (28 days)</td>
<td>Time to recovery (Days)</td>
<td>Time to improvement (Days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>6 Important</td>
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<td>6 Important</td>
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</tr>
</tbody>
</table>

**Baseline/comparator:** Control arm of reference used for intervention.


2. **Inconsistency:** Serious. The direction of the effect is not consistent between the included studies. **Indirectness:** Serious. **Imprecision:** Serious. Wide confidence intervals.

3. **Systematic review [19] with included studies:** Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention.

4. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


6. **Inconsistency:** Serious. The direction of the effect is not consistent between the included studies. **Indirectness:** Serious. **Imprecision:** Serious. Wide confidence intervals.


8. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** Serious. The direction of the effect is not consistent between the included studies. **Indirectness:** Serious. **Imprecision:** Serious. Wide confidence intervals.


10. **Risk of bias:** Serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** Very Serious. The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies. The direction of the effect is not consistent between the included studies. **Indirectness:** Serious.


12. **Risk of bias:** Serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/
lack of blinding of participants and personnel, resulting in potential for performance bias. Indirectness: Serious.


14. Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. Inconsistency: Serious. The direction of the effect is not consistent between the included studies. Indirectness: Serious.


16. Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. Inconsistency: Serious. The direction of the effect is not consistent between the included studies. Indirectness: Serious. Imprecision: Serious. Wide confidence intervals.

17. Systematic review with included studies: [18]. Baseline/comparator: Control arm of reference used for intervention.


19. Primary study[72]. Baseline/comparator: Control arm of reference used for intervention.


Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>Patients with severe COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Remdesivir 5-day treatment</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Remdesivir 10-day treatment</td>
</tr>
</tbody>
</table>

Summary

Evidence informing this recommendation comes from a single randomised trial that compared 5-day to 10-day treatment with remdesivir in hospitalised patients with severe COVID-19 [21]. Patients were eligible if they were at least 12 years of age with PCR-confirmed SARS-CoV-2 infection before randomisation, had radiographic evidence of pulmonary infiltrates and oxygen saturation of 94% or less while breathing ambient air or were receiving supplemental oxygen.

The primary outcome was clinical status on day 14 using a 7-point scale (ranging from hospital discharge to death). Secondary outcomes included adverse events, serious adverse events (including acute respiratory failure/ARDS and septic shock), discontinuation of treatment due to adverse events and clinical recovery.

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias (eligible patients were randomised using an interactive web response system; however no further details were provided and patients in the 10-day group had significantly worse clinical status than those in the 5-day group at enrolment; patients, personnel administering the intervention and outcome assessors were not blinded), and very serious imprecision (only one study with few patients and/or few events).

It is important to note that this publication only presents initial results from the first 400 patients in a trial that includes 6000 patients (NCT04292899). This analysis will be updated when results from the full cohort are available (the primary completion date of the trial is listed as June 2020).

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [16].

Based on the available evidence, it remains uncertain whether a 5-day treatment schedule of remdesivir is more effective and safer than a 10-day treatment schedule.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>14 days after commencing treatment</td>
<td>Odds Ratio 0.73 (CI 95% 0.37 - 1.44) Based on data from 397 patients in 1 studies. 1</td>
<td>107 per 1000 80 per 1000</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases all-cause mortality (total no of events = 37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute respiratory failure or ARDS</td>
<td>Up to 30 days following completion of treatment</td>
<td>Odds Ratio 0.44 (CI 95% 0.21 - 0.93) Based on data from 397 patients in 1 studies. 3</td>
<td>117 per 1000 55 per 1000</td>
<td>Very Low</td>
<td>Remdesivir 5-day treatment may decrease acute respiratory failure or ARDS slightly (total no of events = 34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td>Up to 30 days following completion of treatment</td>
<td>Odds Ratio 0.39 (CI 95% 0.07 - 2.02) Based on data from 397 patients in 1 studies. 5</td>
<td>25 per 1000 9 per 1000</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases septic shock (total no of events = 7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>14 days after commencing treatment</td>
<td>Odds Ratio 1.56 (CI 95% 1.04 - 2.33) Based on data from 397 patients in 1 studies. 7</td>
<td>538 per 1000 644 per 1000</td>
<td>Very Low</td>
<td>Remdesivir 5-day treatment may improve clinical recovery slightly (total no of events = 235)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged from hospital</td>
<td>14 days after commencing treatment</td>
<td>Odds Ratio 1.37 (CI 95% 0.92 - 2.04) Based on data from 397 patients in 1 studies. 9</td>
<td>523 per 1000 600 per 1000</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases number of patients discharged from hospital (total no of events = 223)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Up to 30 days</td>
<td>Odds Ratio 0.5 (CI 95% 0.32 - 0.79) Based on data from 397</td>
<td>345 208</td>
<td>Very Low</td>
<td>Remdesivir 5-day treatment may decrease serious adverse events</td>
</tr>
<tr>
<td>Event Type</td>
<td>Time Frame</td>
<td>Event Count</td>
<td>CI 95%</td>
<td>Difference</td>
<td>Risk of Bias</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------------------------</td>
<td>-----------------</td>
<td>--------</td>
<td>------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Serious adverse events (Day 5)</td>
<td>5 days after commencing treatment</td>
<td>228 per 1000</td>
<td></td>
<td>73 fewer</td>
<td>Very Low</td>
</tr>
<tr>
<td>Adverse events (Day 5)</td>
<td>5 days after commencing treatment</td>
<td>619 per 1000</td>
<td></td>
<td>20 fewer</td>
<td>Very Low</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>During treatment</td>
<td>71 per 1000</td>
<td></td>
<td>26 fewer</td>
<td>Very Low</td>
</tr>
<tr>
<td>Time to recovery</td>
<td></td>
<td>11 (Median)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Imprecision:** Very Serious. Low number of patients, Only data from one study, due to low number of patients experiencing event.

4. **Risk of bias**: **Serious**. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision**: **Very Serious**. Low number of patients, Only data from one study.


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18. **Risk of bias**: **Serious**. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision**: **Very Serious**. Low number of patients, Only data from one study.


20. **Risk of bias**: **Serious**. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision**: **Very Serious**. Low number of patients, Only data from one study.

21. Systematic review with included studies: [21]. **Baseline/comparator**: Control arm of reference used for intervention.

22. **Risk of bias**: **Serious**. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision**: **Very Serious**. Low number of patients, Only data from one study.
Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population</th>
<th>Special populations with severe COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Remdesivir 5-day treatment</td>
</tr>
<tr>
<td>Comparator</td>
<td>Remdesivir 10-day treatment</td>
</tr>
</tbody>
</table>

Summary

Evidence informing this recommendation comes from a single randomised trial that compared 5-day to 10-day treatment with remdesivir in hospitalised patients with severe COVID-19 [21]. Patients were eligible if they were at least 12 years of age with PCR-confirmed SARS-CoV-2 infection before randomisation, had radiographic evidence of pulmonary infiltrates and oxygen saturation of 94% or less while breathing ambient air or were receiving supplemental oxygen.

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It is important to note that this publication only presents initial results from the first 400 patients in a trial that includes nearly 5000 patients (NCT04292899). The trial completed recruitment in July 2020 and we await the results from the full cohort of patients.

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [16].

Based on the available evidence, it remains uncertain whether a 5-day treatment schedule of remdesivir is more effective and safer than a 10-day treatment schedule.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates 10 days</th>
<th>Absolute effect estimates 5 days</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality 14 days after commencing treatment</td>
<td>Odds Ratio 0.73 (CI 95% 0.37 - 1.44) Based on data from 397 patients in 1 studies. (Randomized controlled)</td>
<td>107 per 1000</td>
<td>80 per 1000</td>
<td>Very Low Due to very serious imprecision and serious indirectness ²</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases all-cause mortality (total no of events = 37)</td>
</tr>
<tr>
<td>Acute respiratory failure or ARDS Up to 30 days following completion of treatment</td>
<td>Odds Ratio 0.44 (CI 95% 0.21 - 0.93) Based on data from 397 patients in 1 studies. (Randomized controlled)</td>
<td>117 per 1000</td>
<td>55 per 1000</td>
<td>Very Low Due to serious risk of bias, serious indirectness and very serious imprecision ⁴</td>
<td>Remdesivir 5-day treatment may decrease acute respiratory failure or ARDS slightly (total no of events = 34)</td>
</tr>
</tbody>
</table>
Critical Septic shock
Up to 30 days following completion of treatment

Odds Ratio 0.39
(CI 95% 0.07 - 2.02)
Based on data from 397 patients in 1 studies. 5
(Randomized controlled)

25 per 1000
Difference: 15 fewer per 1000
(CI 95% 23 fewer - 24 more)

9 per 1000

Very Low Due to serious risk of bias, serious indirectness and very serious imprecision 6
We are uncertain whether remdesivir 5-day treatment increases or decreases septic shock (total no of events = 7)

Clinical recovery
14 days after commencing treatment

Odds Ratio 1.56
(CI 95% 1.04 - 2.33)
Based on data from 397 patients in 1 studies. 7
(Randomized controlled)

538 per 1000
Difference: 107 more per 1000
(CI 95% 10 more - 193 more)

644 per 1000

Very Low Due to serious risk of bias, serious indirectness and very serious imprecision 8
Remdesivir 5-day treatment may improve clinical recovery slightly (total no of events = 235)

Discharged from hospital
14 days after commencing treatment

Odds Ratio 1.37
(CI 95% 0.92 - 2.04)
Based on data from 397 patients in 1 studies. 9
(Randomized controlled)

523 per 1000
Difference: 77 more per 1000
(CI 95% 21 fewer - 168 more)

600 per 1000

Very Low Due to serious risk of bias, serious indirectness and very serious imprecision 10
We are uncertain whether remdesivir 5 day treatment increases or decreases number of patients discharged from hospital (total no of events = 223)

Serious adverse events
Up to 30 days following completion of treatment

Odds Ratio 0.5
(CI 95% 0.32 - 0.79)
Based on data from 397 patients in 1 studies. 11
(Randomized controlled)

345 per 1000
Difference: 137 fewer per 1000
(CI 95% 201 fewer - 51 fewer)

208 per 1000

Very Low Due to serious risk of bias, serious indirectness and very serious imprecision 12
Remdesivir 5-day treatment may decrease serious adverse events slightly (total no of events = 110)

Serious adverse events (Day 5)
5 days after commencing treatment

Odds Ratio 0.62
(CI 95% 0.37 - 1.03)
Based on data from 397 patients in 1 studies. 13
(Randomized controlled)

228 per 1000
Difference: 73 fewer per 1000
(CI 95% 129 fewer - 5 more)

154 per 1000

Very Low Due to serious risk of bias, serious indirectness and very serious imprecision 14
Remdesivir 5-day treatment may decrease serious adverse events slightly at day 5 (total no of events = 76)

Adverse events
Up to 30 days following completion of treatment

Odds Ratio 0.86
(CI 95% 0.55 - 1.33)
Based on data from 397 patients in 1 studies. 15

736 per 1000

705 per 1000

Very Low Due to serious risk of bias, serious

We are uncertain whether remdesivir 5-day treatment increases or decreases
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Difference: 30 fewer per 1000 (CI 95% 131 fewer - 52 more)</th>
<th>Indirectness and very serious imprecision ( ^{16} )</th>
<th>Adverse events (total no of events = 286)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events (Day 5)</td>
<td>619 per 1000 599 per 1000</td>
<td>Very Low Due to serious risk of bias, serious indirectness and very serious imprecision ( ^{18} )</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases adverse events at day 5 (total no of events = 242)</td>
</tr>
<tr>
<td>Discontinuation due to adverse events During treatment</td>
<td>71 per 1000 45 per 1000</td>
<td>Very Low Due to serious risk of bias, serious indirectness and very serious imprecision ( ^{20} )</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases number of patients who discontinue treatment due to adverse events (total no of events = 29)</td>
</tr>
<tr>
<td>Time to recovery Days</td>
<td>Measured by: Hazard ratio: 0.81 (0.64 to 1.04) Lower better ( ^{21} ) (Randomized controlled)</td>
<td>CI 95% 11 (Median) 10 (Median)</td>
<td>Very Low Due to serious risk of bias, serious indirectness and very serious imprecision ( ^{22} )</td>
</tr>
</tbody>
</table>

1. **Systematic review** \( ^{20} \) with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.

2. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study, due to low number of patients experiencing event.

3. Systematic review \( ^{20} \) with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.

4. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.

5. Systematic review \( ^{20} \) with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.

6. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.

7. Systematic review \( ^{20} \) with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.

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9. Systematic review \( ^{20} \) with included studies: Goldman 2020. **Baseline/comparator:** Control arm of reference used for intervention.

10. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias,
6.2.2 - Remdesivir for pregnant or breastfeeding women

Use of remdesivir for pregnant or breastfeeding women with COVID-19 outside of a trial setting should not be considered routinely.

As pregnant and breastfeeding women are often excluded from clinical trials, use of remdesivir in this population would be outside a clinical trial setting. Pregnant and breastfeeding women receiving remdesivir should nonetheless be enrolled in national COVID-19 registries. Currently, there is no direct evidence of the effects of remdesivir in pregnant and breastfeeding women. Information about the patients and the intervention (dosages, duration) in the trials used for this recommendation can be found in the Practical info tab.

Due to antagonism observed in vitro, concomitant use of remdesivir with chloroquine or hydroxychloroquine is not recommended. [22]
Practical Info

Treatment
In the two trials where remdesivir was compared to placebo (Beigel 2020, Wang 2020), it was given as a daily intravenous infusion (200 mg initial dose, 100 mg maintenance) for 10 days. A third trial (Goldman 2020) compared a 10-day to a 5-day course of remdesivir but the magnitude of benefit remains uncertain for this treatment strategy. Given that the positive signal for benefit is only apparent in one trial with a 10-day course (Beigel 2020), we suggest considering this length of treatment until further evidence becomes available.

Key inclusion criteria
- > 18 years of age (Beigel 2020, Wang 2020), > 12 years of age (Goldman 2020)
- Laboratory-confirmed SARS-CoV-2 infection (positive RT-PCR)
- Clinical
  - Beigel 2020 [18]
    - Hospitalised with symptoms suggestive of COVID-19 AND one of the following criteria suggestive of lower respiratory tract infection:
      - Radiographic infiltrates by imaging study
      - Peripheral oxygen saturation (SpO2) ≤ 94% on room air
      - Requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)
  - Goldman 2020 [21]
    - Radiographic infiltrates by imaging study
    - Peripheral oxygen saturation (SpO2) ≤ 94% on room air or receiving supplemental oxygen
  - Wang 2020 [72]
    - Pneumonia confirmed by chest imaging AND
    - Oxygen saturation of ≤ 94% on room air OR a ratio of arterial oxygen partial pressure to fractional inspired oxygen of ≤ 300 mm Hg
- Duration of symptoms
  - Beigel 2020: no limit to the duration of symptoms before enrolment
  - Wang 2020: within 12 days of symptom onset
  - Goldman 2020: not specified, confirmed SARS-CoV-2 (positive RT-PCR) within 4 days of randomisation

Key exclusion criteria
- Pregnancy or breastfeeding
- An alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) > 5 times the upper limit of the normal range (Beigel 2020, Goldman 2020)
- Hepatic cirrhosis (Wang 2020 only)
- Impaired renal function (estimated glomerular filtration rate < 30 mL/min per 1.73 m²) or receipt of continuous renal replacement therapy, haemodialysis (Goldman 2020, Wang 2020) or peritoneal dialysis (Wang 2020).
- Allergy to study drug (Beigel 2020)
- Patients who were receiving mechanical ventilation and extracorporeal membrane oxygenation (ECMO) at screening (Goldman 2020)
- Patients with signs of multiorgan failure (Goldman 2020)
- Patients receiving concurrent treatment (within 24 hours before the start of trial treatment) with other agents with putative activity against COVID-19 (Goldman 2020)

Severity at baseline
Beigel 2020
1063 patients
Baseline score on 8-category scale
1. Not hospitalised, no limitations of activities: n=0 (0%)
2. Not hospitalised, limitation of activities, home oxygen requirement, or both: n=0 (0%)
3. Hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalisation was extended for infection-control reasons): n=0 (0%)
4. Hospitalised, not requiring supplemental oxygen, requiring ongoing medical care (COVID-19–related or otherwise): n=127 (12%)
5. Hospitalised, requiring supplemental oxygen: n=421 (40%)
6. Hospitalised, receiving noninvasive ventilation or high-flow oxygen devices: n=197 (19%)
7. Hospitalised, receiving invasive mechanical ventilation or ECMO: n=272 (26%)
8. Death: n=0 (0%)
Baseline score missing n=46 (4%)
Wang 2020
236 patients
Day 1 score on 6-category scale
1. Discharged or having reached discharge criteria (defined as clinical recovery—i.e. normalisation of pyrexia, respiratory rate < 24 breaths per minute, saturation of peripheral oxygen > 94% on room air, and relief of cough, all maintained for at least 72 hrs): n=0 (0%)
2. Hospital admission, not requiring supplemental oxygen: n=3 (1%)
3. Hospital admission, requiring supplemental oxygen: n=194 (82%)
4. Hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation: n=37 (16%)
5. Hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation: n=1 (< 1%)
6. Death: n=1 (< 1%)

Goldman 2020
397 patients
Baseline score on a 7-category scale
1. Death: n=0 (0%) for both groups
2. Receiving invasive mechanical ventilation or ECMO: 5-day group n=4 (2%); 10-day group n=9 (5%)
3. Receiving noninvasive ventilation or high-flow oxygen: 5-day group n=49 (24%); 10-day group n=60 (30%)
4. Receiving low-flow supplemental oxygen: 5-day group n=113 (56%); 10-day group n=107 (54%)
5. Not receiving supplemental oxygen but requiring medical care: 5-day group n=34 (17%); 10-day group n=21 (11%)
6. Hospitalised, requiring neither supplemental oxygen nor ongoing medical care: n=0 (0%) for both groups
7. Not hospitalised: n=0 (0%) for both groups

Key Info

Benefits and harms
There remains uncertainty around the benefits and harms of remdesivir for pregnant or breastfeeding women with COVID-19. Evidence from a trial comparing a 10-day to a 5-day course was too uncertain to inform decisions regarding length of treatment at this point.

Certainty of the Evidence
Certainty of the evidence for most reported outcomes is very low due to serious risk of bias, indirectness and either serious imprecision or inconsistency in the direction of effect between studies. The exception is serious adverse events, which is considered to be of low certainty.

Preference and values
We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. Since there is uncertainty regarding the benefit to harm ratio for women and their babies, the panel believes some women might prefer to wait while others might be more willing to opt for treatment.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. At this point, remdesivir remains an experimental therapy so the potential costs for this therapy outside a research setting are unclear.

Equity
There is a risk of creating inequity as pregnant or breastfeeding women are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. Inequity may be further exacerbated in individuals who are eligible for treatment based on compassionate grounds due to factors that may limit access (such as geographic area).

Acceptability
Important issues, or potential issues not investigated
We have no systematically collected evidence regarding acceptability by pregnant or breastfeeding women.

Feasibility

On 10 July, the Therapeutic Goods Administration granted provisional approval to use remdesivir in hospitalised adults with severe COVID-19 symptoms (requiring oxygen or high level support to breathe).

Implementability may be limited by the current arrangements for accessing remdesivir, in terms of the total number of doses available and more general criteria (such as geographic area).

Rationale

There is currently no direct evidence about the impact of remdesivir on outcomes relevant to pregnant and breastfeeding women with COVID-19 and insufficient data on safety. The effect of remdesivir on mortality is uncertain but it may decrease the time to recovery in non-pregnant adults.

The severity of disease is an important factor when considering the use of remdesivir. For pregnant women with severe or critical COVID-19, the harm to benefit ratio may differ compared to pregnant women with mild or moderate illness. The populations in the three studies published to date approximate to the moderate, severe and critical illness categories outlined in these guidelines [18][21][72]. The studies had insufficient power to perform adequate subgroup analyses. Beigel 2020, however, reported small numerical differences between study arms in the outcomes of patients with critical COVID-19, but no statistically significant difference in the primary outcome (time to recovery) by baseline disease severity. Goldman 2020 compared 5-day to a 10-day course of treatment, but since there is no established benefit for either approach yet, it remains uncertain that their results could inform the length of treatment at this point.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>Pregnant women with COVID-19 [adapted from general adult population]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Remdesivir</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

Summary

Evidence informing this recommendation comes from two randomised trials that compared remdesivir to placebo in adult patients with COVID-19; neither trial included pregnant or breastfeeding women. One study included 1063 patients with moderate to critical illness [18] and the other included 236 patients with severe to critical illness [72]. The evidence is judged to be applicable to pregnant and breastfeeding patients.

In both studies, randomisation was stratified by the level of disease severity, and in particular whether respiratory support was required. Patients were 18 years of age or older and both studies excluded pregnant and breastfeeding women. The mean age of patients receiving remdesivir ranged from 58 to 66 years, with the proportion of women ranging from 35% to 44%. The mean age of those receiving standard care ranged from 59 to 64 years, with the proportion of women ranging from 35% to 36%.

Certainty of the evidence for the majority of outcomes is very low. The exception is serious adverse events, which is considered to be of low certainty. These judgements are based on lack of personnel blinding [18] (which is considered of no relevance in mortality), serious imprecision (due to low number of patients and/or observed events, reliance on a single study or wide confidence intervals) or inconsistency in the direction of effect between studies, and indirectness (due to the absence of pregnant or breastfeeding patients in included studies).

It is important to note that Beigel 2020 [18] provides preliminary results only and does not provide data for 28-day mortality. As such, this study will remain under surveillance and additional results will be included when they become available.
The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension. There is currently insufficient evidence to assess adverse outcomes following treatment with remdesivir in pregnant and breastfeeding women.

Based on the available evidence, it remains uncertain as to whether remdesivir is more effective and safer than placebo in treating pregnant women with COVID-19.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality (Day 14)</strong></td>
<td>Relative risk 0.71 (CI 95% 0.39 - 1.28) Based on data from 1,290 patients in 2 studies.</td>
<td><strong>102</strong> per 1000</td>
<td><strong>Very Low</strong> Due to serious imprecision, inconsistency and indirectness</td>
<td>We are uncertain whether remdesivir increases or decreases all-cause mortality (day 14; total no of events = 108)</td>
</tr>
<tr>
<td>During treatment (14 days)</td>
<td></td>
<td><strong>72</strong> per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difference: <strong>30 fewer</strong> per 1000 ( CI 95% 62 fewer - 29 more )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality (Day 28)</strong></td>
<td>Relative risk 1.09 (CI 95% 0.54 - 2.18) Based on data from 236 patients in 1 studies.</td>
<td><strong>128</strong> per 1000</td>
<td><strong>Very Low</strong> Due to very serious imprecision and serious indirectness</td>
<td>We are uncertain whether remdesivir increases or decreases all-cause mortality (day 28; total no of events = 32)</td>
</tr>
<tr>
<td>During treatment (28 days)</td>
<td></td>
<td><strong>140</strong> per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difference: <strong>12 more</strong> per 1000 ( CI 95% 59 fewer - 151 more )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory failure or ARDS</strong></td>
<td>Relative risk 0.84 (CI 95% 0.47 - 1.53) Based on data from 1,296 patients in 2 studies.</td>
<td><strong>117</strong> per 1000</td>
<td><strong>Very Low</strong> Due to serious imprecision, inconsistency and indirectness</td>
<td>We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (total no of events = 132)</td>
</tr>
<tr>
<td>During treatment (28 days)</td>
<td></td>
<td><strong>98</strong> per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difference: <strong>19 fewer</strong> per 1000 ( CI 95% 62 fewer - 62 more )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Septic shock</strong></td>
<td>Relative risk 1.02 (CI 95% 0.34 - 3.01) Based on data from 1,296 patients in 2 studies.</td>
<td><strong>10</strong> per 1000</td>
<td><strong>Very Low</strong> Due to serious risk of bias, imprecision, inconsistency and indirectness</td>
<td>We are uncertain whether remdesivir increases or decreases septic shock (total no of events = 13)</td>
</tr>
<tr>
<td>During treatment (28 days)</td>
<td></td>
<td><strong>10</strong> per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difference: <strong>0 fewer</strong> per 1000 ( CI 95% 7 fewer - 20 more )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical recovery (Day 28)</strong></td>
<td>Relative risk 0.86 (CI 95% 0.46 - 1.64) Based on data from 1,289 patients in 2 studies.</td>
<td><strong>538</strong> per 1000</td>
<td><strong>Very Low</strong> Due to serious risk of bias and very serious</td>
<td>We are uncertain whether remdesivir improves or worsens clinical recovery (Day 28)</td>
</tr>
</tbody>
</table>

2. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Wide confidence intervals.

<table>
<thead>
<tr>
<th>Serious adverse events</th>
<th>Adverse events</th>
<th>Adverse events leading to discontinuation</th>
<th>Time to recovery (Days)</th>
<th>Time to improvement (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients experiencing one or more serious adverse events</td>
<td>Number of patients experiencing one or more adverse events</td>
<td>During treatment (28 days)</td>
<td>Measured by: Rate ratio</td>
<td>Measured by: Hazard ratio</td>
</tr>
<tr>
<td>Relative risk 0.77 (CI 95% 0.63 - 0.94) Based on data from 1,296 patients in 2 studies. [9] (Randomized controlled)</td>
<td>Relative risk 0.94 (CI 95% 0.8 - 1.11) Based on data from 1,296 patients in 2 studies. [11] (Randomized controlled)</td>
<td>Relative risk 1.29 (CI 95% 0.58 - 2.86) Based on data from 1,296 patients in 2 studies. [13] (Randomized controlled)</td>
<td>Rate ratio 1.32 (1.12 to 1.55) Based on data from: 607 patients in 1 studies. (Randomized controlled) Follow up 28 days</td>
<td>Hazard ratio 1.23 (0.87 to 1.75) Based on data from: 236 patients in 1 studies. (Randomized controlled) Follow up 28 days</td>
</tr>
<tr>
<td>Difference: <strong>75 fewer</strong> per 1000 (CI 95% 291 fewer - 344 more)</td>
<td>Difference: <strong>62 fewer</strong> per 1000 (CI 95% 99 fewer - 16 fewer)</td>
<td>Difference: <strong>22 fewer</strong> per 1000 (CI 95% 74 fewer - 41 more)</td>
<td>Difference: <strong>19 more</strong> per 1000 (CI 95% 28 fewer - 125 more)</td>
<td>Difference: <strong>21 more</strong> per 1000 (CI 95% 11 fewer - 125 more)</td>
</tr>
<tr>
<td>Low</td>
<td>Very Low</td>
<td>Very Low</td>
<td>Very Low</td>
<td>Very Low</td>
</tr>
<tr>
<td>Due to serious risk of bias and indirectness</td>
<td>Due to serious risk of bias, inconsistency and indirectness</td>
<td>Due to serious risk of bias, inconsistency and indirectness</td>
<td>Due to serious risk of bias, imprecision, inconsistency and indirectness</td>
<td>Due to serious risk of bias, imprecision, inconsistency and indirectness</td>
</tr>
<tr>
<td>Remdesivir may decrease serious adverse events slightly (total no of events = 303)</td>
<td>We are uncertain whether remdesivir increases or decreases adverse events</td>
<td>We are uncertain whether remdesivir increases or decreases adverse events leading to discontinuation</td>
<td>We are uncertain whether remdesivir affects time to recovery</td>
<td>We are uncertain whether remdesivir affects time to improvement</td>
</tr>
</tbody>
</table>

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4. **Indirectness:** Serious. Differences between the population of interest and those studied. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


6. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** Serious. The direction of the effect is not consistent between the included studies. **Indirectness:** Serious. Differences between the population of interest and those studied. **Imprecision:** Serious. Wide confidence intervals.


8. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness:** Serious. Differences between the population of interest and those studied. **Imprecision:** Serious. Wide confidence intervals.


10. **Risk of bias:** Serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** Very Serious. The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies., The direction of the effect is not consistent between the included studies.


12. **Risk of bias:** Serious. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness:** Serious. Differences between the population of interest and those studied.


14. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency:** Serious. The direction of the effect is not consistent between the included studies. **Indirectness:** Serious. Differences between the population of interest and those studied. **Imprecision:** Serious. Wide confidence intervals.


16. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency:** Serious. The direction of the effect is not consistent between the included studies. **Indirectness:** Serious. Differences between the population of interest and those studied. **Imprecision:** Serious. Only data from one study.

17. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness:** Serious. Differences between the population of interest and those studied. **Imprecision:** Serious. Only data from one study.

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Clinical Question/ PICO

**Population:** Pregnant women with severe COVID-19 [adapted from general adult population]
### Intervention
Remdesivir 5-day treatment

### Comparator
Remdesivir 10-day treatment

#### Summary
Evidence informing this recommendation comes from a single randomised trial that compared 5-day to 10-day treatment with remdesivir in hospitalised patients with severe COVID-19—the trial did not include pregnant women [21]. Patients were eligible if they were at least 12 years of age with PCR-confirmed SARS-CoV-2 infection before randomisation, had radiographic evidence of pulmonary infiltrates and oxygen saturation of 94% or less while breathing ambient air or were receiving supplemental oxygen. The evidence is judged to be applicable to pregnant women.

The primary outcome was clinical status on day 14 using a 7-point scale (ranging from hospital discharge to death). Secondary outcomes included adverse events, serious adverse events (including acute respiratory failure/ARDS and septic shock), discontinuation of treatment due to adverse events and clinical recovery.

Certainty of the evidence for all reported outcomes is very low. This judgement is based on serious risk of bias (eligible patients were randomised using an interactive web response system; however no further details were provided and patients in the 10-day group had significantly worse clinical status than those in the 5-day group at enrolment; patients, personnel administering the intervention and outcome assessors were not blinded), very serious imprecision (only one study with few patients and/or few events) and serious indirectness (population included adults who were not pregnant).

It is important to note that this publication only presents initial results from the first 400 patients in a trial that includes nearly 5000 patients (NCT04292899). The trial completed recruitment in July 2020 and we await the results from the full cohort of patients.

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [16].

Based on the available evidence, it remains uncertain whether a 5-day treatment schedule of remdesivir is more effective and safer than a 10-day treatment schedule.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong>&lt;br&gt;14 days after commencing treatment</td>
<td>Odds Ratio 0.73 (CI 95% 0.37 - 1.44)&lt;br&gt;Based on data from 397 patients in 1 studies. ¹ (Randomized controlled)</td>
<td>107 per 1000&lt;br&gt;Difference: 27 fewer per 1000 (CI 95% 65 fewer - 40 more)</td>
<td>Very Low&lt;br&gt;Due to very serious imprecision ²</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases all-cause mortality (total no of events = 37)</td>
</tr>
<tr>
<td><strong>Acute respiratory failure or ARDS</strong>&lt;br&gt;Up to 30 days following completion of treatment</td>
<td>Odds Ratio 0.44 (CI 95% 0.21 - 0.93)&lt;br&gt;Based on data from 397 patients in 1 studies. ³ (Randomized controlled)</td>
<td>117 per 1000&lt;br&gt;Difference: 62 fewer per 1000 (CI 95% 90 fewer - 7 fewer)</td>
<td>Very Low&lt;br&gt;Due to serious risk of bias and very serious imprecision ⁴</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases acute respiratory failure or ARDS (total no of events = 34)</td>
</tr>
</tbody>
</table>

¹ Randomized controlled<br>² Very Low<br>³ Randomized controlled<br>⁴ Very Low
<table>
<thead>
<tr>
<th>Event/Outcome</th>
<th>Odds Ratio</th>
<th>CI 95%</th>
<th>Difference</th>
<th>CI 95% (%)</th>
<th>Risk of Bias</th>
<th>Imprecision</th>
<th>Evidence</th>
<th>Uncertainty</th>
<th>Reason for Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic shock following completion of treatment</td>
<td>0.39</td>
<td>0.07 - 2.02</td>
<td>15 fewer</td>
<td>23 fewer - 24 more</td>
<td>Serious</td>
<td>Very Serious</td>
<td>Randomized controlled</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases septic shock (total no of events = 7)</td>
<td></td>
</tr>
<tr>
<td>Clinical recovery 14 days after commencing treatment</td>
<td>1.56</td>
<td>1.04 - 2.33</td>
<td>107 more</td>
<td>10 more - 193 more</td>
<td>Serious</td>
<td>Very Serious</td>
<td>Randomized controlled</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases clinical recovery</td>
<td></td>
</tr>
<tr>
<td>Discharged from hospital 14 days after commencing treatment</td>
<td>1.37</td>
<td>0.92 - 2.04</td>
<td>77 more</td>
<td>21 fewer - 168 more</td>
<td>Serious</td>
<td>Very Serious</td>
<td>Randomized controlled</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases number of patients discharged from hospital (total no of events = 223)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events following completion of treatment</td>
<td>0.5</td>
<td>0.32 - 0.79</td>
<td>137 fewer</td>
<td>201 fewer - 51 fewer</td>
<td>Serious</td>
<td>Very Serious</td>
<td>Randomized controlled</td>
<td>We are uncertain whether remdesivir 5-day treatment slightly increases or decreases serious adverse events (total no of events = 110)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events (Day 5) 5 days after commencing treatment</td>
<td>0.62</td>
<td>0.37 - 1.03</td>
<td>73 fewer</td>
<td>129 fewer - 5 more</td>
<td>Serious</td>
<td>Very Serious</td>
<td>Randomized controlled</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases serious adverse events at day 5 (total no of events = 76)</td>
<td></td>
</tr>
<tr>
<td>Adverse events following completion of treatment</td>
<td>0.86</td>
<td>0.55 - 1.33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases</td>
</tr>
</tbody>
</table>

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2. **Imprecision:** Very Serious. Low number of patients, Only data from one study, due to low number of patients experiencing event.


4. **Risk of bias:** Serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


6. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


8. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


10. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** Very Serious. Low number of patients, Only data from one study, due to [reason].
6.2.3 - Remdesivir for children or adolescents

Weak Recommendation Against

Use of remdesivir for children or adolescents with COVID-19 outside of a trial setting should not be considered routinely.

If treatment is considered—in exceptional circumstances—it should be in consultation with a clinical reference group, such as the ANZPID COVID-19 Clinical Reference Group. Informed consent from parents/caregivers should also be obtained. Currently, there is no direct evidence for the use of remdesivir in children or adolescents. Information about the patients and the intervention (dosages, duration) in the trials used for this recommendation can be found in the Practical info tab.

Due to antagonism observed in vitro, concomitant use of remdesivir with chloroquine or hydroxychloroquine is not recommended [22].

Practical Info

Treatment

Use of remdesivir in children or adolescents with COVID-19 should be considered in consultation with an appropriate clinical reference group. The Australasian Society for Infectious Diseases (ASID) paediatric special interest group (ANZPID) has formed a clinical reference group to advise paediatric infection specialists on therapy for children with COVID-19. The ANZPID COVID-19 Clinical Reference Group can be urgently convened to discuss individual patient management and provide a recommendation to the
treatment team on the use of a disease-modifying treatment when needed. Informed consent from parents/caregivers should also be obtained.

In the two trials where remdesivir was compared to placebo (Beigel 2020, Wang 2020), it was given as a daily intravenous infusion (200 mg initial dose, 100 mg maintenance) for 10 days in adults. A third trial (Goldman 2020) compared a 10-day to a 5-day course of remdesivir in adults but the magnitude of benefit remains uncertain for this treatment strategy. Given that the positive signal for benefit is only apparent in one trial with a 10-day course (Beigel 2020), we suggest considering this length of treatment, until further evidence becomes available.

**Key inclusion criteria**

- > 18 years of age (Beigel 2020, Wang 2020), > 12 years of age (Goldman 2020)
- Laboratory-confirmed SARS-CoV-2 infection (positive RT-PCR)
- Clinical
  - Beigel 2020 [18]
    - hospitalised with symptoms suggestive of COVID-19 AND one of the following criteria suggestive of lower respiratory tract infection:
      - radiographic infiltrates by imaging study
      - peripheral oxygen saturation (SpO2) ≤ 94% on room air
      - requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)
  - Goldman 2020 [21]
    - radiographic infiltrates by imaging study
    - peripheral oxygen saturation (SpO2) ≤ 94% on room air or receiving supplemental oxygen
  - Wang 2020 [72]
    - pneumonia confirmed by chest imaging AND
    - oxygen saturation of ≤ 94% on room air OR a ratio of arterial oxygen partial pressure to fractional inspired oxygen of ≤ 300 mm Hg
- Duration of symptoms
  - Beigel 2020: no limit to the duration of symptoms before enrolment
  - Wang 2020: within 12 days of symptom onset
  - Goldman 2020: not specified, confirmed SARS-CoV-2 (positive RT-PCR) within 4 days of randomisation

**Key exclusion criteria**

- Pregnancy or breastfeeding
- An alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) > 5 times the upper limit of the normal range (Beigel 2020, Goldman 2020)
- Hepatic cirrhosis (Wang 2020 only)
- Impaired renal function (estimated glomerular filtration rate < 30 mL/min per 1.73 m²) or receipt of continuous renal replacement therapy, haemodialysis (Goldman 2020, Wang 2020) or peritoneal dialysis (Wang 2020).
- Allergy to study drug (Beigel 2020)
- Patients who were receiving mechanical ventilation and extracorporeal membrane oxygenation (ECMO) at screening (Goldman 2020)
- Patients with signs of multiorgan failure (Goldman 2020)
- Patients receiving concurrent treatment (within 24 hours before the start of trial treatment) with other agents with putative activity against COVID-19 (Goldman 2020)

**Severity at baseline**

Beigel 2020
1063 patients
Baseline score on 8-category scale
1. Not hospitalised, no limitations of activities: n=0 (0%)
2. Not hospitalised, limitation of activities, home oxygen requirement, or both: n=0 (0%)
3. Hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalisation was extended for infection-control reasons): n=0 (0%)
4. Hospitalised, not requiring supplemental oxygen, requiring ongoing medical care (COVID-19–related or otherwise): n=127 (12%)
5. Hospitalised, requiring supplemental oxygen: n=421 (40%)
6. Hospitalised, receiving noninvasive ventilation or high-flow oxygen devices: n=197 (19%)
7. Hospitalised, receiving invasive mechanical ventilation or ECMO: n=272 (26%)
8. Death: n=0 (0%)
Baseline score missing n=46 (4%)

Wang 2020
236 patients
Day 1 score on 6-category scale
1. Discharged or having reached discharge criteria (defined as clinical recovery—i.e. normalisation of pyrexia, respiratory rate < 24 breaths per minute, saturation of peripheral oxygen > 94% on room air, and relief of cough, all maintained for at least 72 hrs): n=0 (0%)
2. Hospital admission, not requiring supplemental oxygen: n=3 (1%)
3. Hospital admission, requiring supplemental oxygen: n=194 (82%)
4. Hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation: n=37 (16%)
5. Hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation: n=1 (< 1%)
6. Death: n=1 (< 1%)

Goldman 2020
397 patients
Baseline score on a 7-category scale
1. Death: n=0 (0%) for both groups
2. Receiving invasive mechanical ventilation or ECMO: 5-day group n=4 (2%); 10-day group n=9 (5%)
3. Receiving noninvasive ventilation or high-flow oxygen: 5-day group n=49 (24%); 10-day group n=60 (30%)
4. Receiving low-flow supplemental oxygen: 5-day group n=113 (56%); 10-day group n=107 (54%)
5. Not receiving supplemental oxygen but requiring medical care: 5-day group n=34 (17%); 10-day group n=21 (11%)
6. Hospitalised, requiring neither supplemental oxygen nor ongoing medical care: n=0 (0%) for both groups
7. Not hospitalised: n=0 (0%) for both groups

Key Info

Benefits and harms
The two trials of remdesivir versus standard care provide preliminary evidence suggesting that remdesivir as a 10-day treatment has an acceptable safety profile. A third trial that compared a 10-day course to a 5-day course was too uncertain to inform decisions regarding length of treatment at this point. The results are based on adults (aged 44 to 75 years)—the trials did not include children and adolescents. There remains uncertainty around the benefits and harms of remdesivir for children and adolescents with COVID-19.

Certainty of the Evidence
Certainty of the evidence for most reported outcomes is very low due to serious risk of bias, indirectness and either serious imprecision or inconsistency in the direction of effect between studies. The exception is serious adverse events, which is considered to be of low certainty.

Preference and values
We have no systematically collected information regarding the preferences and values of patients or of their parents/caregivers. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers) may prefer to wait, while others may be more willing to take risks.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. At this point, remdesivir remains an experimental therapy so the potential costs for this therapy outside a research setting are unclear.

Equity
There is a risk of creating inequity as some populations, including most children, are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. Inequity may be further
exacerbated in individuals who are eligible for treatment based on compassionate grounds due to factors that may limit access (such as geographic area).

**Acceptability**

We have no systematically collected evidence regarding acceptability. However, obtaining and maintaining intravenous access in children may be more difficult than in adults and may therefore affect acceptability.

**Feasibility**

On 10 July, the Therapeutic Goods Administration granted provisional approval to use remdesivir in hospitalised adolescents (aged 12 years and older weighing at least 40 kg) with severe COVID-19 symptoms (requiring oxygen or high level support to breathe).

Implementability may be limited by the current arrangements for accessing remdesivir, in terms of the total number of doses available and more general criteria (such as geographic area).

**Rationale**

The effect of remdesivir on mortality is uncertain but it may decrease the time to recovery and the risk of serious adverse events in adults. Currently, there is no direct evidence for the use of remdesivir in children or adolescents. Because of this the Taskforce gives a conditional recommendation against the use of remdesivir outside the context of a randomised trial for children and adolescents.

The populations in the three studies published to date (adults aged 44-75 years) approximate to the moderate, severe and critical illness categories outlined in this guideline. The studies had insufficient power to perform adequate subgroup analyses. Beigel 2020, however, reported small numerical differences between study arms in the outcomes of patients with critical COVID-19, but no statistically significant difference in the primary outcome (time to recovery) by baseline disease severity. Goldman 2020 compared a 5-day to a 10-day course of treatment, but since there is no established benefit for either approach yet, it remains uncertain that these results can inform the length of treatment.

**Clinical Question/ PICO**

<table>
<thead>
<tr>
<th><strong>Population</strong></th>
<th>Children and adolescents with COVID-19 [adapted from general adult population]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Remdesivir</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Placebo</td>
</tr>
</tbody>
</table>

**Summary**

Evidence informing this recommendation comes from two randomised trials that compared remdesivir to placebo in adult patients with COVID-19; neither trial included children or adolescents. One study included 1063 patients with moderate to critical illness [14] and the other included 236 patients with severe to critical illness [31]. In both studies, randomisation was stratified by the level of disease severity, and in particular whether respiratory support was required. In both studies, patients had to be 18 years of age or older to be included (mean age ranged from 59 to 66 years in the remdesivir group and 59 to 64 years in the control group). The evidence is judged to be applicable to children and adolescents.

Certainty of the evidence for the majority of outcomes is very low. The exception is serious adverse events, which is considered to be of low certainty. These judgements are based on lack of personnel blinding (which is considered of no relevance in mortality) and either serious imprecision (due to low number of patients and/or observed events, reliance on a single study or wide confidence intervals) or inconsistency in the direction of effect between studies. All outcomes were downgraded for indirectness as results were based on adults.
It is important to note that Beigel 2020 [18] provides preliminary results only and does not provide data for 28-day mortality. As such, this study will remain under surveillance and additional results will be included when they become available.

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [16]. There is currently insufficient evidence to assess adverse outcomes following treatment with remdesivir in children or adolescents.

Based on the available evidence, it remains uncertain as to whether remdesivir is more effective and safer than placebo in treating children or adolescents with COVID-19.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality (Day 14) During treatment (14 days)</td>
<td>Relative risk 0.71 (CI 95% 0.39 - 1.28) Based on data from 1,290 patients in 2 studies.</td>
<td>102 per 1000</td>
<td>Remdesivir</td>
<td>Very Low Due to serious imprecision, inconsistency and indirectness</td>
</tr>
<tr>
<td>All-cause mortality (Day 28) During treatment (28 days)</td>
<td>Relative risk 1.09 (CI 95% 0.54 - 2.18) Based on data from 236 patients in 1 studies.</td>
<td>128 per 1000</td>
<td>Remdesivir</td>
<td>Very Low Due to very serious imprecision and serious indirectness</td>
</tr>
<tr>
<td>Respiratory failure or ARDS During treatment (28 days)</td>
<td>Relative risk 0.84 (CI 95% 0.47 - 1.53) Based on data from 1,296 patients in 2 studies.</td>
<td>117 per 1000</td>
<td>Remdesivir</td>
<td>Very Low Due to serious imprecision, inconsistency and indirectness</td>
</tr>
<tr>
<td>Septic shock During treatment (28 days)</td>
<td>Relative risk 1.02 (CI 95% 0.34 - 3.01) Based on data from 1,296 patients in 2 studies.</td>
<td>10 per 1000</td>
<td>Remdesivir</td>
<td>Very Low Due to serious risk of bias, imprecision, inconsistency and indirectness</td>
</tr>
</tbody>
</table>
### Clinical recovery (Day 28)

**Baseline/comparator:** Control arm of reference used

<table>
<thead>
<tr>
<th>Relative risk</th>
<th>CI 95%</th>
<th>Number of patients</th>
<th>Important</th>
<th>Clinical recovery (Day 28) During treatment (28 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.86</td>
<td>0.46 - 1.64</td>
<td>1,289 patients in 2 studies</td>
<td>6 Important</td>
<td>538 per 1000</td>
</tr>
<tr>
<td>Difference: 75 fewer per 1000</td>
<td>CI 95% 291 fewer - 344 more</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Very Low**

**Due to serious risk of bias and very serious inconsistency**

We are uncertain whether remdesivir improves or worsens clinical recovery (Day 28)

### Serious adverse events

**Number of patients experiencing one or more serious adverse events**

<table>
<thead>
<tr>
<th>Relative risk</th>
<th>CI 95%</th>
<th>Number of patients</th>
<th>Important</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.77</td>
<td>0.63 - 0.94</td>
<td>1,296 patients in 2 studies</td>
<td>6 Important</td>
</tr>
<tr>
<td>Difference: 62 fewer per 1000</td>
<td>CI 95% 99 fewer - 16 fewer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Low**

**Due to serious risk of bias and indirectness**

Remdesivir probably decreases serious adverse events slightly (total no of events = 303)

### Adverse events

**Number of patients experiencing one or more adverse events**

<table>
<thead>
<tr>
<th>Relative risk</th>
<th>CI 95%</th>
<th>Number of patients</th>
<th>Important</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.94</td>
<td>0.8 - 1.11</td>
<td>1,296 patients in 2 studies</td>
<td>6 Important</td>
</tr>
<tr>
<td>Difference: 22 fewer per 1000</td>
<td>CI 95% 74 fewer - 41 more</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Very Low**

**Due to serious risk of bias, inconsistency and indirectness**

We are uncertain whether remdesivir increases or decreases adverse events

### Adverse events leading to discontinuation

**During treatment (28 days)**

<table>
<thead>
<tr>
<th>Relative risk</th>
<th>CI 95%</th>
<th>Number of patients</th>
<th>Important</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.29</td>
<td>0.58 - 2.86</td>
<td>1,296 patients in 2 studies</td>
<td>6 Important</td>
</tr>
<tr>
<td>Difference: 19 more per 1000</td>
<td>CI 95% 28 fewer - 125 more</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Very Low**

**Due to serious risk of bias, imprecision, inconsistency and indirectness**

We are uncertain whether remdesivir increases or decreases adverse events leading to discontinuation

### Time to recovery (Days)

**Measured by: Rate ratio**

<table>
<thead>
<tr>
<th>CI 95%</th>
<th>Number of patients</th>
<th>Important</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.32 (1.12 to 1.55)</td>
<td>607 patients in 1 studies</td>
<td>6 Important</td>
</tr>
<tr>
<td>15 days (Median)</td>
<td>CI 95%</td>
<td></td>
</tr>
</tbody>
</table>

**Very Low**

**Due to serious risk of bias, imprecision and indirectness**

We are uncertain whether remdesivir may affects time to recovery

### Time to improvement (Days)

**Measured by: Hazard ratio**

<table>
<thead>
<tr>
<th>CI 95%</th>
<th>Number of patients</th>
<th>Important</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.23 (0.87 to 1.75)</td>
<td>236 patients in 1 studies</td>
<td>6 Important</td>
</tr>
<tr>
<td>23 days (Median)</td>
<td>CI 95%</td>
<td></td>
</tr>
</tbody>
</table>

**Very Low**

**Due to serious risk of bias, imprecision and indirectness**

We are uncertain whether remdesivir may affects time to improvement

---

for intervention.

2. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Wide confidence intervals.


4. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


6. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Wide confidence intervals.


8. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Wide confidence intervals.


10. **Risk of bias: Serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: Very Serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies. The direction of the effect is not consistent between the included studies.


12. **Risk of bias: Serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness: Serious.** Differences between the population of interest and those studied.


14. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Wide confidence intervals.


16. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: Serious.** The direction of the effect is not consistent between the included studies. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Wide confidence intervals.

17. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study.

18. Primary study[72]. **Baseline/comparator:** Control arm of reference used for intervention.

19. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness: Serious.** Differences between the population of interest and those studied. **Imprecision: Serious.** Only data from one study.
Clinical Question/ PICO

Population: Children and adolescents with severe COVID-19 [adapted from general adult population]
Intervention: Remdesivir 5-day treatment
Comparator: Remdesivir 10-day treatment

Summary

Evidence informing this recommendation comes from a single randomised trial that compared 5-day to 10-day treatment with remdesivir in hospitalised patients with severe COVID-19—the trial did not include children or adolescents [21]. Patients were eligible if they were at least 12 years of age with PCR-confirmed SARS-CoV-2 infection before randomisation, had radiographic evidence of pulmonary infiltrates and oxygen saturation of 94% or less while breathing ambient air or were receiving supplemental oxygen. The median age reported in the trial was 61 years [IQR 50-69] for the 5-day group and 62 years [IQR 50-71] for the 10-day group. The evidence is judged to be applicable to children and adolescents.

The primary outcome was clinical status on day 14 using a 7-point scale (ranging from hospital discharge to death). Secondary outcomes included adverse events, serious adverse events (including acute respiratory failure/ARDS and septic shock), discontinuation of treatment due to adverse events and clinical recovery.

Certainty of the evidence for all reported outcomes is very low. This judgement is based on serious risk of bias (eligible patients were randomised using an interactive web response system; however no further details were provided and patients in the 10-day group had significantly worse clinical status than those in the 5-day group at enrolment; patients, personnel administering the intervention and outcome assessors were not blinded), and very serious imprecision (only one study with few patients and/or few events).

It is important to note that this publication only presents initial results from the first 400 patients in a trial that includes nearly 5000 patients (NCT04292899). The trial completed recruitment in July 2020 and we await the results from the full cohort of patients.

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension [16].

Based on the available evidence, it remains uncertain whether a 5-day treatment schedule of remdesivir is more effective and safer than a 10-day treatment schedule.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Odds Ratio 0.73 (CI 95% 0.37 - 1.44) Based on data from 397 patients in 1 studies. 1 (Randomized controlled)</td>
<td>107 per 1000</td>
<td>Very Low Due to very serious imprecision 2</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases all-cause mortality (total no of events = 37)</td>
</tr>
<tr>
<td>14 days after commencing treatment</td>
<td></td>
<td>80 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Critical</td>
<td></td>
<td>Difference: 27 fewer per 1000 ( CI 95% 65 fewer - 40 more )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute respiratory failure or ARDS</td>
<td>Odds Ratio 0.44 (CI 95% 0.21 - 0.93) Based on data from 397 patients in 1 studies. 3 (Randomized controlled)</td>
<td>117 per 1000</td>
<td>Very Low Due to serious risk of bias and very serious imprecision 4</td>
<td>We are uncertain whether remdesivir 5-day treatment decreases acute respiratory failure or</td>
</tr>
<tr>
<td>Up to 30 days following</td>
<td></td>
<td>55 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>62 fewer per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event</td>
<td>Odds Ratio</td>
<td>CI 95%</td>
<td>Difference</td>
<td>Imprecision</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------</td>
<td>--------</td>
<td>------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Septic shock</td>
<td>0.39</td>
<td>0.07 - 2.02</td>
<td>15 fewer</td>
<td>Very Low</td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>1.56</td>
<td>1.04 - 2.33</td>
<td>107 more</td>
<td>Very Low</td>
</tr>
<tr>
<td>Discharged from hospital</td>
<td>1.37</td>
<td>0.92 - 2.04</td>
<td>77 more</td>
<td>Very Low</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>0.5</td>
<td>0.32 - 0.79</td>
<td>137 fewer</td>
<td>Very Low</td>
</tr>
<tr>
<td>Serious adverse events (Day 5)</td>
<td>0.62</td>
<td>0.37 - 1.03</td>
<td>73 fewer</td>
<td>Very Low</td>
</tr>
<tr>
<td>Adverse events</td>
<td>0.86</td>
<td>0.55 - 1.33</td>
<td>736</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

Australian guidelines for the clinical care of people with COVID-19 - Australian National COVID-19 Clinical Evidence Taskforce
## Adverse events (Day 5)

**5 days after commencing treatment**

<table>
<thead>
<tr>
<th>Event</th>
<th>Baseline/comparator:</th>
<th>Control arm of reference used for intervention.</th>
<th>Risk of bias and very serious imprecision</th>
<th>5-day treatment increases or decreases adverse events (total no of events = 286)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events</strong></td>
<td>Based on data from 397 patients in 1 studies.</td>
<td>Difference: 30 fewer per 1000 (CI 95% 131 fewer - 52 more)</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases adverse events at day 5 (total no of events = 242)</td>
</tr>
<tr>
<td><strong>Odds Ratio</strong></td>
<td>0.92 (CI 95% 0.62 - 1.38)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Per 1000</strong></td>
<td>619</td>
<td>599</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Discontinuation due to adverse events During treatment

<table>
<thead>
<tr>
<th>Event</th>
<th>Baseline/comparator:</th>
<th>Control arm of reference used for intervention.</th>
<th>Risk of bias and very serious imprecision</th>
<th>5-day treatment increases or decreases adverse events (total no of events = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events</strong></td>
<td>Based on data from 397 patients in 1 studies.</td>
<td>Difference: 26 fewer per 1000 (CI 95% 52 fewer - 29 more)</td>
<td>Very Low</td>
<td>We are uncertain whether remdesivir 5-day treatment increases or decreases number of patients who discontinue treatment due to adverse events (total no of events = 29)</td>
</tr>
<tr>
<td><strong>Odds Ratio</strong></td>
<td>0.62 (CI 95% 0.26 - 1.46)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Per 1000</strong></td>
<td>71</td>
<td>45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Time to recovery Days

<table>
<thead>
<tr>
<th>Event</th>
<th>Measured by: Hazard ratio: 0.81 (0.64 to 1.04) (Randomized controlled)</th>
<th>Lower better</th>
<th>Risk of bias and very serious imprecision</th>
<th>5-day treatment increases or decreases time to recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Days</strong></td>
<td>11 (Median)</td>
<td>10 (Median)</td>
<td>CI 95%</td>
<td></td>
</tr>
</tbody>
</table>

2. **Imprecision:** **Very Serious.** Low number of patients, Only data from one study, due to low number of patients experiencing event.
4. **Risk of bias:** **Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** **Very Serious.** Low number of patients, Only data from one study.
6. **Risk of bias:** **Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** **Very Serious.** Low number of patients, Only data from one study.
8. **Risk of bias:** **Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** **Very Serious.** Low number of patients, Only data from one study.

---

**Time to recovery Days**

- **Odds Ratio** 0.81 (0.64 to 1.04)
- **Lower better**
- **Median**
- **Very Low**
- **Due to serious risk of bias and very serious imprecision**
- **We are uncertain whether remdesivir 5-day treatment increases or decreases time to recovery**

---

**Discontinuation due to adverse events During treatment**

- **Odds Ratio** 0.62 (0.26 - 1.46)
- **Based on data from 397 patients in 1 studies.**
- **Difference:** 26 fewer per 1000 (CI 95% 52 fewer - 29 more)
- **Very Low**
- **Due to serious risk of bias and very serious imprecision**
- **We are uncertain whether remdesivir 5-day treatment increases or decreases number of patients who discontinue treatment due to adverse events (total no of events = 29)**

---

**Adverse events (Day 5)**

- **5 days after commencing treatment**
- **Odds Ratio** 0.92 (CI 95% 0.62 - 1.38)
- **Based on data from 397 patients in 1 studies.**
- **Difference:** 30 fewer per 1000 (CI 95% 131 fewer - 52 more)
- **Very Low**
- **Due to serious risk of bias and very serious imprecision**
- **We are uncertain whether remdesivir 5-day treatment increases or decreases adverse events at day 5 (total no of events = 242)**
6.3 - Hydroxychloroquine

**Strong Recommendation Against**

For people with COVID-19, do not use hydroxychloroquine outside of randomised trials with appropriate ethical approval.

**Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use hydroxychloroquine in these populations unless they are eligible to be enrolled in trials.**

**Key Info**

**Benefits and harms**

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are well-known harms with potentially severe adverse events. Although most of the information on side effects and harms is derived from long-term use, potential acute harms include prolonged QT interval and lowered convulsive threshold. Long-term harms include retinopathy and chronic cardiac myopathy, among several others.

**Children and adolescents**
Paediatricians have considerable experience with hydroxychloroquine in children and adolescents for other indications.

**Pregnant and breastfeeding women**
Hydroxychloroquine is used in pregnant and breastfeeding women for the treatment of malaria and autoimmune diseases. Studies of hydroxychloroquine for these indications have shown a favourable safety profile, though further research is needed.

**People requiring palliative care and older people living with frailty or cognitive impairment**
For people requiring palliative care, the benefits for symptom management are uncertain. For older people living with frailty or cognitive impairment there may be additional concerns regarding harms.

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**Certainty of the Evidence**

**General adult population**
Certainty of the evidence for all-cause mortality and requirement of mechanical ventilation/ECMO is moderate (due to imprecision). Certainty is moderate for both adverse events (due to serious risk of bias) and discharge from hospital (due to serious imprecision), low for serious adverse events (due to serious inconsistency and imprecision) and very low for both virological clearance and hospitalisation (due to serious risk of bias and very serious imprecision).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
Certainty of the evidence for all-cause mortality and requirement of mechanical ventilation/ECMO is low (due to imprecision and indirectness). Certainty is low for both adverse events (due to serious risk of bias and indirectness) and discharge from hospital (due to serious imprecision and indirectness), very low for serious adverse events (due to serious inconsistency, indirectness and imprecision) and very low for both virological clearance and hospitalisation (due to serious risk of bias, indirectness and very serious imprecision).

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**Preference and values**

**General adult population**
We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of hydroxychloroquine in pregnancy are unknown.

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**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the potential impact on reduced access to these treatments by patients currently using them for other indications.

---

**Equity**

**General adult population**
We have no systematically collected direct evidence regarding impact on equity. There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for
Rationale

General adult population
Based on the available evidence, hydroxychloroquine is potentially harmful and no more effective than standard care in treating patients with COVID-19. We therefore recommend that hydroxychloroquine should only be administered in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

General adult population, children and adolescents, pregnant and breastfeeding women
Although we have no systematically collected evidence regarding acceptability, hydroxychloroquine is likely to be acceptable to both patients and clinicians.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale

General adult population
Based on the available evidence, hydroxychloroquine is potentially harmful and no more effective than standard care in treating patients with COVID-19. We therefore recommend that hydroxychloroquine should only be administered in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the evidence in the general adult population, use of hydroxychloroquine in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Hydroxychloroquine
Comparator: Standard care

Summary

Evidence informing this recommendation comes from eight randomised trials that compared hydroxychloroquine plus standard care to standard care alone in 5797 patients [27][28][31][40][41][42][43][44]. The vast majority of evidence is from the RECOVERY trial which randomised 4716 hospitalised patients with COVID-19—this trial has reported preliminary results as a preprint but has yet to report complete data on adverse or serious adverse events [41].

There was significant variability in disease severity among patients included in the trials: two trials were of mild illness (776
Mean or median age ranged from 41 to 65 years in the hydroxychloroquine groups and from 39 to 65 years in the control groups. The proportion of women was 42% (range 36 to 72%) in the hydroxychloroquine groups and 40% (range 20 to 66%) in the control groups.

All-cause mortality and incidence of adverse or serious adverse events were the most commonly reported outcomes. The RECOVERY trial also reported requirement for mechanical ventilation and discharge from hospital. Two smaller trials reported virological clearance. Hospitalisation was an outcome in the two trials of mild patients. Incidence of respiratory failure or ARDS was not reported in any of the trials.

Certainty of the evidence for all-cause mortality, requirement for mechanical ventilation/ECMO and discharge from hospital is moderate (due to serious imprecision). Certainty is moderate for adverse events (due to serious risk of bias), low for serious adverse events (due to serious inconsistency and imprecision) and very low for both virological clearance and hospitalisation (due to serious risk of bias and very serious imprecision).

According to the Therapeutic Goods Administration known acute harms for hydroxychloroquine include prolonged QT interval and lowered convulsive threshold. Long-term harms of relevance include retinopathy and chronic cardiac myopathy [33]. There are several known and potential interactions with other drugs [33]. Overdose of hydroxychloroquine may have potentially fatal complications. In pregnancy, it is only recommended when benefits outweigh harms [33].

Based on the available evidence, hydroxychloroquine is potentially harmful and no more effective than standard care in treating patients with COVID-19.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality 1</td>
<td>Relative risk 1.07 (CI 95% 0.97 - 1.19) Based on data from 5,534 patients in 5 studies. 2 (Randomized controlled)</td>
<td>Standard care: 222 per 1000 Hydroxychloroquine: 238 per 1000</td>
<td>Moderate Due to serious imprecision 3</td>
<td>Hydroxychloroquine probably has little or no impact on all-cause mortality (total no of events = 1218)</td>
</tr>
<tr>
<td>Mechanical ventilation or ECMO End of treatment 9 Critical</td>
<td>Relative risk 1.11 (CI 95% 0.89 - 1.37) Based on data from 4,216 patients in 2 studies. 4 (Randomized controlled)</td>
<td>Standard care: 78 per 1000 Hydroxychloroquine: 87 per 1000</td>
<td>Moderate Due to serious imprecision 5</td>
<td>Hydroxychloroquine probably has little or no impact on the need for mechanical ventilation or ECMO (total no of events = 333)</td>
</tr>
<tr>
<td>Virological clearance (negative PCR) Day 7 of treatment 6 Important</td>
<td>Relative risk 0.93 (CI 95% 0.76 - 1.14) Based on data from 180 patients in 2 studies. 6 (Randomized controlled)</td>
<td>Standard care: 489 per 1000 Hydroxychloroquine: 455 per 1000</td>
<td>Very Low Due to serious risk of bias and very serious imprecision 7</td>
<td>We are uncertain whether hydroxychloroquine increases or decreases the likelihood of a negative PCR at day 7 of treatment (total no of events = 85)</td>
</tr>
</tbody>
</table>
1. **Recovery** trial reported mortality at 28 days after commencing treatment


3. **Imprecision**: Serious. Wide confidence intervals.


5. **Imprecision**: Serious. Wide confidence intervals.


7. **Risk of bias**: Serious. Inadequate sequence generation/generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision**: Very Serious. Wide confidence intervals, Low number of patients.


### Adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk</th>
<th><strong>CI 95%</strong></th>
<th><strong>Difference</strong></th>
<th><strong>CI 95%</strong></th>
<th><strong>Moderate</strong></th>
<th><strong>Risk of bias</strong></th>
<th><strong>Imprecision</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory failure or ARDS</strong>: End of treatment</td>
<td>3.35</td>
<td>1.61 - 6.96</td>
<td><strong>322 more</strong></td>
<td>817 more</td>
<td>Due to serious risk of bias</td>
<td>Serious</td>
<td>Very Serious</td>
</tr>
<tr>
<td><strong>Hospitalisation</strong>: End of treatment</td>
<td>1.21</td>
<td>0.21 - 7.1</td>
<td><strong>5 more</strong></td>
<td>140 more</td>
<td>Due to serious inconsistency and serious imprecision</td>
<td>Serious</td>
<td>Very Serious</td>
</tr>
<tr>
<td><strong>Discharge from hospital</strong>: Within 28 days after commencing treatment</td>
<td>0.96</td>
<td>0.91 - 1.01</td>
<td><strong>25 fewer</strong></td>
<td>12 more</td>
<td>Due to serious imprecision</td>
<td>Serious</td>
<td>Very Serious</td>
</tr>
</tbody>
</table>

### Important Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th><strong>Relative Risk</strong></th>
<th><strong>CI 95%</strong></th>
<th><strong>Difference</strong></th>
<th><strong>CI 95%</strong></th>
<th><strong>Moderate</strong></th>
<th><strong>Risk of bias</strong></th>
<th><strong>Imprecision</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxychloroquine probably increases adverse events (total no of events = 321)</td>
<td>3.35</td>
<td>1.61 - 6.96</td>
<td><strong>322 more</strong></td>
<td>817 more</td>
<td>Due to serious risk of bias</td>
<td>Serious</td>
<td>Very Serious</td>
</tr>
<tr>
<td>Hydroxychloroquine may have little or no difference on serious adverse events (total no of events = 22)</td>
<td>1.21</td>
<td>0.21 - 7.1</td>
<td><strong>5 more</strong></td>
<td>140 more</td>
<td>Due to serious inconsistency and serious imprecision</td>
<td>Serious</td>
<td>Very Serious</td>
</tr>
<tr>
<td>Hydroxychloroquine probably has little or no impact on discharge from hospital</td>
<td>0.96</td>
<td>0.91 - 1.01</td>
<td><strong>25 fewer</strong></td>
<td>12 more</td>
<td>Due to serious imprecision</td>
<td>Serious</td>
<td>Very Serious</td>
</tr>
</tbody>
</table>

No studies were found that looked at respiratory failure or ARDS.
Clinical Question/ PICO

**Population:** Special populations with COVID-19  
**Intervention:** Hydroxychloroquine  
**Comparator:** Standard care

**Summary**

Evidence informing this recommendation comes from eight randomised trials that compared hydroxychloroquine plus standard care to standard care alone in 5797 patients [27][28][31][40][41][42][43][44]. The vast majority of evidence is from the RECOVERY trial which randomised 4716 hospitalised patients with COVID-19—this trial has reported preliminary results as a preprint but has yet to report complete data on adverse or serious adverse events [41].

There was significant variability in disease severity among patients included in the trials: two trials were of mild illness (776 patients) [42][43], four of moderate (155 patients) [27][28][40][44], one of moderate and severe (4716 patients) [41], and one of mild, moderate and severe (150 patients) [31].

Mean or median age ranged from 41 to 65 years in the hydroxychloroquine groups and from 39 to 65 years in the control groups. The proportion of women was 42% (range 36 to 72%) in the hydroxychloroquine groups and 40% (range 20 to 66%) in the control groups.

All-cause mortality and incidence of adverse or serious adverse events were the most commonly reported outcomes. The RECOVERY trial also reported requirement for mechanical ventilation and discharge from hospital. Two smaller trials reported virological clearance. Hospitalisation was an outcome in the two trials of mild patients. Incidence of respiratory failure or ARDS was not reported in any of the trials.

Certainty of the evidence for all-cause mortality, requirement for mechanical ventilation/ECMO, discharge from hospital and adverse events is low (due to serious imprecision or risk of bias and indirectness). Certainty for serious adverse events, virological clearance and hospitalisation is very low (due to serious inconsistency, indirectness and imprecision).

According to the Therapeutic Goods Administration known acute harms for hydroxychloroquine include prolonged QT interval and lowered convulsive threshold. Long-term harms of relevance include retinopathy and chronic cardiac myopathy [33]. There are several known and potential interactions with other drugs [33]. Overdose of hydroxychloroquine...
may have potentially fatal complications. In pregnancy, it is only recommended when benefits outweigh harms [33].

Based on the available evidence, hydroxychloroquine/chloroquine is potentially harmful and no more effective than standard care in treating patients with COVID-19.

**Pregnant and breastfeeding women**
Hydroxychloroquine is used in pregnant and breastfeeding women for the treatment of malaria and autoimmune diseases. Studies of hydroxychloroquine for these indications have shown a favourable safety profile, with no increase in fetal malformations [49][50]. There is no evidence to suggest that stillbirth, preterm birth, low birth weight or early childhood disability are more common following treatment with hydroxychloroquine [49][50][51]. While this evidence is reassuring, further research is needed.

**Children and adolescents**
Paediatricians have considerable experience with hydroxychloroquine in children and adolescents for other indications. To date, no specific information on its benefits or harms for children and adolescents has been collected for treating COVID-19 in this population.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
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</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>End of treatment</td>
<td>Relative risk 1.07 (CI 95% 0.97 - 1.19) Based on data from 5,534 patients in 5 studies. (Randomized controlled)</td>
<td><strong>222</strong> per 1000</td>
<td><strong>238</strong> per 1000</td>
<td>Low Due to serious imprecision and indirectness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference: <strong>16 more</strong> per 1000 (CI 95% 7 fewer - 42 more)</td>
<td></td>
<td>Hydroxychloroquine probably has little or no impact on all-cause mortality (total no of events = 1208)</td>
</tr>
<tr>
<td><strong>Respiratory failure or ARDS</strong></td>
<td>End of treatment</td>
<td>Relative risk 1.11 (CI 95% 0.89 - 1.37) Based on data from 4,216 patients in 2 studies. (Randomized controlled)</td>
<td><strong>78</strong> per 1000</td>
<td><strong>87</strong> per 1000</td>
<td>Low Due to serious imprecision and indirectness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference: <strong>9 more</strong> per 1000 (CI 95% 9 fewer - 29 more)</td>
<td></td>
<td>Hydroxychloroquine probably has little or no impact on the need for mechanical ventilation or ECMO (total no of events = 433)</td>
</tr>
<tr>
<td><strong>Virological clearance (negative PCR)</strong></td>
<td>Day 7 of treatment</td>
<td>Relative risk 0.93 (CI 95% 0.76 - 1.14) Based on data from 180 patients in 2 studies. (Randomized controlled)</td>
<td><strong>489</strong> per 1000</td>
<td><strong>455</strong> per 1000</td>
<td>Very Low Due to serious risk of bias and indirectness, and very serious imprecision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference: <strong>34 fewer</strong> per 1000 (CI 95% 117 fewer - 68 more)</td>
<td></td>
<td>We are uncertain whether hydroxychloroquine increases or decreases the likelihood of a negative PCR at day 7 of treatment (total no of events = 85)</td>
</tr>
</tbody>
</table>
1. RECOVERY trial reported mortality at 28 days after commencing treatment
10. Risk of bias: Serious. Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. Indirectness: Serious.

### Adverse events

#### End of treatment

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative risk</th>
<th>(CI)</th>
<th>Observations</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Relative risk 3.35</td>
<td>(CI 95% 1.61 - 6.96)</td>
<td>Based on data from 1,048 patients in 6 studies.</td>
<td>9 (Randomized controlled)</td>
<td></td>
</tr>
<tr>
<td>2. Relative risk 1.21</td>
<td>(CI 95% 0.21 - 7.1)</td>
<td>Based on data from 1,018 patients in 5 studies.</td>
<td>11 (Randomized controlled)</td>
<td></td>
</tr>
<tr>
<td>3. Odds Ratio 0.61</td>
<td>(CI 95% 0.29 - 1.25)</td>
<td>Based on data from 716 patients in 2 studies.</td>
<td>13 (Randomized controlled)</td>
<td></td>
</tr>
<tr>
<td>4. Relative risk 0.96</td>
<td>(CI 95% 0.91 - 1.01)</td>
<td>Based on data from 4,716 patients in 1 studies.</td>
<td>15 (Randomized controlled)</td>
<td></td>
</tr>
</tbody>
</table>

#### Important

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<tbody>
<tr>
<td>1. 137 per 1000</td>
<td>459 per 1000</td>
<td>Difference: 322 more per 1000 (CI 95% 84 more - 817 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. 23 per 1000</td>
<td>28 per 1000</td>
<td>Difference: 5 more per 1000 (CI 95% 18 fewer - 140 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. 52 per 1000</td>
<td>32 per 1000</td>
<td>Difference: 20 fewer per 1000 (CI 95% 36 fewer - 12 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. 628 per 1000</td>
<td>603 per 1000</td>
<td>Difference: 25 fewer per 1000 (CI 95% 57 fewer - 6 more)</td>
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</tbody>
</table>

### Hospitalisation

#### End of treatment

<table>
<thead>
<tr>
<th>Event</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1. Low Due to serious risk of bias and indirectness.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Very Low Due to serious inconsistency, indirectness and imprecision.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. We are uncertain whether hydroxychloroquine increases or decreases hospitalisation (total no of events = 22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Hydroxychloroquine probably has little or no impact on discharge from hospital.</td>
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</tbody>
</table>

### Discharge from hospital

#### Within 28 days after commencing treatment

<table>
<thead>
<tr>
<th>Event</th>
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<tbody>
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<tr>
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</tbody>
</table>
6.4 - Baloxavir marboxil

**Strong Recommendation Against**

For people with COVID-19, do not use baloxavir marboxil outside of randomised trials with appropriate ethical approval.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use baloxavir marboxil in these populations unless they are eligible to be enrolled in trials.

**Key Info**

**Benefits and harms**

**General adult population**

In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with baloxavir marboxil, including diarrhoea, bronchitis, nausea, sinusitis and headache.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

There are additional concerns regarding harms as baloxavir marboxil has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Certainty of the Evidence**

**General adult population**

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias due to lack of blinding, and very serious imprecision due to the low number of patients and/or observed events and the reliance on a single study.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.
Preference and values

General adult population
We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of baloxavir marboxil in pregnancy are unknown.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

General adult population, children and adolescents, pregnant and breastfeeding women
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale

General adult population
There is currently limited evidence about the impact of baloxavir marboxil on patient-relevant outcomes in COVID-19. The panel has significant concerns about the potential harms of unproven treatments. We therefore recommend that baloxavir marboxil should only be administered in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited
evidence in the general adult population, use of baloxavir marboxil in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Baloxavir marboxil</td>
</tr>
<tr>
<td>Comparator</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

Summary

Evidence informing this recommendation comes from a single randomised trial that compared baloxavir marboxil to standard care in 20 hospitalised adults patients with COVID-19 [75]. Patients concomitantly used lopinavir-ritonavir, darunavir-cobicistat and/or arbidol. It is unclear whether pregnant or breastfeeding women were eligible. Mean age was 54 years in the baloxavir marboxil group (30% women) and 47 years in the control group (30% women).

The study results are only available as a preprint paper (posted to medRxiv on 5 May 2020) and have therefore not been peer-reviewed. We follow up with the corresponding author every two months to request an update on the study’s publication status.

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias due to lack of blinding, and very serious imprecision due to the low number of patients and/or observed events and the reliance on a single study.

The Therapeutic Goods Administration highlights several mild side effects associated with baloxavir marboxil, including diarrhoea, bronchitis, nausea, sinusitis and headache. In addition, post-marketing surveillance has identified cases of anaphylactic reactions, angioedema, vomiting and other gastrointestinal and skin/subcutaneous tissue disorders [76].

Based on the available evidence, there remains significant uncertainty whether baloxavir marboxil is more effective and safer than standard care in treating patients with COVID-19.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality During treatment (14 days)</td>
<td>Based on data from 20 patients in 1 studies. ¹</td>
<td>⁴⁰⁰ per 1000 ⁶⁰⁰ per 1000</td>
<td>Very Low Due to serious risk of bias and very serious imprecision ³</td>
<td>There were no deaths in the study</td>
</tr>
<tr>
<td>Respiratory support and ARDS During treatment (14 days)</td>
<td>Odds Ratio 2.25 (CI 95% 0.38 - 13.47) Based on data from 20 patients in 1 studies. ² (Randomized controlled)</td>
<td>Difference: <strong>200 more</strong> per 1000 ( CI 95% 198 fewer - 500 more )</td>
<td>We are uncertain whether baloxavir marboxil increases or decreases respiratory support and ARDS (total no of events = 10)</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation or</td>
<td>Odds Ratio 3.32 (CI 95% 0.12 - 91.6)</td>
<td>⁰ ¹⁰⁰</td>
<td>Very Low</td>
<td>There were too few who required mechanical</td>
</tr>
</tbody>
</table>

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3. **Risk of bias:** Serious. **Imprecision:** Very Serious. Low number of patients. Only data from one study.
5. **Risk of bias:** Serious. **Imprecision:** Very Serious. Low number of patients. Only data from one study.
6. Systematic review [74] with included studies: [75]. **Baseline/comparator:** Control arm of reference used for intervention.
7. Systematic review [74] with included studies: [75]. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Risk of bias:** Serious. **Imprecision:** Very Serious. Low number of patients. Only data from one study.

### Clinical Question/ PICO
- **Population:** Special populations with COVID-19
- **Intervention:** Baloxavir marboxil
- **Comparator:** Standard care

<table>
<thead>
<tr>
<th>ECMO</th>
<th>Clinical improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>During treatment (14 days)</td>
<td>End of treatment (14 days)</td>
</tr>
<tr>
<td>9 Critical</td>
<td>6 Important</td>
</tr>
</tbody>
</table>

**ECMO** Based on data from 20 patients in 1 studies. 6 (Randomized controlled)

**Clinical improvement**

**Odds Ratio 1.5**

(95% CI 0.26 - 8.82)

Based on data from 20 patients in 1 studies. 8 (Randomized controlled)

<table>
<thead>
<tr>
<th>500 per 1000</th>
<th>600 per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Difference:</strong> 100 more per 1000</td>
<td><strong>Difference:</strong> 100 more per 1000</td>
</tr>
<tr>
<td>(95% CI 294 fewer - 398 more)</td>
<td>(95% CI 500 fewer - 600 more)</td>
</tr>
</tbody>
</table>

**Risk of bias and very serious imprecision** 5

Ventilation or ECMO to determine whether baloxavir marboxil makes a difference (total no of events = 1)

**Serious adverse events**

During treatment (14 days)

6 Important

**Adverse events**

During treatment (14 days)

7 Important

Data for number of patients experiencing one or more events were not reported

Data for number of patients experiencing one or more events were not reported

We are uncertain whether baloxavir marboxil increases or decreases clinical improvement (total no of events = 11)
Summary
Evidence informing this recommendation comes from a single randomised trial that compared baloxavir marboxil to standard care in 20 hospitalised adults patients with COVID-19 [75]. Patients concomitantly used lopinavir-ritonavir, darunavir-cobicistat and/or arbidol. It is unclear whether pregnant or breastfeeding women were eligible. Mean age was 54 years in the baloxavir marboxil group (30% women) and in the control group 47 years (30% women).

The study results are only available as a preprint paper (posted to medRxiv on 5 May 2020) and have therefore not been peer-reviewed. We follow up with the corresponding author every two months to request an update on the study’s publication status.

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias due to lack of blinding, serious indirectness due to limited inclusion of these populations, and very serious imprecision due to the low number of patients and/or observed events and the reliance on a single study.

The Therapeutic Goods Administration highlights several mild side effects associated with baloxavir marboxil, including diarrhoea, bronchitis, nausea, sinusitis and headache. In addition, post-marketing surveillance has identified cases of anaphylactic reactions, angioedema, vomiting and other gastrointestinal and skin/subcutaneous tissue disorders [76].

Based on the available evidence, there remains significant uncertainty whether baloxavir marboxil is more effective and safer than standard care in treating patients with COVID-19.

Children and adolescents
There is insufficient safety data on the use of baloxavir marboxil in children or adolescents for other indications.

Pregnant and breastfeeding women
No studies pertained to the safety of baloxavir marboxil (for any indication) when used in pregnant or breastfeeding women.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During treatment</td>
<td>Based on data from 20 patients in 1 studies.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(14 days)</td>
<td>9 Critical</td>
<td></td>
<td></td>
<td>There were no deaths in the study</td>
</tr>
<tr>
<td><strong>Respiratory support and ARDS</strong></td>
<td>Odds Ratio 2.25 (CI 95% 0.38 - 13.47) Based on data from 20 patients in 1 studies. (Randomized controlled)</td>
<td><strong>400 more</strong> per 1000</td>
<td>Very Low Due to serious risk of bias, serious indirectness and very serious imprecision</td>
<td>We are uncertain whether baloxavir marboxil increases or decreases respiratory support and ARDS (total no of events = 10)</td>
</tr>
<tr>
<td>During treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(14 days)</td>
<td>9 Critical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mechanical ventilation or ECMO</strong></td>
<td>Odds Ratio 3.32 (CI 95% 0.12 - 91.6) Based on data from 20 patients in 1 studies.</td>
<td>100 per 1000</td>
<td>Very Low Due to serious risk of bias, serious indirectness and</td>
<td>There were too few who required mechanical ventilation or ECMO to determine whether baloxavir marboxil</td>
</tr>
<tr>
<td>During treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event Type</td>
<td>Data Description</td>
<td>Risk of Bias</td>
<td>Indirectness</td>
<td>Imprecision</td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>During treatment (14 days)</td>
<td>Serious</td>
<td>Serious</td>
<td>Very Serious</td>
</tr>
<tr>
<td>Adverse events</td>
<td>During treatment (14 days)</td>
<td>Serious</td>
<td>Serious</td>
<td>Very Serious</td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>End of treatment (14 days)</td>
<td>Serious</td>
<td>Serious</td>
<td>Very Serious</td>
</tr>
</tbody>
</table>

**Systematic review [74] with included studies: Lou 2020.**

- **Baseline/comparator:** Control arm of reference used for intervention.

**Risk of bias**
- Serious
- Indirectness: Serious
- Imprecision: Very Serious

**Clinical improvement**
- Odds Ratio 1.5
  - (CI 95% 0.26 - 8.82)
  - Based on data from 20 patients in 1 studies.  

**Adverse events**
- During treatment (14 days)

**Serious adverse events**
- During treatment (14 days)

**Clinical improvement**
- End of treatment (14 days)

---

3. **Risk of bias:** Serious. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.
5. **Risk of bias:** Serious. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.
6. Systematic review [74] with included studies: [75]. **Baseline/comparator:** Control arm of reference used for intervention.
7. Systematic review [74] with included studies: [75]. **Baseline/comparator:** Control arm of reference used for intervention.
9. **Risk of bias:** Serious. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.
6.5 - Chloroquine

**Strong Recommendation Against**

For people with COVID-19, do not use chloroquine outside of randomised trials with appropriate ethical approval.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use chloroquine in these populations unless they are eligible to be enrolled in trials.

**Key Info**

**Benefits and harms**

**General adult population**

In addition to uncertainty around benefits for patients with COVID-19, there are well-known harms with potentially severe adverse events. Although most of the information on side effects and harms associated with chloroquine is derived from long-term use, potential acute harms include prolonged QT interval and lowered convulsive threshold.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

There are additional concerns regarding harms as chloroquine has not been sufficiently tested in these populations. Chloroquine is used in pregnant and breastfeeding women for the treatment of malaria and autoimmune diseases in some countries. The available evidence is limited, though it is not associated with pregnancy loss, stillbirth or neonatal death [53]. For people requiring palliative care, the benefits for symptom management are uncertain.

**Certainty of the Evidence**

**General adult population**

Certainty of the evidence for each outcome is very low. This is based on serious risk of bias due to non-blinding of participants and personnel and incomplete outcome data, and very serious imprecision due to the low number of patients and/or events for some outcomes and the reliance on a single study.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, certainty of the evidence is additionally considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Preference and values**

**General adult population**

We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of chloroquine in pregnancy are unknown.

**Resources and other considerations**

Important issues, or potential issues not investigated
We have no systematically collected evidence regarding cost-benefit.

**Equity**

**General adult population**
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**Special populations (people requiring palliative care and older people living with frailty or cognitive impairment)**
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

**Acceptability**

**General adult population, children and adolescents, pregnant and breastfeeding women**
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

**People requiring palliative care and older people living with frailty or cognitive impairment**
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

**Feasibility**

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. In addition, although chloroquine is registered on the Australian Register of Therapeutic Goods (ARTG), it is not marketed in Australia and is therefore not readily available.

**Rationale**

**General adult population**
There is currently limited evidence about the impact of chloroquine on patient-relevant outcomes in COVID-19. The panel has significant concerns about the potential harms of unproven treatments. We therefore recommend that chloroquine should only be administered in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of chloroquine in these populations should be avoided until evidence becomes available.

**Clinical Question/ PICO**

- **Population:** Patients with COVID-19
- **Intervention:** Chloroquine
- **Comparator:** Standard care
Summary
Evidence informing this recommendation comes from a single randomised trial that compared chloroquine plus standard care to standard care alone in 30 hospitalised adult patients with moderate COVID-19 \[40\]. It is unclear if pregnant women were eligible for inclusion. Mean age in the chloroquine group was 45 years (± 14 years) and 39% were men. In the control group mean age was 51 years (± 15 years) and 58% were men.

The study results are only available as a preprint paper (posted to medRxiv on 22 June 2020) and have therefore not been peer-reviewed. We follow up with the corresponding author every two months to request an update on the study’s publication status.

Reported outcomes include all-cause mortality, disease progression (from moderate to critical/severe), adverse events, median time to clinical recovery and median time from randomisation to termination of oxygen therapy. The study did not report results for respiratory failure or ARDS, or the requirement for mechanical ventilation/ECMO.

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias (lack of blinding of patients, personnel and outcome assessors, and incomplete reporting of data) and very serious imprecision (low number of patients and/or low number of observed events, and the reliance on a single study).

Although listed on the Australian Register of Therapeutic Goods (ARTG), chloroquine is not marketed in Australia and is not available for general use. Based on the available evidence, there remains significant uncertainty whether chloroquine is more effective and safer than standard care in treating patients with COVID-19.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 28 days after commencing treatment</td>
<td>Based on data from 30 patients in 1 studies. (^1) (Randomized controlled)</td>
<td></td>
<td>2</td>
<td>There were no deaths</td>
</tr>
<tr>
<td>Progression to severe or critical disease</td>
<td>Within 28 days after commencing treatment</td>
<td>Based on data from 30 patients in 1 studies. (^3) (Randomized controlled)</td>
<td></td>
<td>4</td>
<td>No patients progressed to severe or critical disease</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Within 28 days after commencing treatment</td>
<td>Relative risk 2.67 (CI 95% 0.68 - 10.46) Based on data from 30 patients in 1 studies. (^2) (Randomized controlled)</td>
<td>167 per 1000 (\text{difference:} 279 \text{ more per} \ 1000) (CI 95% 53 fewer - 1,580 more)</td>
<td>Very Low Due to serious risk of bias and very serious imprecision (^6)</td>
<td>We are uncertain whether chloroquine increases or decreases adverse events (total no of events = 10)</td>
</tr>
</tbody>
</table>
1. Systematic review [34] with included studies: Chen L 2020. **Baseline/comparator:** Control arm of reference used for intervention.

2. **Risk of bias:** **Serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Imprecision:** **Very Serious.** Low number of patients, Only data from one study.

3. Systematic review [34] with included studies: Chen L 2020. **Baseline/comparator:** Control arm of reference used for intervention.

4. **Risk of bias:** **Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Imprecision:** **Very Serious.** Low number of patients, Only data from one study.

5. Systematic review [34] with included studies: Chen L 2020. **Baseline/comparator:** Control arm of reference used for intervention.

6. **Risk of bias:** **Serious.** Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision:** **Very Serious.** Low number of patients, Only data from one study.

7. **Risk of bias:** **Serious.** Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision:** **Very Serious.** Only data from one study, Low number of patients.

8. **Risk of bias:** **Serious.** Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision:** **Very Serious.** Low number of patients, Only data from one study.

9. **Risk of bias:** **Serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up.

### Serious adverse events

**Within 28 days after commencing treatment**

<table>
<thead>
<tr>
<th>event</th>
<th>description</th>
<th>risk</th>
<th>imprecision</th>
<th>note</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Important</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>event</th>
<th>description</th>
<th>risk</th>
<th>imprecision</th>
<th>note</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>There were no serious adverse events</td>
<td>Serious</td>
<td>Very Serious</td>
<td></td>
</tr>
</tbody>
</table>

### Time to clinical recovery

**Median time to clinical recovery (Days)**

<table>
<thead>
<tr>
<th>measure</th>
<th>description</th>
<th>risk</th>
<th>imprecision</th>
<th>note</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Important</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>measure</th>
<th>description</th>
<th>risk</th>
<th>imprecision</th>
<th>note</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5</td>
<td>(Median)</td>
<td></td>
<td>CI 95%</td>
<td></td>
</tr>
<tr>
<td>5.5</td>
<td>(Median)</td>
<td></td>
<td>CI 95%</td>
<td></td>
</tr>
</tbody>
</table>

**Very Low** Due to serious risk of bias and very serious imprecision

We are uncertain whether chloroquine increases or decreases time to clinical recovery

### Time to termination of oxygen therapy

**Median time from randomisation to termination of oxygen therapy (Days)**

<table>
<thead>
<tr>
<th>measure</th>
<th>description</th>
<th>risk</th>
<th>imprecision</th>
<th>note</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Important</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>measure</th>
<th>description</th>
<th>risk</th>
<th>imprecision</th>
<th>note</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>(Median)</td>
<td></td>
<td>CI 95%</td>
<td></td>
</tr>
<tr>
<td>8.5</td>
<td>(Median)</td>
<td></td>
<td>CI 95%</td>
<td></td>
</tr>
</tbody>
</table>

**Very Low** Due to serious risk of bias and very serious imprecision

We are uncertain whether chloroquine increases or decreases time to termination of oxygen therapy

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follow up. **Imprecision: Very Serious.** Low number of patients, Only data from one study.

### Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population</th>
<th>Special populations with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>Comparator</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

### Summary

Evidence informing this recommendation comes from a single randomised trial that compared chloroquine plus standard care to standard care alone in 30 hospitalised patients with moderate COVID-19 [40]. Inclusion was limited to patients aged 18 years and older. It is unclear if pregnant women were eligible for inclusion. Mean age in the chloroquine group was 45 years (± 14 years) and 39% were men. In the control group mean age was 51 years (± 15 years) and 58% were men.

The study results are only available as a preprint paper (posted to medRxiv on 22 June 2020) and have therefore not been peer-reviewed. We follow up with the corresponding author every two months to request an update on the study’s publication status.

Reported outcomes include all-cause mortality, disease progression (from moderate to critical/severe), adverse events, median time to clinical recovery and median time from randomisation to termination of oxygen therapy. The study did not report results for respiratory failure or ARDS, or the requirement for mechanical ventilation/ECMO.

Certainty of the evidence for all outcomes is very low. This judgement is based on serious risk of bias (lack of blinding of patients, personnel and outcome assessors, and incomplete reporting of data), serious indirectness (limited inclusion of these populations) and very serious imprecision (low number of patients and/or low number of observed events, and the reliance on a single study).

Although listed on the Australian Register of Therapeutic Goods (ARTG), chloroquine is not marketed in Australia and is not available for general use. Based on the available evidence, there remains significant uncertainty whether chloroquine is more effective and safer than standard care in treating patients with COVID-19.

### Children and adolescents

Paediatricians have considerable experience with using chloroquine in children and adolescents for other indications. To date, no specific information on benefits or harms for children and adolescents with COVID-19 has been collected.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
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<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 28 days after commencing treatment</td>
<td>Based on data from 30 patients in 1 studies.</td>
<td>2</td>
<td>2</td>
<td>There were no deaths</td>
</tr>
<tr>
<td>Progression to critical</td>
<td></td>
<td></td>
<td>4</td>
<td>4</td>
<td>No patients progressed</td>
</tr>
</tbody>
</table>
**severe or critical disease**
Within 28 days after commencing treatment

- Based on data from 30 patients in 1 studies. \(^3\)
  (Randomized controlled)

**Adverse events**
Within 28 days after commencing treatment

- Relative risk 2.67 (CI 95% 0.68 - 10.46)
  Based on data from 30 patients in 1 studies. \(^5\)
  (Randomized controlled)

**Serious adverse events**
Within 28 days after commencing treatment

- Based on data from 30 patients in 1 studies.
  (Randomized controlled)

**Time to clinical recovery**
Median time to clinical recovery (Days)

- Measured by: Median time to clinical recovery; chloroquine: 5.5 days (IQR 3.25-7.5), control: 7.5 days (IQR 5.0-16.25)
  Lower better
  (Randomized controlled)

**Time to termination of oxygen therapy**
Median time from randomisation to termination of oxygen therapy (Days)

- Measured by: Median time to termination of oxygen therapy; chloroquine: 8.5 days (IQR 0-9.25); control: 8 days (IQR 3.25-14)
  Lower better
  (Randomized controlled)

### Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rate per 1000</th>
<th>Difference</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe or critical disease</td>
<td>167</td>
<td>279 more</td>
<td>0.68 - 10.46</td>
</tr>
<tr>
<td>Adverse events</td>
<td>446</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to clinical recovery</td>
<td>7.5 (Median)</td>
<td>5.5 (Median)</td>
<td></td>
</tr>
<tr>
<td>Time to termination of oxygen therapy</td>
<td>8 (Median)</td>
<td>8.5 (Median)</td>
<td></td>
</tr>
</tbody>
</table>

**Risk of bias:** Serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Incomplete data and/or large loss to follow up. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.

**We are uncertain whether chloroquine increases or decreases adverse events (total no of events = 10)**

**We are uncertain whether chloroquine increases or decreases time to clinical recovery**

**We are uncertain whether chloroquine increases or decreases time to termination of oxygen therapy**

---

1. Systematic review [34] with included studies: Chen L 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias:** Serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Incomplete data and/or large loss to follow up. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.
3. Systematic review [34] with included studies: Chen L 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.

5. Systematic review [34] with included studies: Chen L 2020. **Baseline/comparator:** Control arm of reference used for intervention.

6. **Risk of bias:** Serious. Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.

7. **Risk of bias:** Serious. Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.

8. **Risk of bias:** Serious. Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.

9. **Risk of bias:** Serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.

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**6.6 - Colchicine**

**Strong Recommendation Against**

For people with COVID-19, do not use colchicine outside of randomised trials with appropriate ethical approval.

**Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use colchicine in these populations unless they are eligible to be enrolled in trials.**

**Key Info**

**Benefits and harms**

**General adult population**

In addition to uncertainty around benefits for patients with COVID-19, there are known side effects and harms associated with colchicine including diarrhoea. Overdose of colchicine can cause severe diarrhoea and dehydration, bone marrow suppression, metabolic acidosis and shock.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

There are additional concerns regarding harms as colchicine has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain. Studies of colchicine in pregnancy for some rheumatological conditions have shown no increase in major fetal anomalies or pregnancy loss [56].

**Certainty of the Evidence**

Certainty of the evidence for each outcome is low or very low due to very serious imprecision (low number of patients and reliance on a single study) and serious risk of bias.
Rationale

General adult population
There is currently limited evidence about the impact of colchicine on patient-relevant outcomes in COVID-19. The panel has significant concerns about the potential harms of unproven treatments. We therefore recommend that colchicine should only be administered in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of colchicine in these populations should be avoided until evidence becomes available.

Preference and values

General adult population
We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of colchicine in pregnancy are unknown.

Resources and other considerations

We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.

Equity

General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

General adult population, children and adolescents, pregnant and breastfeeding women
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility
Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale

General adult population
There is currently limited evidence about the impact of colchicine on patient-relevant outcomes in COVID-19. The panel has significant concerns about the potential harms of unproven treatments. We therefore recommend that colchicine should only be administered in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of colchicine in these populations should be avoided until evidence becomes available.
Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Colchicine
Comparator: Standard care

Summary
Evidence informing this recommendation comes from a single randomised trial that compared colchicine plus usual care to usual care alone in 105 hospitalised adult patients with laboratory-confirmed COVID-19—pregnant and breastfeeding women were ineligible. Fifty-eight percent were men and the median age was 64 years (IQR 54-76 years) [55].

Reported outcomes include all-cause mortality, clinical deterioration (reduction of 2 points on the clinical status scale based on the WHO R&D Blueprint Committee definition), requirement of mechanical ventilation, adverse events, serious adverse events and discontinuation due to adverse events. Outcomes were measured within three weeks following randomisation or until hospital discharge.

Certainty of the evidence is low for all-cause mortality, mechanical ventilation, clinical deterioration and discontinuation due to adverse events. This judgement is based on very serious imprecision due to the reliance on a single study and the low number of patients and/or low number of observed events. Certainty of the evidence for adverse events and serious adverse events is very low due to the serious imprecision specified above and serious risk of bias. Patients, personnel involved in administering treatment and outcome assessors were not blinded, which may have affected the reporting and/or severity of these events.

According to the Therapeutic Goods Administration, known acute harms for colchicine include diarrhoea or stomach cramps. Colchicine overdose can cause severe diarrhoea and dehydration, bone marrow suppression, metabolic acidosis and shock [54]. There are several known and potential interactions with other drugs [54]. Colchicine should be avoided in pregnancy and during lactation and in children under 2 years of age. Caution should be taken when prescribing colchicine to elderly patients who may be more susceptible to cumulative toxicity.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong> Within 21 days after commencing treatment</td>
<td>Relative risk 0.23 (CI 95% 0.03 - 1.97) Based on data from 105 patients in 1 studies. (Randomized controlled)</td>
<td>80/1000 for Standard care and 18/1000 for Colchicine</td>
<td>Low Due to very serious imprecision 2</td>
<td>There were too few who experienced all-cause mortality to determine whether colchicine makes a difference (total no of events = 5)</td>
</tr>
<tr>
<td><strong>Mechanical ventilation</strong> Within 21 days after commencing treatment</td>
<td>Relative risk 0.15 (CI 95% 0.02 - 1.22) Based on data from 105 patients in 1 studies. (Randomized controlled)</td>
<td>120/1000 for Standard care and 18/1000 for Colchicine</td>
<td>Low Due to very serious imprecision 4</td>
<td>There were too few who experienced mechanical ventilation to determine whether colchicine makes a difference (total no of events = 7)</td>
</tr>
</tbody>
</table>
### Adverse events

Within 21 days after commencing treatment

<table>
<thead>
<tr>
<th>Relative risk 2.61 (CI 95% 1.67 - 4.07)</th>
<th>300 per 1000</th>
<th>783 per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference: <strong>483 more</strong> per 1000 (CI 95% 201 more - 921 more)</td>
<td>Very Low</td>
<td>We are uncertain whether colchicine increases or decreases adverse events (total no of events = 58)</td>
</tr>
</tbody>
</table>

Based on data from 105 patients in 1 studies. *(Randomized controlled)*

### Serious adverse events

Within 21 days after commencing treatment

<table>
<thead>
<tr>
<th>Relative risk 0.13 (CI 95% 0.02 - 1.02)</th>
<th>140 per 1000</th>
<th>18 per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference: <strong>122 fewer</strong> per 1000 (CI 95% 137 fewer - 3 more)</td>
<td>Low</td>
<td>There were too few who experienced clinical deterioration to determine whether colchicine makes a difference (total no of events = 8)</td>
</tr>
</tbody>
</table>

Based on data from 105 patients in 1 studies. *(Randomized controlled)*

### Clinical deterioration

Within 21 days after commencing treatment

<table>
<thead>
<tr>
<th>Relative risk 4.55 (CI 95% 0.22 - 92.62)</th>
<th>0 per 1000</th>
<th>0 per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference: <strong>0 fewer</strong> per 1000 (CI 95% 0 fewer - 0 fewer)</td>
<td>Low</td>
<td>There were too few who experienced discontinuation due to adverse events to determine whether colchicine makes a difference (total no of events = 2)</td>
</tr>
</tbody>
</table>

Based on data from 105 patients in 1 studies. *(Randomized controlled)*

### Discontinuation due to adverse events

Within 21 days after commencing treatment

<table>
<thead>
<tr>
<th>Relative risk 4.55 (CI 95% 0.22 - 92.62)</th>
<th>0 per 1000</th>
<th>0 per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference: <strong>0 fewer</strong> per 1000 (CI 95% 0 fewer - 0 fewer)</td>
<td>Low</td>
<td>There were too few who experienced discontinuation due to adverse events to determine whether colchicine makes a difference (total no of events = 2)</td>
</tr>
</tbody>
</table>

Based on data from 105 patients in 1 studies. *(Randomized controlled)*

---

1. Systematic review [38] with included studies: Deftereos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias:** No serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** Very Serious. Low number of patients, Only data from one study.
3. Systematic review [38] with included studies: Deftereos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of bias:** No serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision:** Very Serious. Low number of patients, Only data from one study.
5. Systematic review [38] with included studies: Deftereos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision:** Very Serious. Low number of patients, Only data from one study.
7. Systematic review [38] with included studies: Deftereos 2020. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of bias: Serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: Very Serious.** Low number of patients, Only data from one study.

9. Systematic review [38] with included studies: Deftereos 2020. **Baseline/comparator:** Control arm of reference used for intervention.

10. **Risk of bias: No serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Very Serious.** Only data from one study, Low number of patients.

11. Systematic review [38] with included studies: Deftereos 2020. **Baseline/comparator:** Control arm of reference used for intervention.

12. **Risk of bias: No serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: Very Serious.** Low number of patients, Only data from one study.

### Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population</th>
<th>Special populations with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Colchicine</td>
</tr>
<tr>
<td>Comparator</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

### Summary

Evidence informing this recommendation comes from a single randomised trial that compared colchicine plus usual care to usual care alone in 105 hospitalised adult patients with laboratory-confirmed COVID-19—pregnant and breastfeeding women were ineligible. Fifty-eight percent were men and the median age was 64 years (IQR 54-76 years) [55].

Reported outcomes include all-cause mortality, clinical deterioration (reduction of 2 points on the clinical status scale based on the WHO R&D Blueprint Committee definition), requirement of mechanical ventilation, adverse events, serious adverse events and discontinuation due to adverse events. Outcomes were measured within three weeks following randomisation or until hospital discharge.

Certainty of the evidence is very low for all outcomes. This judgement is based on very serious imprecision due to the reliance on a single study and the low number of patients and/or low number of observed events, and serious indirectness due to limited inclusion of these populations. Certainty of the evidence for adverse events was additionally downgraded for risk of bias since patients, personnel and outcome assessors were not blinded, which may have affected the reporting of these events.

According to the Therapeutic Goods Administration, known acute harms for colchicine include diarrhoea or stomach cramps. Colchicine overdose can cause severe diarrhoea and dehydration, bone marrow suppression, metabolic acidosis and shock [54]. There are several known and potential interactions with other drugs [54]. Colchicine should be avoided in pregnancy and during lactation and in children under 2 years of age. Caution should be taken when prescribing colchicine to elderly patients who may be more susceptible to cumulative toxicity.

**Children and adolescents**

Paediatricians have limited experience with colchicine in children and adolescents for other indications. To date, no specific information on its benefits or harms has been collected for treating COVID-19 in this population.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk</th>
<th>Confidence Interval</th>
<th>Based on</th>
<th>Criticality</th>
<th>Study Details</th>
<th>Risk of Bias</th>
<th>Imprecision</th>
<th>Indirectness</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>0.23</td>
<td>(CI 95% 0.03 - 1.97)</td>
<td>105 patients</td>
<td><strong>9 Critical</strong></td>
<td>randomized controlled study</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>There were too few who experienced all-cause mortality to determine whether colchicine makes a difference (total no of events = 5)</td>
</tr>
<tr>
<td><strong>Mechanical ventilation</strong></td>
<td>0.15</td>
<td>(CI 95% 0.02 - 1.22)</td>
<td>105 patients</td>
<td><strong>9 Critical</strong></td>
<td>randomized controlled study</td>
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<td>There were too few who experienced mechanical ventilation to determine whether colchicine makes a difference (total no of events = 7)</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>2.61</td>
<td>(CI 95% 1.67 - 4.07)</td>
<td>105 patients</td>
<td><strong>6 Important</strong></td>
<td>randomized controlled study</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>We are uncertain whether colchicine increases or decreases adverse events (total no of events = 58)</td>
</tr>
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<td><strong>Serious adverse events</strong></td>
<td>0.13</td>
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<td><strong>6 Important</strong></td>
<td>randomized controlled study</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>There were too few who experienced serious adverse events to determine whether colchicine makes a difference (total no of events = 8)</td>
</tr>
<tr>
<td><strong>Clinical deterioration</strong></td>
<td>4.55</td>
<td>(CI 95% 0.22 - 92.62)</td>
<td>105 patients</td>
<td><strong>6 Important</strong></td>
<td>randomized controlled study</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>There were too few who experienced clinical deterioration to determine whether colchicine makes a difference (total no of events = 8)</td>
</tr>
<tr>
<td><strong>Discontinuation due to adverse events</strong></td>
<td>1.00</td>
<td>(CI 95% 0.02 - 1.02)</td>
<td>105 patients</td>
<td><strong>6 Important</strong></td>
<td>randomized controlled study</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>There were too few who experienced discontinuation due to adverse events to determine whether colchicine makes a difference (total no of events = 2)</td>
</tr>
</tbody>
</table>

**Adverse events**
- Relative risk: 2.61
- Confidence Interval: (CI 95% 1.67 - 4.07)
- Based on: 105 patients in 1 study
- Criticality: 6 Important
- Study: Randomized controlled
- Difference: 483 more per 1000 (CI 95% 201 more - 921 more)
- Risk of Bias: Low
- Imprecision: Low
- Indirectness: Low
- Conclusion: We are uncertain whether colchicine increases or decreases adverse events (total no of events = 58)

**Clinical deterioration**
- Relative risk: 0.13
- Confidence Interval: (CI 95% 0.02 - 1.02)
- Based on: 105 patients in 1 study
- Criticality: 6 Important
- Study: Randomized controlled
- Difference: 122 fewer per 1000 (CI 95% 137 fewer - 3 more)
- Risk of Bias: Low
- Imprecision: Low
- Indirectness: Low
- Conclusion: There were too few who experienced clinical deterioration to determine whether colchicine makes a difference (total no of events = 8)

**Discontinuation due to adverse events**
- Relative risk: 4.55
- Confidence Interval: (CI 95% 0.22 - 92.62)
- Based on: 105 patients in 1 study
- Criticality: 6 Important
- Study: Randomized controlled
- Difference: 0 fewer per 1000 (CI 95% 0 fewer - 0 fewer)
- Risk of Bias: Low
- Imprecision: Low
- Indirectness: Low
- Conclusion: There were too few who experienced discontinuation due to adverse events to determine whether colchicine makes a difference (total no of events = 2)
Strong Recommendation Against

For people with COVID-19, do not use convalescent plasma outside of randomised trials with appropriate ethical approval.

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use convalescent plasma in these populations unless they are eligible to be enrolled in trials.*

**Key Info**

**Benefits and harms**

**General adult population**

There is uncertainty around benefits and harms associated with convalescent plasma in patients with COVID-19.
Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment

There are additional concerns regarding harms as convalescent plasma has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain. There is insufficient evidence pertaining to the safety of convalescent plasma for pregnant or breastfeeding women (for any indication) [57].

Certainty of the Evidence

General adult population
Certainty of the evidence is low for mortality and very low all other outcomes due to serious risk of bias (lack of blinding of outcome assessors) and very serious imprecision (due to the low number of patients and observed events).

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

Preference and values

General adult population
We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of convalescent plasma in pregnancy are unknown.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

General adult population, children and adolescents, pregnant and breastfeeding women
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

**People requiring palliative care and older people living with frailty or cognitive impairment**
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

**Feasibility**
Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Rationale**

**General adult population**
There is currently limited evidence about the impact of convalescent plasma on patient-relevant outcomes in COVID-19 [57]. The panel has significant concerns about the potential harms of unproven treatments. We therefore recommend that convalescent plasma should only be administered in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of convalescent plasma in these populations should be avoided until evidence becomes available.

**Clinical Question/ PICO**

| Population: | Patients with COVID-19 |
| Intervention: | Convalescent plasma |
| Comparator: | Standard care |

**Summary**
Evidence informing this recommendation comes from a single randomised trial that compared convalescent plasma to standard care in 103 hospitalised adult patients with severe or critical COVID-19 [80].

Certainty of the evidence is low for all-cause mortality and very low for all other outcomes. This judgement is based on serious risk of bias due to lack of blinding, and very serious imprecision due to the low number of patients and observed events and the reliance on a single study. Mortality was not downgraded for risk of bias as this outcome is unlikely to be biased by lack of blinding.

Information pertaining to the safety of convalescent plasma for the treatment of COVID-19 is not currently available. The present study did not clearly state the total number of adverse events associated with its use.

Based on the available evidence, there remains significant uncertainty whether convalescent plasma is more effective and safer than standard care in treating patients with COVID-19.
<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Based on data from</th>
<th>Difference</th>
<th>95% CI</th>
<th>Risk of bias</th>
<th>Imprecision</th>
<th>Clinical outcome</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Based on data from</th>
<th>Difference</th>
<th>95% CI</th>
<th>Risk of bias</th>
<th>Imprecision</th>
<th>Hospital outcome</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Based on data from</th>
<th>Difference</th>
<th>95% CI</th>
<th>Risk of bias</th>
<th>Imprecision</th>
<th>Viral outcome</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Based on data from</th>
<th>Difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.59</td>
<td>0.22 - 1.59</td>
<td>101 patients in 1</td>
<td>83 fewer</td>
<td>0.22 - 1.59</td>
<td>Low</td>
<td>Very Serious</td>
<td>We are uncertain whether convalescent plasma increases or decreases all-cause mortality (total no of events = 20)</td>
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</tr>
<tr>
<td>Clinical improvement</td>
<td>1.42</td>
<td>0.65 - 3.09</td>
<td>103 patients in 1</td>
<td>87 more</td>
<td>0.65 - 3.09</td>
<td>Very Low</td>
<td>Due to serious risk of bias and very serious imprecision</td>
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<tr>
<td>Hospital discharge</td>
<td>1.85</td>
<td>0.83 - 4.1</td>
<td>101 patients in 1</td>
<td>150 more</td>
<td>0.83 - 4.1</td>
<td>Very Low</td>
<td>Due to serious risk of bias and very serious imprecision</td>
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</tr>
<tr>
<td>Viral nucleic acid negative</td>
<td>11.39</td>
<td>3.91 - 33.18</td>
<td>87 patients in 1</td>
<td>497 more</td>
<td>3.91 - 33.18</td>
<td>Very Low</td>
<td>We are uncertain whether convalescent plasma increases or decreases viral nucleic acid negative (72 hours; total no of events = 56)</td>
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</tbody>
</table>

2. **Imprecision: Very Serious.** Low number of patients, Only data from one study, Low number of patients, Only data from one study.
4. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Very Serious.** Low number of patients, Only data from one study.
6. **Risk of bias: Serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: Very Serious.** Low number of patients, Only data from one study.
8. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: Very Serious.** Low number of patients, Only data from one study.

### Clinical Question/ PICO

- **Population:** Special populations with COVID-19
- **Intervention:** Convalescent plasma
- **Comparator:** Standard care

### Summary

Evidence informing this recommendation comes from a single randomised trial that compared convalescent plasma to standard care in 103 hospitalised adult patients with severe or critical COVID-19 [80].

Certainty of the evidence is very low for all outcomes. This judgement is based on serious risk of bias due to lack of blinding, serious indirectness due to limited inclusion of these populations, and very serious imprecision due to the low number of patients and observed events and the reliance on a single study. Mortality was not downgraded for risk of bias as this outcome is unlikely to be biased by lack of blinding.

Information pertaining to the safety of convalescent plasma for the treatment of COVID-19 is not currently available. The present study did not clearly state the total number of adverse events associated with its use.

Based on the available evidence, there remains significant uncertainty whether convalescent plasma is more effective and safer than standard care in treating patients with COVID-19.

### Children and adolescents

There is insufficient safety data on the use of convalescent plasma in children and adolescents for other indications.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>Within 28 days after commencing treatment</td>
<td>Odds Ratio 0.59 (CI 95% 0.22 - 1.59) Based on data from 101 patients in 1 studies. ¹ (Randomized controlled)</td>
<td><strong>240</strong> per 1000 <strong>157</strong> per 1000</td>
<td><strong>Very Low</strong> Due to very serious imprecision and serious indirectness ² ³</td>
</tr>
<tr>
<td><strong>Clinical improvement</strong></td>
<td>Within 28 days after commencing treatment</td>
<td>Odds Ratio 1.42 (CI 95% 0.65 - 3.09) Based on data from 103 patients in 1 studies. ³ (Randomized controlled)</td>
<td><strong>431</strong> per 1000 <strong>518</strong> per 1000</td>
<td><strong>Very Low</strong> Due to serious risk of bias, serious indirectness and very serious imprecision ⁴</td>
</tr>
</tbody>
</table>
### 6.8 - Darunavir-cobicistat

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio</th>
<th>CI 95%</th>
<th>Difference</th>
<th>Imprecision</th>
<th>Risk of Bias</th>
<th>Indirectness</th>
<th>Baseline/comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital discharge within 28 days after commencing treatment</td>
<td>1.85</td>
<td>0.83 - 4.1</td>
<td>150 more</td>
<td>Very Low</td>
<td>Serious</td>
<td>Serious</td>
<td>Control arm of reference</td>
</tr>
<tr>
<td>Viral nucleic acid negative (72 hours)</td>
<td>11.39</td>
<td>3.91 - 33.18</td>
<td>497 more</td>
<td>Very Low</td>
<td>Serious</td>
<td>Serious</td>
<td>Control arm of reference</td>
</tr>
</tbody>
</table>

**Strong Recommendation Against**

For people with COVID-19, do not use darunavir-cobicistat outside of randomised trials with appropriate ethical approval.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use darunavir-cobicistat in these populations unless they are eligible to be enrolled in trials.
Key Info

Benefits and harms

General adult population
In addition to uncertainty around benefits for patients with COVID-19, there are well-known short-term harms associated with darunavir-cobicistat including severe skin reactions. There are several known and potential interactions with drugs that inhibit CYP3A4 and anti-arrhythmic drugs.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
The benefits and harms associated with darunavir-cobicistat in pregnant women and young children with COVID-19 are not well established. Darunavir plus cobicistat is not recommended for the treatment of HIV in pregnant women because of inadequate safety data for cobicistat. Caution should be taken when prescribing darunavir-cobicistat to children, adolescents or elderly patients.

Certainty of the evidence

General adult population
Certainty of the evidence for each outcome is very low due to serious risk of bias and very serious imprecision (low number of patients and/or observed events and reliance on a single study).

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

Preference and values

General adult population
We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of darunavir-cobicistat in pregnancy are unknown.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring...
There is currently limited evidence about the impact of darunavir-cobicistat on patient-relevant outcomes in COVID-19. The panel has significant concerns about the potential harms of unproven treatments. We therefore recommend that darunavir-cobicistat should only be administered in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment

There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of darunavir-cobicistat in these populations should be avoided until evidence becomes available.

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale

General adult population

There is currently limited evidence about the impact of darunavir-cobicistat on patient-relevant outcomes in COVID-19. The panel has significant concerns about the potential harms of unproven treatments. We therefore recommend that darunavir-cobicistat should only be administered in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment

There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of darunavir-cobicistat in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

Population: Darunavir-cobicistat for COVID-19

Intervention: Darunavir-cobicistat

Comparator: Standard care

Summary

Evidence informing this recommendation comes from a single randomised trial that compared darunavir-cobicistat plus usual care to usual care alone in 30 hospitalised adult patients with laboratory confirmed SARS-CoV-2 infection and mild-to-moderate symptoms of COVID-19 [61]. Patients considered unlikely to complete the study (e.g. severely or critically ill) or deemed not suitable by the investigators were excluded. Mean age was 47 years (SD 2.8) and 60% were men.

Reported outcomes were viral clearance at days 3, 5 and 7, progression to critical illness, all-cause mortality and adverse events. Outcomes were measured within 14 days of randomisation.

Certainty of the evidence for viral clearance and adverse events is very low. This judgement is based on very serious imprecision (reliance on a single study and the low number of patients and/or low number of observed events) and serious risk of bias (patients, personnel and outcome assessors were not blinded which may have affected the reporting and/or severity of these events).
<table>
<thead>
<tr>
<th>Timeframe</th>
<th>measurements</th>
<th>Standard care</th>
<th>Darunavir-cobicistat</th>
<th>the Evidence (Quality of evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong> 14 days after commencing treatment</td>
<td>Based on data from 30 patients in 1 studies. (^1) (Randomized controlled)</td>
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<tr>
<td></td>
<td>2 There were no deaths in the study</td>
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<tr>
<td><strong>Progression to critical illness</strong> 14 days after commencing treatment</td>
<td>Based on data from 30 patients in 1 studies. (^2) (Randomized controlled)</td>
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<td></td>
<td>4 There were too few who experienced progression to critical illness to determine whether darunavir-cobicistat makes a difference (total no of events = 1)</td>
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<tr>
<td><strong>Adverse events</strong> Within 14 days of commencing treatment</td>
<td>Odds Ratio 1.31 (CI 95% 0.31 - 5.48) Based on data from 30 patients in 1 studies. (^3) (Randomized controlled)</td>
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<td></td>
<td>6 Very Low Due to serious risk of bias and very serious imprecision (^4) We are uncertain whether darunavir-cobicistat increases or decreases adverse events within 14 days (total no of events = 15)</td>
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<tr>
<td><strong>Viral clearance Day 7 of treatment</strong></td>
<td>Relative risk 0.78 (CI 95% 0.39 - 1.54) Based on data from 30 patients in 1 studies. (^5) (Randomized controlled)</td>
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<td>8 Very Low Due to serious risk of bias and very serious imprecision (^6) We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 7 (total no of events = 16)</td>
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<tr>
<td><strong>Viral clearance Day 5 of treatment</strong></td>
<td>Odds Ratio 1.45 (CI 95% 0.26 - 8.01) Based on data from 30 patients in 1 studies. (^7) (Randomized controlled)</td>
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<td>10 Very Low Due to serious risk of bias and very serious imprecision (^8) We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 5 (total no of events = 5)</td>
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<tr>
<td><strong>Viral clearance Day 3 of treatment</strong></td>
<td>Odds Ratio 1 (CI 95% 0.17 - 5.98) Based on data from 30 patients in 1 studies. (^9) (Randomized controlled)</td>
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<tr>
<td></td>
<td>12 Very Low Due to serious risk of bias and very serious imprecision (^10) We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 3 (total no of events = 6)</td>
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</table>

1. Systematic review [58] with included studies: Chen J 2020. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias.
Clinical Question/ PICO

**Population:** Special populations with COVID-19

**Intervention:** Darunavir-cobicistat

**Comparator:** Standard care

**Summary**

Evidence informing this recommendation comes from a single randomised trial that compared darunavir-cobicistat plus usual care to usual care alone in 30 hospitalised adult patients with laboratory confirmed SARS-CoV-2 infection and mild-to-moderate symptoms of COVID-19 [61]. Patients considered unlikely to complete the study (e.g. severely or critically ill) or deemed not suitable by the investigators were excluded. Mean age was 47 years (SD 2.8) and 60% were men.

Reported outcomes were viral clearance at days 3, 5 and 7, progression to critical illness, all-cause mortality and adverse events. Outcomes were measured within 14 days of randomisation.

Certainty of the evidence for viral clearance and adverse events is very low. This judgement is based on very serious imprecision (reliance on a single study and the low number of patients and/or low number of observed events), serious indirectness (limited inclusion of these populations) and serious risk of bias (patients, personnel and outcome assessors were not blinded which may have affected the reporting and/or severity of these events).

**Children and adolescents**

Paediatricians have limited experience of darunavir-cobicistat in children and adolescents for other indications. To date, no
specific information on its benefits or harms for children and adolescents has been collected for treating COVID-19 in this population.

**Pregnant and breastfeeding women**

Darunavir plus cobicistat is not recommended for the treatment of HIV in pregnant women because of inadequate safety data for cobicistat.\[62\]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>Based on data from 30 patients in 1 studies.</td>
<td>467 per 1000</td>
<td>Very Low</td>
<td>There were no deaths in the study</td>
</tr>
<tr>
<td>14 days after commencing treatment</td>
<td>(Randomized controlled)</td>
<td>534 per 1000</td>
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<td>Difference: 67 more</td>
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<td>(CI 95% 253 fewer - 361 more)</td>
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<tr>
<td><strong>Progression to critical illness</strong></td>
<td>Based on data from 30 patients in 1 studies.</td>
<td>600 per 1000</td>
<td>Very Low</td>
<td>There were too few who experienced progression to critical illness to determine whether darunavir-cobicistat makes a difference (total no of events = 1)</td>
</tr>
<tr>
<td>14 days after commencing treatment</td>
<td>(Randomized controlled)</td>
<td>468 per 1000</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Difference: 132 fewer</td>
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<tr>
<td></td>
<td></td>
<td>(CI 95% 366 fewer - 324 more)</td>
<td></td>
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</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>Odds Ratio 1.31</td>
<td>200 per 1000</td>
<td>Very Low</td>
<td>We are uncertain whether darunavir-cobicistat increases or decreases adverse events within 14 days (total no of events = 15)</td>
</tr>
<tr>
<td>Within 14 days of commencing treatment</td>
<td>(CI 95% 0.31 - 5.48)</td>
<td>266 per 1000</td>
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<tr>
<td></td>
<td>Based on data from 30 patients in 1 studies.</td>
<td>Difference: 66 more</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Randomized controlled)</td>
<td>(CI 95% 139 fewer - 467 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Viral clearance</strong></td>
<td>Relative risk 0.78</td>
<td>600 per 1000</td>
<td>Very Low</td>
<td>We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 7 (total no of events = 16)</td>
</tr>
<tr>
<td>Day 7 of treatment</td>
<td>(CI 95% 0.39 - 1.54)</td>
<td>468 per 1000</td>
<td></td>
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<tr>
<td></td>
<td>Based on data from 30 patients in 1 studies.</td>
<td>Difference: 132 fewer</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(Randomized controlled)</td>
<td>(CI 95% 366 fewer - 324 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Viral clearance</strong></td>
<td>Odds Ratio 1.45</td>
<td>200 per 1000</td>
<td>Very Low</td>
<td>We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 5 (total no of events = 5)</td>
</tr>
<tr>
<td>Day 5 of treatment</td>
<td>(CI 95% 0.26 - 8.01)</td>
<td>266 per 1000</td>
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<tr>
<td></td>
<td>Based on data from 30 patients in 1 studies.</td>
<td>Difference: 66 more</td>
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<tr>
<td></td>
<td>(Randomized controlled)</td>
<td>(CI 95% 139 fewer - 467 more)</td>
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</tbody>
</table>
**6.9 - Favipiravir**

**Strong Recommendation Against**

For people with COVID-19, do not use favipiravir outside of randomised trials with appropriate ethical approval.

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use favipiravir in these populations unless they are eligible to be enrolled in trials.*
Key Info

Benefits and harms

**General adult population**
As the safety profile for favipiravir is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as favipiravir has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

Certainty of the Evidence

**General adult population**
Certainty of the evidence is low for mortality and very low for all other outcomes due to serious risk of bias (lack of blinding of outcome assessors) and very serious imprecision (due to the low number of patients and observed events).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

Preference and values

**General adult population**
We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of favipiravir in pregnancy are unknown.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

**General adult population**
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.
Rationale

**General adult population**
There is currently limited evidence about the impact of favipiravir on patient-relevant outcomes in COVID-19. The panel has significant concerns about the potential harms of unproven treatments. We therefore recommend that favipiravir should only be administered in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Clinical Question/ PICO

- **Population:** Patients with COVID-19
- **Intervention:** Favipiravir
- **Comparator:** Standard care

Summary

Evidence informing this recommendation comes from a single randomised trial that compared favipiravir to standard care in 19 hospitalised adults patients with COVID-19 [75]. Patients concomitantly used lopinavir-ritonavir, darunavir-cobicistat and/or arbidol. It is unclear whether pregnant or breastfeeding women were eligible. Mean age was 58 years in the favipiravir group (22% women) and 47 years in the control group (30% women).

The study results are only available as a preprint paper (posted to medRxiv on 5 May 2020) and have therefore not been peer-reviewed. We follow up with the corresponding author every two months to request an update on the study's publication status.

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias due to lack of blinding and very serious imprecision due to the low number of patients and/or observed events and the reliance on a single study.

As of 6 May 2020, favipiravir (Avigan) is not approved for use in Australia. The safety profile for favipiravir is incompletely characterised in humans.

Based on the available evidence, there remains significant uncertainty whether favipiravir is more effective and safer than standard care in treating patients with COVID-19.
<table>
<thead>
<tr>
<th>Timeframe</th>
<th>measurements</th>
<th>Standard care</th>
<th>Favipiravir</th>
<th>the Evidence (Quality of evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td><strong>During treatment (14 days)</strong></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td></td>
<td></td>
<td>There were no deaths in the study</td>
</tr>
<tr>
<td><strong>Respiratory failure or ARDS</strong></td>
<td><strong>During treatment (14 days)</strong></td>
<td></td>
<td></td>
<td>Very Low</td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td></td>
<td></td>
<td>Due to serious risk of bias and very serious imprecision 4</td>
</tr>
<tr>
<td></td>
<td>Odds Ratio 1.2 (CI 95% 0.19 - 7.44)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>Based on data from 19 patients in 1 studies. 1</td>
<td></td>
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<tr>
<td><strong>Mechanical ventilation or ECMO</strong></td>
<td><strong>During treatment (14 days)</strong></td>
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<tr>
<td></td>
<td>9 Critical</td>
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<td></td>
<td>Based on data from 19 patients in 1 studies. 5</td>
<td></td>
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</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td><strong>During treatment (14 days)</strong></td>
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<td></td>
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<td></td>
<td>9 Critical</td>
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<td></td>
<td>Data for number of patients experiencing one or more events were not reported</td>
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<tr>
<td><strong>Adverse events</strong></td>
<td><strong>During treatment (14 days)</strong></td>
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<tr>
<td></td>
<td>6 Important</td>
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<td>Data for number of patients experiencing one or more events were not reported</td>
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<tr>
<td><strong>Clinical improvement</strong></td>
<td><strong>End of treatment (14 days)</strong></td>
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<td>6 Important</td>
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<td></td>
<td>Odds Ratio 1.25 (CI 95% 0.21 - 7.62)</td>
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<tr>
<td></td>
<td>Based on data from 19 patients in 1 studies. 8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Question/ PICO

Population: Special populations with COVID-19
Intervention: Favipiravir
Comparator: Standard care

Summary
Evidence informing this recommendation comes from a single randomised trial that compared favipiravir to standard care in 19 hospitalised adults patients with COVID-19 [75]. Patients concomitantly used lopinavir-ritonavir, darunavir-cobicistat and/or arbidol. It is unclear whether pregnant or breastfeeding women were eligible. Mean age was 58 years in the favipiravir group (22% women) and 47 years in the control group (30% women).

The study results are only available as a preprint paper (posted to medRxiv on 5 May 2020) and have therefore not been peer-reviewed. We follow up with the corresponding author every two months to request an update on the study's publication status.

Certainty of the evidence is very low. This judgement is based on serious risk of bias due to lack of blinding, serious indirectness (limited inclusion of these populations) and very serious imprecision due to the low number of patients and/or observed events and the reliance on a single study.

As of 6 May 2020, favipiravir (Avigan) is not approved for use in Australia. The safety profile for favipiravir is incompletely characterised in humans.

Based on the available evidence, there remains significant uncertainty whether favipiravir is more effective and safer than standard care in treating patients with COVID-19.

Children and adolescents
There is insufficient safety data on the use of favipiravir in children and adolescents for other indications.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality During treatment (14 days)</td>
<td>Based on data from 19 patients in 1 studies.</td>
<td></td>
<td>2</td>
<td>There were no deaths in the study</td>
</tr>
</tbody>
</table>


6. Systematic review [73] with included studies: [75]. **Baseline/comparator**: Control arm of reference used for intervention.

### Respiratory failure or ARDS

<table>
<thead>
<tr>
<th>Event</th>
<th>Risk</th>
<th>Odds Ratio</th>
<th>CI 95%</th>
<th>Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>During treatment (14 days)</td>
<td>9 Critical</td>
<td>1.2</td>
<td>0.19 - 7.44</td>
<td>Based on data from 19 patients in 1 studies.</td>
</tr>
</tbody>
</table>

**Odds Ratio**: 1.2 (CI 95% 0.19 - 7.44)  
Based on data from 19 patients in 1 studies.  
Based on data from 19 patients in 1 studies.  
Based on data from 19 patients in 1 studies.

**Difference**: 44 more per 1000  
( CI 95% 288 fewer - 432 more )  
Very Low  
Due to serious risk of bias, serious indirectness and very serious imprecision

We are uncertain whether favipiravir increases or decreases respiratory failure or ARDS (total no of events = 8)

### Mechanical ventilation or ECMO

<table>
<thead>
<tr>
<th>Event</th>
<th>Risk</th>
<th>Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>During treatment (14 days)</td>
<td>9 Critical</td>
<td>Based on data from 19 patients in 1 studies.</td>
</tr>
</tbody>
</table>

**Data for number of patients requiring mechanical ventilation or ECMO in the study**

### Serious adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Risk</th>
<th>Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>During treatment (14 days)</td>
<td>9 Critical</td>
<td>Data for number of patients experiencing one or more events were not reported</td>
</tr>
</tbody>
</table>

### Adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Risk</th>
<th>Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>During treatment (14 days)</td>
<td>6 Important</td>
<td>Data for number of patients experiencing one or more events were not reported</td>
</tr>
</tbody>
</table>

### Clinical improvement

<table>
<thead>
<tr>
<th>Event</th>
<th>Risk</th>
<th>Odds Ratio</th>
<th>CI 95%</th>
<th>Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of treatment (14 days)</td>
<td>6 Important</td>
<td>1.25</td>
<td>0.21 - 7.62</td>
<td>Based on data from 19 patients in 1 studies.</td>
</tr>
</tbody>
</table>

**Odds Ratio**: 1.25 (CI 95% 0.21 - 7.62)  
Based on data from 19 patients in 1 studies.  
Based on data from 19 patients in 1 studies.

**Difference**: 56 more per 1000  
( CI 95% 326 fewer - 384 more )  
Very Low  
Due to serious risk of bias, serious indirectness and very serious imprecision

We are uncertain whether favipiravir increases or decreases clinical improvement (total no of events = 10)
6.10 - Interferon β-1a

**Strong Recommendation Against**

For people with COVID-19, do not use interferon β-1a outside of randomised trials with appropriate ethical approval.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use interferon β-1a in these populations unless they are eligible to be enrolled in trials.

### Key Info

#### Benefits and harms

**General adult population**

In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with interferon β-1a including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation.

**Children and adolescents, people requiring palliative care and older people living with frailty or cognitive impairment**

There are additional concerns regarding harms as interferon β-1a has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Pregnant and breastfeeding women**

Evidence suggests that interferon β-1a in pregnant women is not associated with an increase in early pregnancy loss, stillbirths or congenital anomalies.

#### Certainty of the Evidence

**General adult population**

Certainty of the evidence is low for mortality and very low for all other outcomes due to very serious risk of bias (lack of blinding, non-reporting of allocation method and potential for missing outcome data) and very serious imprecision (low number of patients and observed events).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

#### Preference and values

**General adult population**

We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.

---

7. Systematic review [73] with included studies: [75]. **Baseline/comparator:** Control arm of reference used for intervention.


9. **Risk of bias:** Serious. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.
**Rationale**

**General adult population**
There is currently limited evidence about the impact of interferon β-1a on patient-relevant outcomes in COVID-19. The panel has significant concerns about the potential harms of unproven treatments. We therefore recommend that interferon β-1a should only be administered in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of interferon β-1a in pregnancy are unknown.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

**Equity**

**General adult population**
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

**Acceptability**

**General adult population, children and adolescents, pregnant and breastfeeding women**
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

**People requiring palliative care and older people living with frailty or cognitive impairment**
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

**Feasibility**

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Rationale**

**General adult population**
There is currently limited evidence about the impact of interferon β-1a on patient-relevant outcomes in COVID-19. The panel has significant concerns about the potential harms of unproven treatments. We therefore recommend that interferon β-1a should only be administered in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of interferon β-1a in these populations should be avoided until evidence becomes available.
Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: interferon β-1a
Comparator: Standard care

Summary
Evidence informing this recommendation comes from a single randomised trial that compared interferon β-1a with standard care in 81 hospitalised adult patients with severe COVID-19 [81].

Certainty of the evidence is low for all-cause mortality and very low for all other outcomes. This judgement is based on serious risk of bias due to lack of blinding and insufficient information regarding allocation concealment and potential missing outcome data, and very serious imprecision due to the low number of patients and observed events and the reliance on a single study. Mortality was not downgraded for risk of bias as this outcome is unlikely to be affected by lack of blinding.

The Therapeutic Goods Administration highlights several potential side effects associated with the use of interferon β-1a, including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation. The use of interferon β-1a is also associated with immune reactions that can produce flu-like symptoms [83][84].

Based on the available evidence, there remains significant uncertainty whether interferon β-1a is more effective and safer than standard care in treating patients with COVID-19.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality (Day 28)</td>
<td>Within 28 days after commencing treatment</td>
<td>Odds Ratio 0.3 (CI 95% 0.11 - 0.83) Based on data from 81 patients in 1 studies.¹</td>
<td>436 per 1000 (CI 95% 358 fewer - 45 fewer)</td>
<td>Low Due to very serious imprecision²</td>
<td>We are uncertain whether interferon β-1a decreases all-cause mortality (day 28; total no of events = 25)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Within 28 days after commencing treatment</td>
<td>Odds Ratio 0.72 (CI 95% 0.29 - 1.76) Based on data from 81 patients in 1 studies.³</td>
<td>436 per 1000 (CI 95% 253 fewer - 140 more)</td>
<td>Very Low Due to very serious risk of bias and very serious imprecision⁴</td>
<td>We are uncertain whether interferon β-1a increases or decreases mechanical ventilation (total no of events = 32)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Within 28 days after commencing treatment</td>
<td>Odds Ratio 1.88 (CI 95% 0.64 - 5.47) Based on data from 91 patients in 1 studies.⁵</td>
<td>143 per 1000 (CI 95% 47 fewer - 334 more)</td>
<td>Very Low Due to very serious risk of bias and very serious imprecision⁶</td>
<td>We are uncertain whether interferon β-1a improves or worsens septic shock (total no of events = 17)</td>
</tr>
</tbody>
</table>

2. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


4. **Risk of bias:** Very Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Incomplete data and/or large loss to follow up. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


6. **Risk of bias:** Very Serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


8. **Risk of bias:** Very Serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


10. **Risk of bias:** Very Serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Imprecision:** Very Serious. Low number of patients, Only data from one study.

---

**Clinical Question/ PICO**

**Population:** Special populations with COVID-19

**Intervention:** interferon β-1a
Summary
Evidence informing this recommendation comes from a single randomised trial that compared interferon β-1a with standard care in 81 hospitalised adult patients with severe COVID-19 [81].

Certainty of the evidence is very low for all outcomes. This judgement is based on serious risk of bias due to lack of blinding and insufficient information regarding allocation concealment and potential missing outcome data, very serious imprecision due to the low number of patients and observed events and the reliance on a single study, and serious indirectness (limited inclusion of these populations). Mortality was not downgraded for risk of bias as this outcome is unlikely to be affected by lack of blinding.

The Therapeutic Goods Administration highlights several potential side effects associated with the use of interferon β-1a, including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation. The use of interferon β-1a is also associated with immune reactions that can produce flu-like symptoms [83][84].

Based on the available evidence, there remains significant uncertainty whether interferon β-1a is more effective and safer than standard care in treating patients with COVID-19.

Children and adolescents
Paediatricians have limited experience with interferon β-1a in children and adolescents for other indications. To date, no specific information on its benefits or harms has been collected for treating COVID-19 in this population.

Pregnant and breastfeeding women
Interferon β-1a is used in pregnancy for the treatment of multiple sclerosis. Evidence has shown no correlation between the use of Interferon β-1a and increases in early pregnancy loss, stillbirths or congenital anomalies [63].

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
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</thead>
<tbody>
<tr>
<td>All-cause mortality (Day 28) Within 28 days after commencing treatment</td>
<td>Odds Ratio 0.3 (CI 95% 0.11 - 0.83) Based on data from 81 patients in 1 studies.</td>
<td>436 per 1000 Control 188 per 1000 interferon β-1a Difference: 248 fewer per 1000 (CI 95% 358 fewer - 45 fewer)</td>
<td>Very Low Due to serious indirectness and very serious imprecision 2</td>
<td>We are uncertain whether interferon β-1a decreases all-cause mortality (day 28; total no of events = 25)</td>
</tr>
<tr>
<td>Mechanical ventilation Within 28 days after commencing treatment</td>
<td>Odds Ratio 0.72 (CI 95% 0.29 - 1.76) Based on data from 81 patients in 1 studies.</td>
<td>436 per 1000 Control 357 per 1000 interferon β-1a Difference: 78 fewer per 1000 (CI 95% 253 fewer - 140 more)</td>
<td>Very Low Due to very serious risk of bias, serious indirectness and very serious imprecision 4</td>
<td>We are uncertain whether interferon β-1a increases or decreases mechanical ventilation (total no of events = 32)</td>
</tr>
<tr>
<td>Septic shock Within 28 days after commencing</td>
<td>Odds Ratio 1.88 (CI 95% 0.64 - 5.47) Based on data from 91</td>
<td>143 per 1000 interferon β-1a 238 per 1000 Control</td>
<td>Very Low Due to very serious risk of</td>
<td>We are uncertain whether interferon β-1a improves or worsens</td>
</tr>
</tbody>
</table>

2. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


4. **Risk of bias:** Very Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Incomplete data and/or large loss to follow up. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


6. **Risk of bias:** Very Serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


8. **Risk of bias:** Very Serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.


10. **Risk of bias:** Very Serious. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Indirectness:** Serious. **Imprecision:** Very Serious. Low number of patients, Only data from one study.
6.11 - Lopinavir-ritonavir

**Strong Recommendation Against**

For people with COVID-19, do not use lopinavir-ritonavir outside of randomised trials with appropriate ethical approval.

The Taskforce notes the release of the press statement from the chief investigators of the RECOVERY trial on 29 June that found no clinical benefit from using lopinavir-ritonavir in hospitalised patients with COVID-19. On 4 July WHO announced the lopinavir-ritonavir treatment arm of the Solidarity Trial had been discontinued with immediate effect. We await publication of the results of both trials.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use lopinavir-ritonavir in these populations unless they are eligible to be enrolled in trials.

**Key Info**

**Benefits and harms**

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with lopinavir-ritonavir. Although most of this information is derived from long-term use, potential acute harms include: gastrointestinal symptoms, hyperglycaemia, pancreatitis, lipid elevations, hepatic impairment, QT interval prolongation and PR interval prolongation. Chronic harms include: increased risk of bleeding in patients with haemophilia, fat redistribution and immune reconstitution syndrome, among others. Lopinavir-ritonavir interacts with CYP3A and may result in increased plasma concentrations of the other drugs. Harms associated with short-term use have been reported in three trials [29][30][66]. These include transient elevation of alanine aminotransferase and gastrointestinal symptoms, such as diarrhoea.

**Children and adolescents**
Paediatricians have considerable experience with the use of lopinavir-ritonavir in children and adolescents for other indications.

**Pregnant and breastfeeding women**
Lopinavir-ritonavir is recommended for pregnant and breastfeeding women living with HIV as part of highly active antiretroviral therapy. Studies of women receiving lopinavir-ritonavir for this indication have shown a favourable safety profile.

**People requiring palliative care and older people living with frailty or cognitive impairment**
The benefits of lopinavir-ritonavir for symptom management for this population are uncertain.

**Certainty of the Evidence**

**General adult population**
Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias and inconsistency, and very serious imprecision due to the low number of patients and/or the low number of observed events.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Preference and values**

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
Rationale

General adult population
There is currently limited evidence about the impact of lopinavir-ritonavir on patient-relevant outcomes in COVID-19. The panel has significant concerns about the potential harms of unproven treatments. We therefore recommend that lopinavir-ritonavir should only be administered in the context of randomised trials with appropriate ethical approval.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of lopinavir-ritonavir in these populations should be avoided until evidence becomes available.

Frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of lopinavir-ritonavir during pregnancy and breastfeeding are unknown in the context of COVID-19.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the potential impact on reduced access to these treatments by patients currently using them for other indications.

Equity

General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

General adult population
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

People requiring palliative care and older people living with frailty or cognitive impairment
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.
Clinical Question/ PICO

Population: Patients with COVID-19  
Intervention: Lopinavir-ritonavir  
Comparator: Standard care

Summary

Evidence informing this recommendation comes from three randomised trials that compared lopinavir-ritonavir plus standard care to standard care alone in 287 patients with COVID-19 [29][30][66]. One study was of 199 patients with severe illness [30], another of 60 patients with moderate or severe illness [66] and the third of 28 patients with mild or moderate illness [29].

Two of the studies excluded pregnant and breastfeeding women and for one their eligibility was unclear [66]. Mean or median age ranged from 41 to 58 years in the lopinavir-ritonavir groups and from 44 to 58 years in the control groups. The proportion of women was 44% (range 38 to 59%) in the lopinavir-ritonavir groups and 44% (range 41 to 59%) in the control groups.

Two studies provided data on mortality, respiratory failure or ARDS and requirement of mechanical ventilation or ECMO [29][30]. All studies reported data on adverse events and serious adverse events. One study reported data relating to clinical improvement at day 14 after treatment initiation [30].

Certainty of the evidence for all outcomes is very low. This judgement is based on: serious risk of bias due to lack of personnel blinding and selective outcome reporting; serious imprecision due to the low number of patients and/or low number of observed events; and serious inconsistency in respiratory failure/ARDS, adverse events and serious adverse events (which may be related to the difference in illness severity between the studies).

According to the Therapeutic Goods Administration there are well-known side effects and harms associated with lopinavir-ritonavir. Although most of the information on side effects and harms is derived from long-term use, potential acute harms include: gastrointestinal symptoms, hyperglycaemia, pancreatitis, lipid elevations, hepatic impairment, QT interval prolongation, and PR interval prolongation. Chronic harms include: increased risk of bleeding in patients with haemophilia, fat redistribution and immune reconstitution syndrome, among others. Lopinavir-ritonavir interacts with CYP3A and may result in increased plasma concentrations of the other drugs [64].

Based on the available evidence, there remains significant uncertainty whether lopinavir-ritonavir is more effective and safer than standard care in treating patients with COVID-19.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
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<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td>End of treatment</td>
<td>Relative risk 0.77 (CI 95% 0.45 - 1.3) Based on data from 250 patients in 2 studies. ^1</td>
<td>214 per 1000</td>
<td>Very Low</td>
<td>We are uncertain whether lopinavir-ritonavir increases or decreases mortality (total no of events = 44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Randomized controlled)</td>
<td>165 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td>Difference: 49 fewer per 1000 ( CI 95% 118 fewer - 64 more )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory failure or ARDS</strong></td>
<td>End of treatment</td>
<td>Relative risk 0.59 (CI 95% 0.34 - 1.02) Based on data from 225 patients in 2 studies. ^7</td>
<td>233 per 1000</td>
<td>Very Low</td>
<td>We are uncertain whether lopinavir-ritonavir increases or decreases respiratory failure or ARDS (total no of events = 44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Randomized controlled)</td>
<td>137 per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td>Difference: 96 fewer per 1000 ( CI 95% 154 fewer - 5 more )</td>
<td></td>
<td></td>
<td></td>
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</tbody>
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1. Systematic review [65] with included studies: [29], Cao 2020. **Baseline/comparator:** Control arm of reference used for intervention.

2. **Risk of bias:** Serious. **Imprecision:** Very Serious. Wide confidence intervals, Low number of patients.


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Selective outcome reporting. **Imprecision: Very Serious.** Wide confidence intervals, Low number of patients.

### Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>Special populations with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Lopinavir-ritonavir</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Standard care</td>
</tr>
</tbody>
</table>

### Summary

Evidence informing this recommendation comes from three randomised trials that compared lopinavir-ritonavir plus standard care to standard care alone in 287 patients with COVID-19 [29][30][66]. One study was of 199 patients with severe illness [30], another of 60 patients with moderate or severe illness [66] and the third of 28 patients with mild or moderate illness [29].

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Certainty of the evidence for all outcomes is very low. This judgement is based on: serious risk of bias due to lack of personnel blinding and selective outcome reporting; serious imprecision due to the low number of patients and/or low number of observed events; and serious inconsistency in respiratory failure/ARDS, adverse events and serious adverse events (which may be related to the difference in illness severity between the studies).

According to the Therapeutic Goods Administration there are well-known side effects and harms associated with lopinavir-ritonavir. Although most of the information on side effects and harms is derived from long-term use, potential acute harms include: gastrointestinal symptoms, hyperglycaemia, pancreatitis, lipid elevations, hepatic impairment, QT interval prolongation, and PR interval prolongation. Chronic harms include: increased risk of bleeding in patients with haemophilia, fat redistribution and immune reconstitution syndrome, among others. Lopinavir-ritonavir interacts with CYP3A and may result in increased plasma concentrations of the other drugs [64].

Based on the available evidence, there remains significant uncertainty whether lopinavir-ritonavir is more effective and safer than standard care in treating patients with COVID-19.

### Children and adolescents

Paediatricians have considerable experience with lopinavir-ritonavir in children and adolescents for other indications. To date, no specific information on its benefits or harms for children and adolescents has been collected for treating COVID-19 in this population.

### Pregnant and breastfeeding women

Lopinavir-ritonavir is recommended for treating pregnant or breastfeeding women living with HIV, as part of highly active antiretroviral therapy. Studies of women receiving lopinavir-ritonavir for this indication has shown a favourable safety profile, with no increase in stillbirth, preterm birth, low birth weight or birth defects [67][68][69][70][71]. Based on the available evidence, there remains uncertainty whether lopinavir-ritonavir is more effective and safer than standard care in treating pregnant or breastfeeding women with COVID-19.
### Quality of evidence

<table>
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<tr>
<th>Mortality</th>
<th>Relative risk 0.77 (CI 95% 0.45 - 1.3)</th>
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<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mechanical ventilation or ECMO</th>
<th>Relative risk 1.53 (CI 95% 0.49 - 4.76)</th>
<th>56 per 1000</th>
<th>86 per 1000</th>
<th>Very Low Due to serious indirectness and very serious imprecision</th>
<th>We are uncertain whether lopinavir/ritonavir increases or decreases mechanical ventilation or ECMO (total no of events = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of treatment</td>
<td>Based on data from 215 patients in 2 studies.</td>
<td>Difference: 30 more per 1000 (CI 95% 29 fewer - 211 more)</td>
<td></td>
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<td></td>
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<tr>
<td>9 Critical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serious adverse events</th>
<th>Relative risk 0.63 (CI 95% 0.39 - 1.02)</th>
<th>302 per 1000</th>
<th>190 per 1000</th>
<th>Very Low Due to serious risk of bias, serious indirectness and very serious imprecision</th>
<th>We are uncertain whether lopinavir-ritonavir increases or decreases serious adverse events (total no of events = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of treatment</td>
<td>Based on data from 222 patients in 2 studies.</td>
<td>Difference: 112 fewer per 1000 (CI 95% 184 fewer - 6 more)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6 Important</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Relative risk 1.39 (CI 95% 0.48 - 4.05)</th>
<th>358 per 1000</th>
<th>498 per 1000</th>
<th>Very Low Due to serious indirectness and very serious imprecision</th>
<th>We are uncertain whether lopinavir-ritonavir increases or decreases adverse events (total no of events = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of treatment</td>
<td>Based on data from 287 patients in 3 studies.</td>
<td>Difference: 140 more per 1000 (CI 95% 186 fewer - 1,092 more)</td>
<td></td>
<td></td>
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<tr>
<td>6 Important</td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical improvement</th>
<th>Relative risk 1.52 (CI 95% 1.05 - 2.19)</th>
<th>305 per 1000</th>
<th>464 per 1000</th>
<th>Very Low Due to serious indirectness and very serious imprecision</th>
<th>We are uncertain whether lopinavir-ritonavir improves or worsens clinical improvement (total no of events = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 14 after treatment</td>
<td>Based on data from 241 patients in 2 studies.</td>
<td>Difference: 159 more per 1000 (CI 95% 15 more - 363 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

2. **Risk of bias**: Serious. **Indirectness**: Serious. **Imprecision**: Very Serious. Wide confidence intervals, Low number of patients.
6.12 - Ruxolitinib

**Strong Recommendation Against**

For people with COVID-19, do not use ruxolitinib outside of randomised trials with appropriate ethical approval.

**Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use ruxolitinib in these populations unless they are eligible to be enrolled in trials.**

### Key Info

**Benefits and harms**

- **General adult population**
  
  In addition to uncertainty around the benefits for patients with COVID-19, there are well-known side effects and harms of ruxolitinib. Although most of the information on side effects and harms is derived from long-term use, potential harms include thrombocytopenia and other haematological adverse reactions, and increased incidence of bacterial and other infections.

- **Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
  
  There are additional concerns regarding harms as ruxolitinib has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain. No studies pertained to the safety of ruxolitinib (for any indication) for pregnant or breastfeeding women.

**Certainty of the Evidence**

*Very Low*
### General adult population
Certainty of the evidence is low for mortality and very low for all other outcomes due to serious risk of bias (lack of blinding of outcome assessors) and very serious imprecision (low number of patients and observed events).

### Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

### Preference and values
**General adult population**
We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to opt for the treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of ruxolitinib in pregnancy are unknown.

### Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Equity
**General adult population**
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

### Acceptability
**General adult population, children and adolescents, pregnant and breastfeeding women**
We have no systematically collected evidence regarding acceptability. Substantial variability is expected as some patients would accept the treatment and others not.

**People requiring palliative care and older people living with frailty or cognitive impairment**
Because the benefit to harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

### Feasibility
**Important issues, or potential issues not investigated**
Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Rationale

**General adult population**

There is currently limited evidence about the impact of ruxolitinib on patient-relevant outcomes in COVID-19. The panel has significant concerns about the potential harms of unproven treatments. We therefore recommend that ruxolitinib should only be administered in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of ruxolitinib in these populations should be avoided until evidence becomes available.

**Clinical Question/ PICO**

- **Population:** Patients with COVID-19
- **Intervention:** Ruxolitinib
- **Comparator:** Placebo

**Summary**

Evidence informing this recommendation comes from a single randomised trial that compared ruxolitinib to placebo (vitamin C) in 41 hospitalised adult patients with severe COVID-19—pregnant and breastfeeding women were ineligible. Median age in the ruxolitinib group was 63 years (40% women) and in the control group 64 years (43% women) [82].

Certainty of the evidence is low for all-cause mortality and very low for all other outcomes. This judgement is based on serious risk of bias due to lack of blinding of outcome assessors, and very serious imprecision due to the low number of patients and observed events and the reliance on a single study. Mortality was not downgraded for risk of bias as this outcome is unlikely to be affected by lack of blinding.

The Therapeutic Goods Administration highlights several potential side effects associated with the use of ruxolitinib, including thrombocytopaenia and other haematological adverse reactions, and increased incidence of bacterial and other infections. Cases of progressive multifocal leukoencephalopathy and non-melanoma skin cancer have also been reported in patients treated with ruxolitinib [85].

Based on the available evidence, there remains significant uncertainty whether ruxolitinib is more effective and safer than standard care in treating patients with COVID-19.

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<tr>
<th>Outcome</th>
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<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality (Day 28)</td>
<td>Within 28 days after commencing treatment</td>
<td>Odds Ratio 0.13 (CI 95% 0.01 - 2.67) Based on data from 41 patients in 1 studies. ¹ (Randomized controlled)</td>
<td>143 per 1000 Placebo</td>
<td>21 per 1000 Ruxolitinib</td>
<td>Low Due to very serious imprecision ² We are uncertain whether ruxolitinib increases or decreases all-cause mortality (day 28; total no of events = 3)</td>
</tr>
</tbody>
</table>

¹ Critical

²
<table>
<thead>
<tr>
<th>Condition</th>
<th>Odds Ratio</th>
<th>CI 95%</th>
<th>Difference</th>
<th>CI 95%</th>
<th>Risk of Bias</th>
<th>Imprecision</th>
<th>Certainty</th>
<th>Events</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic shock</td>
<td>0.19</td>
<td>0.01 - 4.22</td>
<td>75 fewer</td>
<td>94 fewer - 212 more</td>
<td>Very Low</td>
<td>Very Low</td>
<td>Uncertain</td>
<td>2</td>
<td>We are uncertain whether ruxolitinib increases or decreases septic shock (total no of events = 2)</td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>2</td>
<td>0.58 - 6.94</td>
<td>171 more</td>
<td>125 fewer - 410 more</td>
<td>Very Low</td>
<td>Very Low</td>
<td>Uncertain</td>
<td>21</td>
<td>We are uncertain whether ruxolitinib improves or worsens clinical improvement (total no of events = 21)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>1.35</td>
<td>0.36 - 5.04</td>
<td>65 more</td>
<td>160 fewer - 383 more</td>
<td>Very Low</td>
<td>Very Low</td>
<td>Uncertain</td>
<td>13</td>
<td>We are uncertain whether ruxolitinib increases or decreases adverse events (total no of events = 13)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>0.09</td>
<td>0.0 - 1.89</td>
<td>169 fewer</td>
<td>190 fewer - 117 more</td>
<td>Very Low</td>
<td>Very Low</td>
<td>Uncertain</td>
<td>4</td>
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<td>Clinical deterioration</td>
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<tr>
<td>Mechanical ventilation</td>
<td>0.22</td>
<td>0.04 - 1.24</td>
<td>234 fewer</td>
<td>313 fewer - 49 more</td>
<td>Very Low</td>
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<td>Uncertain</td>
<td>9</td>
<td>We are uncertain whether ruxolitinib increases or decreases mechanical ventilation (total no of events = 9)</td>
</tr>
<tr>
<td>Time to improvement</td>
<td>Lower better</td>
<td>CI 95%</td>
<td>15</td>
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<td>Uncertain</td>
<td>15</td>
<td>We are uncertain whether ruxolitinib increases or decreases time to improvement</td>
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**Clinical Question/ PICO**

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Intervention: Ruxolitinib  
Comparator: Placebo

Summary

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The Therapeutic Goods Administration highlights several potential side effects associated with the use of ruxolitinib, including thrombocytopaenia and other haematological adverse reactions, and increased incidence of bacterial and other infections. Cases of progressive multifocal leukoencephalopathy and non-melanoma skin cancer have also been reported in patients treated with ruxolitinib [85].

Based on the available evidence, there remains significant uncertainty whether ruxolitinib is more effective and safer than standard care in treating patients with COVID-19.

Children and adolescents

There is insufficient safety data on the use of ruxolitinib in children and adolescents for other indications.

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</tr>
<tr>
<td>Septic shock Within 28 days after commencing treatment</td>
<td>Odds Ratio 0.19 (CI 95% 0.01 - 4.22) Based on data from 41 patients in 1 studies, ³ (Randomized controlled)</td>
<td><strong>95</strong> per 1000 <strong>19</strong> per 1000</td>
<td>Very Low Due to serious risk of bias, serious indirectness and very serious imprecision ⁴</td>
<td>We are uncertain whether ruxolitinib increases or decreases septic shock (total no of events = 2)</td>
</tr>
<tr>
<td>Clinical improvement At day 14 of treatment</td>
<td>Odds Ratio 2 (CI 95% 0.58 - 6.94) Based on data from 41 patients in 1 studies, ⁵ (Randomized controlled)</td>
<td><strong>429</strong> per 1000 <strong>600</strong> per 1000</td>
<td>Very Low Due to serious risk of bias, serious indirectness and very serious</td>
<td>We are uncertain whether ruxolitinib improves or worsens clinical improvement (total no of events = 21)</td>
</tr>
</tbody>
</table>

¹ Randomized controlled
² Serious risk of bias
³ Serious risk of bias
⁴ Serious risk of bias
⁵ Serious risk of bias

Australian guidelines for the clinical care of people with COVID-19 - Australian National COVID-19 Clinical Evidence Taskforce
Australian guidelines for the clinical care of people with COVID-19 - Australian National COVID-19 Clinical Evidence Taskforce

### Adverse events
Within 28 days after commencing treatment

- **Odds Ratio 1.35** (CI 95% 0.36 - 5.04)
  - Based on data from 41 patients in 1 studies. (Randomized controlled)

- **286** per 1000
  - **Difference: 65 more** per 1000 (CI 95% 160 fewer - 383 more)

**Very Low**
**Due to serious risk of bias, serious indirectness and very serious imprecision**

**We are uncertain whether ruxolitinib increases or decreases adverse events (total no of events = 13)**

### Serious adverse events
Within 28 days after commencing treatment

- **Odds Ratio 0.09** (CI 95% 0 - 1.89)
  - Based on data from 41 patients in 1 studies. (Randomized controlled)

- **190** per 1000
  - **Difference: 169 fewer** per 1000 (CI 95% 190 fewer - 117 more)

**Very Low**
**Due to serious risk of bias, serious indirectness and very serious imprecision**

**We are uncertain whether ruxolitinib increases or decreases serious adverse events (total no of events = 4)**

### Clinical deterioration
At day 14 of treatment

- **Odds Ratio 0.09** (CI 95% 0 - 1.89)
  - Based on data from 41 patients in 1 studies. (Randomized controlled)

- **190** per 1000
  - **Difference: 169 fewer** per 1000 (CI 95% 190 fewer - 117 more)

**Very Low**
**Due to serious risk of bias, serious indirectness and very serious imprecision**

**We are uncertain whether ruxolitinib improves or worsens clinical deterioration (total no of events = 4)**

### Mechanical ventilation
Within 28 days after commencing treatment

- **Odds Ratio 0.22** (CI 95% 0.04 - 1.24)
  - Based on data from 41 patients in 1 studies. (Randomized controlled)

- **333** per 1000
  - **Difference: 234 fewer** per 1000 (CI 95% 313 fewer - 49 more)

**Very Low**
**Due to serious risk of bias, serious indirectness and very serious imprecision**

**We are uncertain whether ruxolitinib increases or decreases mechanical ventilation (total no of events = 9)**

### Time to improvement
Median days to improvement

- **Lower better** (Median) (Randomized controlled)

- **15** (Median)
  - CI 95%

**Very Low**
**Due to serious risk of bias, serious indirectness and very serious imprecision**

**We are uncertain whether ruxolitinib increases or decreases time to improvement**

### Time to discharge
Median days to discharge

- **Lower better** (Median) (Randomized controlled)

- **16** (Median)
  - CI 95%

**Very Low**
**Due to serious risk of bias, serious indirectness and very serious imprecision**

**We are uncertain whether ruxolitinib increases or decreases time to discharge**
6.13 - Other disease-modifying treatments

For people with COVID-19, do not use other disease-modifying treatments outside of randomised trials with appropriate ethical approval.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use other disease-modifying treatments in these populations unless they are eligible to be enrolled in trials.
Key Info

Benefits and harms

General adult population
Currently, there is no direct evidence to inform the potential benefits or harms of other disease-modifying treatments in patients with COVID-19.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
There may be additional concerns regarding harms for these populations. For people requiring palliative care, the benefits for symptom management may be uncertain.

Certainty of the Evidence
We have no COVID-19 specific randomised trials for other potential disease-modifying treatments.

Preference and values

General adult population
We have no systematically collected information regarding patients' preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while others may be more willing to opt for treatment.

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations, given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of any disease-modifying treatments during pregnancy may be unknown.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

Equity

General adult population
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

Children and adolescents, pregnant and breastfeeding women
Because the benefit to harm ratio is uncertain, this recommendation protects these more vulnerable populations.

People requiring palliative care and older people living with frailty or cognitive impairment
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit to harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

General adult population, children and adolescents, pregnant and breastfeeding women
We have no systematically collected evidence regarding acceptability for other disease-modifying treatments. Substantial variability is expected as some patients would accept treatment and others not.
Rationale

**General adult population**
There is currently limited evidence about the impact of other disease-modifying treatments on patient-relevant outcomes in COVID-19. The panel has significant concerns about the potential harms of unproven treatments.

In line with the ANZICS, ASID, AHPPC and IDSA recommendations, we therefore recommend that other disease-modifying treatments should only be administered in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of other disease-modifying treatments in these populations should be avoided until evidence becomes available.

### Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

### Important issues, or potential issues not investigated

Feasibility

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.
7 - Chemoprophylaxis

7.1 - Hydroxychloroquine for post-exposure prophylaxis

**Strong Recommendation Against**

For people exposed to individuals with COVID-19, only administer hydroxychloroquine for post-exposure prophylaxis in the context of randomised trials with appropriate ethical approval.

_The Taskforce is continually monitoring research on chemoprophylaxis. As evidence accumulates the Taskforce will continue to review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease)._

**Key Info**

**Benefits and harms**

In addition to uncertainty around the benefits for patients with COVID-19, there are well-known harms, with potentially severe adverse events. Although most of the information on side effects and harms is derived from long-term use, potential acute harms include prolonged QT interval and lowered convulsive threshold. Long-term harms include retinopathy and chronic cardiac myopathy, among several others.

There are several known and potential interactions with other drugs. Although overdose of hydroxychloroquine may have potentially fatal complications, this is unlikely when taken at prophylactic doses. In pregnancy, it is only recommended when benefits outweigh harms.

**Certainty of the Evidence**

Certainty of the evidence is low or very low due to very serious imprecision based on the reliance on a single trial and low number of events for some outcomes.

**Preference and values**

We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to take risks.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the potential impact on reduced access to these treatments by patients currently using them for other indications.

**Equity**

We have no systematically collected direct evidence regarding impact on equity. There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent. Because the benefit to harm ratio is uncertain, it is worth noting that this recommendation will protect more vulnerable populations, such as children.

**Acceptability**

Treatment is likely to be acceptable to both patients and clinicians. However, we have not systematically collected evidence...
There is currently limited evidence about the impact of prophylactic hydroxychloroquine on the prevention of infection in people exposed to COVID-19.

The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

We therefore recommend that chemoprophylaxis should only be administered in the context of randomised trials with appropriate ethical approval.

Clinical Question/ PICO

**Population:** People exposed to COVID-19  
**Intervention:** Hydroxychloroquine post-exposure prophylaxis  
**Comparator:** Placebo

Summary

Evidence informing this recommendation comes from a single randomised trial that compared post-exposure prophylaxis using hydroxychloroquine to placebo [87]. All people included in the trial were asymptomatic at the time of the first dose of treatment (100 randomised patients were excluded from the analysis due to developing symptoms after randomisation but prior to commencement of treatment).

Certainty of the evidence is very low to low for all outcomes due to serious or very serious imprecision based on low number of patients and/or low number of observed events, risk of bias and the reliance on a single study.

According to the Therapeutic Goods Administration known acute harms for hydroxychloroquine include prolonged QT interval and lowered convulsive threshold. Long-term harms of relevance include retinopathy and chronic cardiac myopathy [33]. There are several known and potential interactions with other drugs [33]. Although overdose of hydroxychloroquine may have potentially fatal complications, this is unlikely when taken at prophylactic doses. In pregnancy, it is only recommended when benefits outweigh harms [33].

Based on the available evidence, there remains significant uncertainty whether post-exposure prophylactic hydroxychloroquine is more effective at preventing COVID-19 infection than placebo.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
</table>
| Laboratory confirmed diagnosis | Odds Ratio 1.21 (CI 95% 0.49 - 2.94)  
Based on data from 821 patients in 1 studies. |  
Placebo: 22 per 1000  
Hydroxychloroquine post-exposure prophylaxis: 26 per 1000 | Very Low  
Due to serious risk of bias and very serious | We are uncertain whether hydroxychloroquine post-exposure |
1. Systematic review [86] with included studies: Boulware 2020. **Baseline/comparator:** Control arm of reference used for

<table>
<thead>
<tr>
<th>Event</th>
<th>Odds Ratio</th>
<th>CI 95%</th>
<th>Difference:</th>
<th>per 1000</th>
<th>per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Critical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms compatible with COVID-19</td>
<td>0.84</td>
<td>0.55 - 1.27</td>
<td>4 more</td>
<td>135</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>per 1000</td>
<td>per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19 fewer</td>
<td>143</td>
<td>119</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>per 1000</td>
<td>per 1000</td>
</tr>
<tr>
<td>Confirmed or probable infection</td>
<td>0.81</td>
<td>0.54 - 1.21</td>
<td>24 fewer</td>
<td>168</td>
<td>401</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>per 1000</td>
<td>per 1000</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 14 days after commencing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>3.32</td>
<td>2.33 - 4.72</td>
<td>233 more</td>
<td>20</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>per 1000</td>
<td>per 1000</td>
</tr>
<tr>
<td>Discontinuation due to adverse</td>
<td>2.14</td>
<td>0.91 - 5.01</td>
<td>22 more</td>
<td>401</td>
<td>401</td>
</tr>
<tr>
<td>events</td>
<td></td>
<td></td>
<td></td>
<td>per 1000</td>
<td>per 1000</td>
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<td></td>
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</tbody>
</table>

**Hydroxychloroquine post-exposure prophylaxis may make little or no difference to the development of symptoms compatible with COVID-19 (total no of events = 20)**

**Hydroxychloroquine post-exposure prophylaxis may make little or no difference to confirmed or probable infection (total no of events = 107)**

**There were no deaths in the study**

**Hydroxychloroquine post-exposure prophylaxis may increase adverse events**

**We are uncertain whether hydroxychloroquine post-exposure prophylaxis increases or decreases discontinuation due to adverse events (total no of events = 25)**

---

1. Systematic review [86] with included studies: Boulware 2020. **Baseline/comparator:** Control arm of reference used for
intervention.

2. **Risk of bias: Serious.** Incomplete data and/or large loss to follow up. **Imprecision: Very Serious.** Only data from one study and few events.

3. The presence of one or more compatible symptoms, which could include diarrhea. Based on the "Council of State and Territorial Epidemiologists interim standardized surveillance case definition and national notification for 2019 novel coronavirus disease"


5. **Risk of bias: Serious.** Incomplete data and/or large loss to follow up. **Imprecision: Serious.** Only data from one study.

6. confirmed cases: positivity for SARS-CoV-2 on PCR assay; probable cases: the presence of cough, shortness of breath, or difficulty breathing, or the presence of two or more symptoms of fever, chills, rigors, myalgia, headache, sore throat, and new olfactory and taste disorders.


8. **Risk of bias: Serious.** Incomplete data and/or large loss to follow up. **Imprecision: Serious.** Only data from one study.


10. **Imprecision: Very Serious.** Low number of patients, Only data from one study, no events.


12. **Risk of bias: Serious.** Incomplete data and/or large loss to follow up. **Imprecision: Serious.** Only data from one study.


14. **Risk of bias: Serious.** Incomplete data and/or large loss to follow up. **Imprecision: Very Serious.** Only data from one study and few events.
8 - Respiratory support

Current evidence suggests that about 19% of patients with COVID-19 experience hypoxic respiratory failure, 14% of whom will develop severe disease requiring oxygen therapy and 5% requiring mechanical ventilation within an ICU setting \[88\]. The majority of early guidelines generally base recommendations on indirect evidence from studies involving SARS, MERS and influenza, although it is presently unclear if patients with COVID-19 would benefit from alternative strategies to optimise the effective administration of respiratory support.

**Consensus Recommendation**

**Guiding principles of care**

For patients with COVID-19 for whom respiratory support (HFNO/NIV) is being considered, decisions should balance likelihood of patient benefit against the risk of infection for healthcare workers. For patients with COVID-19 receiving respiratory support (HFNO/NIV) or requiring intubation, use single rooms or negative pressure rooms wherever possible and ensure contact, droplet and airborne precautions are in place.

> The relative risk of infection to healthcare workers associated with specific oxygen therapies remains uncertain and may vary from site to site.

### 8.1 - High-flow nasal oxygen therapy

**Recommendation Strength Not Set**

High-flow nasal oxygen (HFNO) therapy is a form of respiratory support where oxygen is delivered, often in conjunction with compressed air and humidification. It delivers high flow oxygen via large diameter nasal cannula that is humidified and heated. Flow rates can be given up to 60 L/min in adults and 25 L/min in children with an oxygen/air blender supplying oxygen at 21-100%.

High-flow humidified oxygen should be considered when unable to maintain \(\text{SaO}_2 \geq 92\)% despite conventional oxygen delivery at > 6 L/min or an \(\text{FiO}_2\) 0.4

**Clinical Question/ PICO**

- **Population:** Patients with COVID-19
- **Intervention:** High-flow nasal oxygen therapy
- **Comparator:** Conventional oxygen therapy

**Summary**

Evidence informing this recommendation comes from two rapid systematic reviews commissioned by the WHO to summarise the evidence for the efficacy, safety (review 1), and risk of aerosol generation and infection transmission (review 2) during high-flow nasal cannula (HFNC) use among patients with acute hypoxaemic respiratory failure due to COVID-19 \[95\].

**Review 1: Effectiveness**

<table>
<thead>
<tr>
<th>Study design</th>
<th>Randomised trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>High-flow nasal cannula (HFNC)</td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
<td>Conventional oxygen therapy</td>
</tr>
</tbody>
</table>
Synthesis method | Meta-analysis
--- | ---

Results | Included 12 RCTs (n = 2217 patients). Decreased risk of requiring intubation and escalation of oxygen therapy (defined as crossover to HFNC in the control group or initiation of non-invasive or invasive ventilation in either group) in favour of HFNC over conventional oxygen therapy. There was no significant difference in mortality, intensive care unit length of stay, hospital length of stay, patient-reported dyspnea and patient-reported comfort. Treatment-reported complications were not pooled due to variability in reporting but were generally minimal across studies and comparable between interventions.

Review 2: Risk of dispersal

Study design | Simulation studies and one prospective crossover study
--- | ---

Population | Healthy adult volunteers (two simulation studies), model human patient simulators (two simulation studies), and critically ill patients who received supplemental oxygen therapy (one crossover study). No studies available in patients with COVID-19, which was considered a limitation in applicability (indirect evidence).

Intervention | High-flow nasal oxygen (HFNO)

Comparison | None (three simulation studies); CPAP (one simulation study); conventional therapy with face mask (one crossover study)

Synthesis method | None, individual study results only

Results | Five studies were included, of which three were simulation studies and none were randomised trials. No studies included patients with COVID-19. In summary, the findings were very uncertain and no conclusions could be drawn. One simulation study found HFNO increased cough-generated droplet dispersion compared to no HFNO. A prospective cohort study found HFNO did not disperse gram-negative bacteria in air samples or set plates at 0.4 m and 1.5 m compared to a facemask. Another simulation study without a control group detected water and yeast colony formation at 0.3 m. Of two studies reporting aerosol dispersion, one found HFNO does not increase the risk of aerosol dispersion, while the second found higher flow rates resulted in increased regions of high aerosol density compared with continuous positive airway pressure (CPAP).

For both reviews, certainty of the evidence is deemed to be low to very low due to indirectness (not based on COVID-19 patients), risk of bias and lack of precision in some outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>Relative risk 0.94 (CI 95% 0.67 - 1.31) Based on data from 1,407 patients in 4 studies. 1 (Randomized controlled) Follow up 7 to 90 days</td>
<td>272 per 1000 256 per 1000</td>
<td>Low Due to serious imprecision and indirectness 2</td>
<td>HFNO may have little or no difference on mortality</td>
</tr>
<tr>
<td>9 Critical</td>
<td></td>
<td>Difference: 16 fewer per 1000 ( CI 95% 90 fewer - 84 more )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Invasive ventilation

<table>
<thead>
<tr>
<th>Relative risk</th>
<th>Confidence Interval</th>
<th>Patients</th>
<th>Studies</th>
<th>Follow up</th>
<th>Difference</th>
<th>CI</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.85</td>
<td>(0.74 - 0.99)</td>
<td>1,687</td>
<td>8</td>
<td>2 to 28 days</td>
<td>43 fewer per 1000</td>
<td>74 fewer - 3 fewer</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

### Escalation of therapy (HFNC, NIV or intubation)

<table>
<thead>
<tr>
<th>Relative risk</th>
<th>Confidence Interval</th>
<th>Patients</th>
<th>Studies</th>
<th>Follow up</th>
<th>Difference</th>
<th>CI</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.71</td>
<td>(0.51 - 0.98)</td>
<td>1,703</td>
<td>8</td>
<td>2 to 28 days</td>
<td>93 fewer per 1000</td>
<td>157 fewer - 6 fewer</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

### ICU length of stay (Days)

<table>
<thead>
<tr>
<th>Difference</th>
<th>CI</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD 1.38 fewer</td>
<td>0.9 fewer - 3.66 fewer</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

### Hospital length of stay (Days)

<table>
<thead>
<tr>
<th>Difference</th>
<th>CI</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD 0.67 more</td>
<td>1.41 fewer - 0.08 more</td>
<td>Low</td>
</tr>
</tbody>
</table>

### Patient-reported dyspnea

<table>
<thead>
<tr>
<th>Variable score</th>
<th>Patients</th>
<th>Studies</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMD 0.66 lower</td>
<td>894</td>
<td>7</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

### Patient-reported comfort

<table>
<thead>
<tr>
<th>Variable score</th>
<th>Patients</th>
<th>Studies</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMD 0.12 lower</td>
<td>1,233</td>
<td>7</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

### Dispersal of droplets and aerosols

One simulation study found HFNO increased cough-generated droplet dispersion compared to no HFNO. A prospective cohort study found HFNO did not disperse gram-negative bacteria in air samples or set plates at 0.4 m and 1.5 m compared to a facemask. Another simulation study without a control group detected water and yeast colony formation at 0.3 m. Of two studies reporting aerosol dispersion, one found HFNO does not...
In negative pressure rooms, use high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

Use the lowest flow necessary to maintain oxygen saturation ≥ 92%.

Clinical Question/ PICO
- **Population:** Patients with COVID-19
- **Intervention:** High-flow nasal oxygen therapy
- **Comparator:** Conventional oxygen therapy

**Summary**
Evidence informing this recommendation comes from two rapid systematic reviews commissioned by the WHO to summarise the evidence for the efficacy, safety (review 1), and risk of aerosol generation and infection transmission (review 2) during high-flow nasal cannula (HFNC) use among patients with acute hypoxaemic respiratory failure due to COVID-19 [95].

**Review 1: Effectiveness**
- **Study design:** Randomised trials
- **Population:** Critically ill patients with acute hypoxaemic respiratory failure of any cause. No studies available in patients with COVID-19.
- **Intervention:** High-flow nasal cannula (HFNC)
- **Comparison:** Conventional oxygen therapy
- **Synthesis method:** Meta-analysis
Results

Included 12 RCTs (n = 2217 patients). Decreased risk of requiring intubation and escalation of oxygen therapy (defined as crossover to HFNC in the control group or initiation of non-invasive or invasive ventilation in either group) in favour of HFNC over conventional oxygen therapy. There was no significant difference in mortality, intensive care unit length of stay, hospital length of stay, patient-reported dyspnea and patient-reported comfort. Treatment-reported complications were not pooled due to variability in reporting but were generally minimal across studies and comparable between interventions.

Review 2: Risk of dispersal

Study design Simulation studies and one prospective crossover study

Population Healthy adult volunteers (two simulation studies), model human patient simulators (two simulation studies), and critically ill patients who received supplemental oxygen therapy (one crossover study). No studies available in patients with COVID-19, which was considered a limitation in applicability (indirect evidence).

Intervention High-flow nasal oxygen (HFNO)

Comparison None (three simulation studies); CPAP (one simulation study); conventional therapy with face mask (one crossover study)

Synthesis method None, individual study results only

Results

Five studies were included, of which three were simulation studies and none were randomised trials. No studies included patients with COVID-19. In summary, the findings were very uncertain and no conclusions could be drawn. One simulation study found HFNO increased cough-generated droplet dispersion compared to no HFNO. A prospective cohort study found HFNO did not disperse gram-negative bacteria in air samples or set plates at 0.4 m and 1.5 m compared to a facemask. Another simulation study without a control group detected water and yeast colony formation at 0.3 m. Of two studies reporting aerosol dispersion, one found HFNO does not increase the risk of aerosol dispersion, while the second found higher flow rates resulted in increased regions of high aerosol density compared with continuous positive airway pressure (CPAP).

For both reviews, certainty of the evidence is deemed to be low to very low due to indirectness (not based on COVID-19 patients), risk of bias and lack of precision in some outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>Critical 9</td>
<td>Relative risk 0.94 (CI 95% 0.67 - 1.31) Based on data from 1,407 patients in 4 studies. 1 (Randomized controlled) Follow up 7 to 90 days</td>
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Weak Recommendation

In single rooms or shared ward spaces with cohorting of confirmed COVID-19 patients only, consider using high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

Use the lowest flow necessary to maintain oxygen saturation ≥ 92%.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: High-flow nasal oxygen therapy
Comparator: Conventional oxygen therapy

Summary

Evidence informing this recommendation comes from two rapid systematic reviews commissioned by the WHO to summarise the evidence for the efficacy, safety (review 1), and risk of aerosol generation and infection transmission (review 2) during high-flow nasal cannula (HFNC) use among patients with acute hypoxaemic respiratory failure due to COVID-19 [95].

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in increased regions of high aerosol density compared with continuous positive airway pressure (CPAP).
Results

Included 12 RCTs (n = 2217 patients). Decreased risk of requiring intubation and escalation of oxygen therapy (defined as crossover to HFNC in the control group or initiation of non-invasive or invasive ventilation in either group) in favour of HFNC over conventional oxygen therapy. There was no significant difference in mortality, intensive care unit length of stay, hospital length of stay, patient-reported dyspnea and patient-reported comfort. Treatment-reported complications were not pooled due to variability in reporting but were generally minimal across studies and comparable between interventions.

Review 2: Risk of dispersal

Study design

Simulation studies and one prospective crossover study

Population

Healthy adult volunteers (two simulation studies), model human patient simulators (two simulation studies), and critically ill patients who received supplemental oxygen therapy (one crossover study). No studies available in patients with COVID-19, which was considered a limitation in applicability (indirect evidence).

Intervention

High-flow nasal oxygen (HFNO)

Comparison

None (three simulation studies); CPAP (one simulation study); conventional therapy with face mask (one crossover study)

Synthesis method

None, individual study results only

Results

Five studies were included, of which three were simulation studies and none were randomised trials. No studies included patients with COVID-19. In summary, the findings were very uncertain and no conclusions could be drawn. One simulation study found HFNO increased cough-generated droplet dispersion compared to no HFNO. A prospective cohort study found HFNO did not disperse gram-negative bacteria in air samples or set plates at 0.4 m and 1.5 m compared to a facemask. Another simulation study without a control group detected water and yeast colony formation at 0.3 m. Of two studies reporting aerosol dispersion, one found HFNO does not increase the risk of aerosol dispersion, while the second found higher flow rates resulted in increased regions of high aerosol density compared with continuous positive airway pressure (CPAP).

For both reviews, certainty of the evidence is deemed to be low to very low due to indirectness (not based on COVID-19 patients), risk of bias and lack of precision in some outcomes.

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1. Systematic review with included studies: [93]. **Baseline/comparator**: Control arm of reference used for intervention.
2. **Indirectness**: Serious. Differences between the population of interest and those studied. **Imprecision**: Serious.
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11. **Risk of bias**: Serious. Substantial risk of bias in all five studies. **Inconsistency**: No serious. **Indirectness**: Serious. **Imprecision**: No serious. **Publication bias**: No serious.

**Strong Recommendation Against**

In *shared wards* or *emergency department cubicles* do not use high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19.

**Clinical Question/ PICO**

**Population:** Patients with COVID-19  
**Intervention:** High-flow nasal oxygen therapy  
**Comparator:** Conventional oxygen therapy

**Summary**

Evidence informing this recommendation comes from two rapid systematic reviews commissioned by the WHO to summarise the evidence for the efficacy, safety (review 1), and risk of aerosol generation and infection transmission (review 2) during high-flow nasal cannula (HFNC) use among patients with acute hypoxaemic respiratory failure due to COVID-19 [95].

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Review 2: Risk of dispersal

Study design: Simulation studies and one prospective crossover study

Population: Healthy adult volunteers (two simulation studies), model human patient simulators (two simulation studies), and critically ill patients who received supplemental oxygen therapy (one crossover study). No studies available in patients with COVID-19, which was considered a limitation in applicability (indirect evidence).

Intervention: High-flow nasal oxygen (HFNO)

Comparison: None (three simulation studies); CPAP (one simulation study); conventional therapy with face mask (one crossover study)

Synthesis method: None, individual study results only

Results: Five studies were included, of which three were simulation studies and none were randomised trials. No studies included patients with COVID-19. In summary, the findings were very uncertain and no conclusions could be drawn. One simulation study found HFNO increased cough-generated droplet dispersion compared to no HFNO. A prospective cohort study found HFNO did not disperse gram-negative bacteria in air samples or set plates at 0.4 m and 1.5 m compared to a facemask. Another simulation study without a control group detected water and yeast colony formation at 0.3 m. Of two studies reporting aerosol dispersion, one found HFNO does not increase the risk of aerosol dispersion, while the second found higher flow rates resulted in increased regions of high aerosol density compared with continuous positive airway pressure (CPAP).

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### Escalation of therapy (HFNC, NIV or intubation)

Relative risk 0.71 (CI 95% 0.51 - 0.98) Based on data from 1,703 patients in 8 studies. 
Follow up 2 to 28 days

**320** per 1000  
Difference: **93 fewer** per 1000 (CI 95% 157 fewer - 6 fewer)

**Very Low**  
Due to serious risk of bias, imprecision and indirectness

We are uncertain whether HFNO increases or decreases escalation of therapy (HFNC, NIV or intubation)

### ICU length of stay (Days)

Based on data from: 972 patients in 2 studies.

**Difference: MD 1.38 fewer** (CI 95% 0.9 fewer - 3.66 fewer)

**Very Low**  
Due to serious imprecision, inconsistency and indirectness

We are uncertain whether HFNO increases or decreases ICU length of stay

### Hospital length of stay (Days)

Based on data from: 1,247 patients in 4 studies.

**Difference: MD 0.67 more** (CI 95% 1.41 fewer - 0.08 more)

**Low**  
Due to serious imprecision and indirectness

HFNO may have little or no difference on hospital length of stay

### Patient-reported dyspnea

Based on data from: 894 patients in 7 studies.

**Difference: SMD 0.66 lower** (CI 95% 1.68 lower - 0.35 higher)

**Very Low**  
Due to serious risk of bias, imprecision and indirectness

We are uncertain whether HFNO improves or worsens patient reported dyspnea

### Patient-reported comfort

Based on data from: 1,233 patients in 7 studies.

**Difference: SMD 0.12 lower** (CI 95% 0.61 lower - 0.37 higher)

**Very Low**  
Due to serious risk of bias, imprecision, inconsistency and indirectness

We are uncertain whether HFNO improves or worsens patient reported comfort

### Dispersal of droplets and aerosols

One simulation study found HFNO increased cough-generated droplet dispersion compared to no HFNO. A prospective cohort study found HFNO did not disperse gram-negative bacteria in air samples or set plates at 0.4 m and 1.5 m compared to a facemask. Another simulation study without a control group detected water and yeast colony formation at 0.3 m. Of two studies reporting aerosol dispersion, one found HFNO does not increase the risk of aerosol dispersion, while the second found higher flow rates resulted in increased regions of high aerosol density compared with continuous positive airway pressure (CPAP).

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1. Systematic review with included studies: [93]. **Baseline/comparator**: Control arm of reference used for intervention.
Strong Recommendation Against

During inter-hospital patient transfer/retrieval do not use high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19.

Clinical Question/ PICO

- **Population:** Patients with COVID-19
- **Intervention:** High-flow nasal oxygen therapy
- **Comparator:** Conventional oxygen therapy

Summary

Evidence informing this recommendation comes from two rapid systematic reviews commissioned by the WHO to summarise the evidence for the efficacy, safety (review 1), and risk of aerosol generation and infection transmission (review 2) during high-flow nasal cannula (HFNC) use among patients with acute hypoxaemic respiratory failure due to COVID-19 [95].

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Population
Healthy adult volunteers (two simulation studies), model human patient simulators (two simulation studies), and critically ill patients who received supplemental oxygen therapy (one crossover study). No studies available in patients with COVID-19, which was considered a limitation in applicability (indirect evidence).

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Synthesis method
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4. Very Low Due to serious risk of bias, imprecision and indirectness
5. Very Low Due to serious risk of bias, imprecision and indirectness
6. Very Low Due to serious risk of bias, imprecision and indirectness
1. Systematic review with included studies: [93]. **Baseline/comparator**: Control arm of reference used for intervention.

2. **Indirectness**: Serious. Differences between the population of interest and those studied. **Imprecision**: Serious.

3. Systematic review with included studies: [93]. **Baseline/comparator**: Control arm of reference used for intervention.

4. **Risk of bias**: Serious. **Indirectness**: Serious. **Imprecision**: Serious.

5. Systematic review with included studies: [93]. **Baseline/comparator**: Control arm of reference used for intervention.

### ICU length of stay (Days)

- **Follow up**: 2 to 28 days
- **Baseline/comparator**: Control arm of reference used for intervention
- **Difference**: MD 1.38 fewer (CI 95% 0.9 fewer - 3.66 fewer)
- **Risk of bias**: Serious. **Indirectness**: Serious. **Imprecision**: Serious. We are uncertain whether HFNO increases or decreases ICU length of stay

### Hospital length of stay (Days)

- **Follow up**: 2 to 28 days
- **Baseline/comparator**: Control arm of reference used for intervention
- **Difference**: MD 0.67 more (CI 95% 1.41 fewer - 0.08 more)
- **Risk of bias**: Serious. **Indirectness**: Serious. **Imprecision**: Serious. HFNO may have little or no difference on hospital length of stay

### Patient-reported dyspnea

- **Follow up**: 2 to 28 days
- **Baseline/comparator**: Control arm of reference used for intervention
- **Difference**: SMD 0.66 lower (CI 95% 1.68 lower - 0.35 higher)
- **Risk of bias**: Serious. **Indirectness**: Serious. **Imprecision**: Serious. We are uncertain whether HFNO improves or worsens patient reported dyspnea

### Dispersal of droplets and aerosols

- **Follow up**: 2 to 28 days
- **Baseline/comparator**: Control arm of reference used for intervention
- **Difference**: SMD 0.12 lower (CI 95% 0.61 lower - 0.37 higher)
- **Risk of bias**: Serious. **Indirectness**: Serious. **Imprecision**: Serious. We are uncertain whether HFNO improves or worsens patient reported comfort

### Patient-reported comfort

- **Follow up**: 2 to 28 days
- **Baseline/comparator**: Control arm of reference used for intervention
- **Difference**: SMD 0.66 lower (CI 95% 1.68 lower - 0.35 higher)
- **Risk of bias**: Serious. **Indirectness**: Serious. **Imprecision**: Serious. We are uncertain whether HFNO improves or worsens patient reported comfort

### Dispersal of droplets and aerosols

- **Follow up**: 2 to 28 days
- **Baseline/comparator**: Control arm of reference used for intervention
- **Difference**: SMD 0.12 lower (CI 95% 0.61 lower - 0.37 higher)
- **Risk of bias**: Serious. **Indirectness**: Serious. **Imprecision**: Serious. We are uncertain whether HFNO improves or worsens patient reported comfort

---

One simulation study found HFNO increased cough-generated droplet dispersion compared to no HFNO. A prospective cohort study found HFNO did not disperse gram-negative bacteria in air samples or set plates at 0.4 m and 1.5 m compared to a facemask. Another simulation study without a control group detected water and yeast colony formation at 0.3 m. Of two studies reporting aerosol dispersion, one found HFNO does not increase the risk of aerosol dispersion, while the second found higher flow rates resulted in increased regions of high aerosol density compared to continuous positive airway pressure (CPAP).
8.2 - Non-invasive ventilation

**Recommendation Strength Not Set**

Non-invasive ventilation (NIV), also known as non-invasive positive pressure ventilation (NIPPV) or bilevel positive pressure support (BiPAP), is a form of respiratory support. Bilevel positive pressure is delivered throughout the respiratory cycle by a firm-fitting nasal-face mask. The patient breathes spontaneously and triggers the device to cycle.

A higher level of pressure is provided during the inspiratory phase to enhance ventilation, while a lower level of continuous positive pressure is delivered during the expiratory phase (also known as positive end-expiratory pressure or PEEP). Supplemental oxygen can also be delivered through the device.

---

**Consensus Recommendation**

In **negative pressure rooms**, consider using NIV therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

**Rationale**

Non-invasive ventilation (NIV) may be associated with a high failure rate, delayed intubation, and possibly increased risk of aerosolisation with poor mask fit.

**Adaptation**

The recommendation is adapted from published recommendations by ANZICS [7]. Wording has been adapted for clarity and applicability to the Australian context.

---

**Consensus Recommendation**

In **single rooms** or **shared ward spaces with cohorting of confirmed COVID-19 patients only**, consider using NIV therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

**Rationale**

Non-invasive ventilation (NIV) may be associated with a high failure rate, delayed intubation, and possibly increased risk of aerosolisation with poor mask fit.
Adaptation
The recommendation is adapted from published recommendations by ANZICS [7]. Wording has been adapted for clarity and applicability to the Australian context.

**Consensus Recommendation**

In shared wards or emergency department cubicles, do not use NIV therapy for patients with hypoxaemia associated with COVID-19.

Rationale
Routine use of non-invasive ventilation (NIV) is not recommended as it may be associated with a high failure rate, delayed intubation, and possibly increased risk of aerosolisation with poor mask fit.

Adaptation
The recommendation is adapted from published recommendations by ANZICS [7]. Wording has been adapted for clarity and applicability to the Australian context.

**Consensus Recommendation**

During inter-hospital patient transfer/retrieval, do not use NIV therapy for patients with hypoxaemia associated with COVID-19.

Rationale
Routine use of non-invasive ventilation (NIV) is not recommended as it may be associated with a high failure rate, delayed intubation, and possibly increased risk of aerosolisation with poor mask fit.

Adaptation
The recommendation is adapted from published recommendations by ANZICS [7]. Wording has been adapted for clarity and applicability to the Australian context.

**Consensus Recommendation**

In patients with COVID-19 for whom NIV is appropriate for an alternate clinical presentation (e.g. concomitant COPD with type 2 respiratory failure and hypercapnoea, APO), ensure airborne and other infection control precautions are optimised.

Rationale
Routine use of non-invasive ventilation (NIV) is not recommended as it may be associated with a high failure rate, delayed intubation, and possibly increased risk of aerosolisation with poor mask fit.

Adaptation
The recommendation is adapted from published recommendations by ANZICS [7]. Wording has been adapted for clarity and applicability to the Australian context.
8.3 - Respiratory management of the deteriorating patient

**Consensus Recommendation**

In patients with COVID-19 who are deteriorating, consider early endotracheal intubation and invasive mechanical ventilation.

*Patients can deteriorate rapidly 5 to 10 days after onset of symptoms.*

**Adaptation**

The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign [88]. Wording has been adapted for clarity and applicability to the Australian context.

8.4 - Videolaryngoscopy

**Weak Recommendation**

In adults with COVID-19 undergoing endotracheal intubation, consider using videolaryngoscopy over direct laryngoscopy if available and the operator is trained in its use.

**Key Info**

**Benefits and harms**

| Small net benefit, or little difference between alternatives |

Time to intubation varied depending on the experience of the operator and the setting. Another important consideration is the potential risk of contamination to the operator due to the infectious nature of COVID-19. In a simulation study using a manikin, the distance between the operator and patient's mouth increased when using video compared to direct laryngoscopy, thus potentially benefitting operators in the case of COVID-19.

**Certainty of the Evidence**

| Very Low |

For the two critical outcomes—distance between patient and operator, and time to successful intubation—certainty of the evidence is very low due to serious risk of bias, inconsistency, indirectness and imprecision.

**Preference and values**

| No substantial variability expected |

We have no systematically collected information regarding patients’ preferences and values. Although there is uncertainty regarding the time to successful intubation, we are reasonably confident that patients would find videolaryngoscopy an acceptable intervention compared to direct laryngoscopy.

**Resources and other considerations**

| Important issues, or potential issues not investigated |

We have no systematically collected evidence regarding cost-benefit. The main costs associated with videolaryngoscopy are attributed to the initial equipment outlay, maintenance and operator training. The panel clarified in the recommendation that videolaryngoscopy should only be considered if available and operators are trained in its use.

**Equity**

| Important issues, or potential issues not investigated |

There is a risk of creating inequity as people who live in rural and remote areas may have limited access to videolaryngoscopy and experienced operators. Due to costs and maintenance, there will be variation in the type of clinical settings likely to have...
access to the appropriate equipment; larger, specialised centres in urban areas are more likely to provide access than those in smaller more remote centres.

The panel noted that rural and remote hospitals do not routinely have access to videolaryngoscopy. The outcome of time to successful intubation is dependent on operator expertise and would likely take longer in non-specialist centres. However, the panel felt that most people intubating would be trained in videolaryngoscopy, although experience would vary. The panel clarified in the recommendation that videolaryngoscopy should only be considered if available and operators are trained in its use.

**Acceptability**

Videolaryngoscopy is generally a well-accepted intervention, and there are no important issues regarding acceptability.

**Feasibility**

Feasibility is affected by the initial equipment costs, maintenance and operator training. The panel clarified in the recommendation that videolaryngoscopy should only be considered if available and operators are trained in its use.

**Rationale**

Videolaryngoscopy allows for increased distance between operator and patient.

---

**Clinical Question/ PICO**

- **Population:** Patients requiring emergency intubation
- **Intervention:** Videolaryngoscopy
- **Comparator:** Direct laryngoscopy

**Summary**

Evidence informing this recommendation comes from a systematic review of video versus direct laryngoscopy for the emergency intubation of adults in the inpatient setting [102]. A simulation study is also included that evaluated the distance between a dummy's mouth and physician's face during intubation [107].

**Effectiveness and adverse events**

<table>
<thead>
<tr>
<th>Study design</th>
<th>Randomised trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Critically ill patients requiring emergency intubation in emergency departments or intensive care units. No studies available in patients with COVID-19.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Videolaryngoscopy</td>
</tr>
<tr>
<td>Comparator</td>
<td>Direct laryngoscopy</td>
</tr>
<tr>
<td>Synthesis method</td>
<td>Meta-analysis</td>
</tr>
</tbody>
</table>

We included six of the eight randomised trials (1023 patients) in the Rombev review [100],[101],[103],[104],[105],[106]. (Two were excluded because patients were intubated before hospital admission.) We included an additional randomised trial of 163 patients that was published after the Rombev review [99]. This study did not change the overall results for the outcomes, but did improve the precision of the estimate for inadvertent oesophageal intubation.

**Results**

There was no difference between video and direct laryngoscopy with respect to successful intubation at first attempt or time to successful intubation. In the four randomised trials that reported inadvertent oesophageal intubation, the use of videolaryngoscopy was associated with fewer of these adverse events, however the number was small (27 events).
### Operator distance (Hall 2020)

<table>
<thead>
<tr>
<th>Study design</th>
<th>Crossover study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>25 doctors of mixed experience performing tracheal intubation on a high-fidelity manikin.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Videolaryngoscopy</td>
</tr>
<tr>
<td>Comparison</td>
<td>Direct laryngoscopy</td>
</tr>
<tr>
<td>Results</td>
<td>Videolaryngoscopy may extend the mouth-to-mouth distance from laryngoscopist to patient compared to direct laryngoscopy.</td>
</tr>
</tbody>
</table>

Certainty of the evidence is low to very low due to indirectness (not based on COVID-19 patients or exclusively patients with ARDS), risk of bias, lack of precision in some outcomes and small number of adverse events.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-pass intubation success</td>
<td>Relative risk 1.05 (CI 95% 0.94 - 1.17) Based on data from 1,186 patients in 7 studies. 1 (Randomized controlled)</td>
<td>716 per 1000 752 per 1000 Difference: 36 more per 1000 (CI 95% 43 fewer - 122 more)</td>
<td>Very Low Due to serious risk of bias, inconsistency and indirectness 2</td>
<td>We are uncertain whether videolaryngoscopy increases or decreases first-pass intubation success.</td>
</tr>
<tr>
<td>Oesophageal intubation</td>
<td>Relative risk 0.4 (CI 95% 0.17 - 0.93) Based on data from 795 patients in 4 studies. 3 (Randomized controlled)</td>
<td>50 per 1000 20 per 1000 Difference: 30 fewer per 1000 (CI 95% 41 fewer - 3 fewer)</td>
<td>Low Due to serious risk of bias and indirectness 4</td>
<td>Videolaryngoscopy may decrease oesophageal intubation.</td>
</tr>
<tr>
<td>Operator distance in cm 5</td>
<td>Measured by: distance analysed from videorecording High better Based on data from: 25 patients in 1 studies. 6 (Randomized controlled)</td>
<td>16.4 centimetres (Mean) 35.6 centimetres (Mean) Difference: MD 19.2 higher (CI 95% 13.28 lower - 25.12 higher)</td>
<td>Very Low Due to serious risk of bias, indirectness and imprecision 7</td>
<td>Videolaryngoscopy may increase the operator distance.</td>
</tr>
<tr>
<td>Time to successful intubation</td>
<td>Based on data from 988 patients in 6 studies.</td>
<td>The heterogeneity for this outcome was too high to combine in a meta-analysis. Two studies reported shorter time to successful intubation with direct laryngoscopy, two with videolaryngoscopy, and two reported the same or very similar durations.</td>
<td>Very Low Due to serious risk of bias, indirectness and imprecision, and very serious inconsistency 8</td>
<td>We are uncertain whether videolaryngoscopy increases or decreases time to successful intubation.</td>
</tr>
</tbody>
</table>

8.5 - Neuromuscular blockers

Neuromuscular blocking agents (NMBAs) are a pharmaceutical intervention that may facilitate protective lung ventilation in patients who are mechanically ventilated with moderate to severe acute respiratory distress syndrome (ARDS). NMBAs may reduce patient-ventilator dyssynchrony and facilitate improved oxygenation by various mechanisms, including reducing the inspiratory muscle effort and the work of breathing, and reducing ventilator-induced lung injury.

**Weak Recommendation Against**

For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, do not routinely use continuous infusions of neuromuscular blocking agents (NMBAs).

However, if protective lung ventilation cannot be achieved, consider using NMBAs for up to 48 hours. If indicated, consider cisatracurium as first-line agent, if cisatracurium is not available alternatives include atracurium or vecuronium by infusion.
Key Info

Benefits and harms
There is no substantial net benefit to using neuromuscular blockers. Prolonged use of NMBAs could have negative effects on intubated patients, such as muscle weakness and difficulty weaning from mechanical ventilation.

Certainty of the Evidence
Outcomes identified as most critical were 90-day mortality and muscle weakness at 28 days. No studies were identified that included patients with COVID-19. Certainty of the evidence for all outcomes is very low, mostly due to serious inconsistency, indirectness and imprecision. There were substantial methodological inconsistencies between the trials.

Preference and values
We have no systematically collected information regarding patients’ preferences and values. Since there is uncertainty regarding the critical outcome of muscle weakness, some patients might consider NMBAs unacceptable. The inability to move or communicate while being treated with neuromuscular blockers is likely to be an additional consideration for patients.

Resources and other considerations
We have no systematically collected evidence regarding cost-benefit. There are potential resource considerations due to supply issues for some neuromuscular blockers (e.g. cisatracurium).

Equity
There is a risk of creating inequity as some populations may have limited access to neuromuscular blockers, particularly if there is a shortage.

Acceptability
Neuromuscular blockers may be less acceptable because of possible harms—patients and clinicians may consider the benefits are not worth the risk. In addition to the risk of muscle weakness, patients and their families may deem it unacceptable to be paralysed and non-responsive.

Feasibility
Feasibility may be affected by potential supply issues for some neuromuscular blockers (e.g. cisatracurium).

Rationale
Routine use of continuous infusions of neuromuscular blockers could have negative effects on intubated patients, such as muscle weakness and difficulty weaning from mechanical ventilation.

Clinical Question/ PICO
Population: Mechanically ventilated adults with COVID-19 and persistent ventilator dyssynchrony, the need for ongoing deep sedation, prone ventilation or persistently high plateau pressures
Intervention: Continuous infusion of NMLA
Comparator: No continuous infusion of NMLA
Summary

Evidence informing this recommendation comes from five randomised trials involving 1461 adults with acute respiratory distress syndrome. Currently, there is no evidence in patients with COVID-19. The five trials compared continuous infusions of neuromuscular blocking agents with cisatracurium for up to 48 hours to no continuous infusions of NMBA [109][110][111][112][113].

For all critical outcomes, it is uncertain whether infusion of neuromuscular blockers makes a difference. The ROSE trial, which had a different sedation strategy to the other trials and implemented a higher PEEP strategy, is the largest (1006 participants) and most recent trial, and may be the most reflective of current practice [110]. There were no differences for the mortality outcomes, but the trial found a small increase in muscle weakness at 28 days in the neuromuscular blocker group.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day mortality</td>
<td>Relative risk 0.78 (CI 95% 0.58 - 1.06) Based on data from 1,461 patients in 5 studies.</td>
<td>372 per 1000 290 per 1000</td>
<td>Very Low Due to serious inconsistency, indirectness and imprecision 2</td>
<td>We are uncertain whether neuromuscular blockers improve or worsen 28-day mortality (total no of events in trials = 513).</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>Relative risk 0.81 (CI 95% 0.62 - 1.06) Based on data from 1,461 patients in 5 studies.</td>
<td>441 per 1000 357 per 1000</td>
<td>Very Low Due to serious inconsistency, indirectness and imprecision 4</td>
<td>We are uncertain whether neuromuscular blockers improve or worsen 90-day mortality (total no of events in trials = 612).</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>Relative risk 0.72 (CI 95% 0.57 - 0.91) Based on data from 455 patients in 4 studies.</td>
<td>438 per 1000 315 per 1000</td>
<td>Very Low Due to serious imprecision and very serious indirectness 6</td>
<td>We are uncertain whether neuromuscular blockers increase or decrease ICU mortality (total no of events in trials = 171).</td>
</tr>
<tr>
<td>ICU weakness at day 28</td>
<td>Relative risk 1.23 (CI 95% 0.81 - 1.88) Based on data from 356 patients in 4 studies.</td>
<td>230 per 1000 283 per 1000</td>
<td>Very Low Due to serious risk of bias and imprecision, and very serious indirectness 8</td>
<td>We are uncertain whether neuromuscular blockers increase or decrease ICU weakness at day 28 (total no of events in trials = 91).</td>
</tr>
<tr>
<td>Barotrauma</td>
<td>Relative risk 0.55 (CI 95% 0.35 - 0.85) Based on data from 1,426 patients in 4 studies.</td>
<td>74 per 1000 41 per 1000</td>
<td>Very Low Due to serious risk of bias, indirectness and Indirectness 10</td>
<td>We are uncertain whether neuromuscular blockers improve or worsen barotrauma (total no of events in trials = 81).</td>
</tr>
</tbody>
</table>

2. **Inconsistency:** Serious. The magnitude of statistical heterogeneity was high, with $I^2:50\%$. Clinical heterogeneity - ROSE trial has a different sedation strategy than the other trials. **Indirectness:** Serious. Differences between the population of interest and those studied: no studies in patients with COVID-19. Only one study (largest study) used a high PEEP strategy. **Imprecision:** Serious. Substantial methodological differences between the studies. ROSE trial has a different sedation strategy than the other trials. **Publication bias:** No serious.


4. **Inconsistency:** Serious. The magnitude of statistical heterogeneity was high, with $I^2:56\%$. Clinical heterogeneity - ROSE trial has a different sedation strategy than the other trials. **Indirectness:** Serious. Differences between the population of interest and those studied: no studies in patients with COVID-19. The largest trial, with the most applicable strategy reflecting current clinical practice, did not report on this outcome. **Imprecision:** Serious. Low number of patients. **Publication bias:** No serious.


6. **Inconsistency:** No serious. **Indirectness:** Very Serious. Differences between the population of interest and those studied: no studies in patients with COVID-19. The largest trial, with the most applicable strategy reflecting current clinical practice, did not report on this outcome. **Imprecision:** Very Low. Due to serious risk of bias, inconsistency and indirectness, and very serious imprecision.


8. **Risk of bias:** Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** No serious. **Indirectness:** Very Serious. Differences between the population of interest and those studied: no studies in COVID-19 patients. The largest trial, with the most applicable strategy reflecting current clinical practice, only included a very small subset of patients for this outcome. **Imprecision:** Serious. Low number of patients. **Publication bias:** No serious.


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### Mechanical ventilation duration

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Days</th>
<th>Median</th>
<th>Median</th>
<th>Difference</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>6</td>
<td>18</td>
<td>20</td>
<td>2 higher</td>
<td>Very Low</td>
</tr>
<tr>
<td>Important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>We are uncertain whether neuromuscular blockers increase or decrease mechanical ventilation duration.</td>
</tr>
</tbody>
</table>

**Measured by:** Days. Based on data from: 92 patients in 2 studies. **(Randomized controlled)**

### Ventilator-free days at day 28

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Days</th>
<th>Median</th>
<th>Median</th>
<th>Difference</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>6</td>
<td>9.6</td>
<td>9.9</td>
<td>0.3 higher</td>
<td>Very Low</td>
</tr>
<tr>
<td>Important</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>We are uncertain whether neuromuscular blockers improve or worsen ventilator-free days at day 28.</td>
</tr>
</tbody>
</table>

**Measured by:** Days. Based on data from: 1,462 patients in 5 studies. **(Randomized controlled)**

### MRC score at day 28

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Median</th>
<th>Median</th>
<th>Difference</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC score at day 28</td>
<td>49.8</td>
<td>45.9</td>
<td>4.1 lower</td>
<td>Very Low</td>
</tr>
<tr>
<td>Important</td>
<td></td>
<td></td>
<td></td>
<td>We are uncertain whether neuromuscular blockers improve or worsen MRC score at day 28.</td>
</tr>
</tbody>
</table>

**Measured by:** Medical Research Council (MRC) scale. Scale: 0-60 High better. Based on data from: 1,346 patients in 2 studies. (Randomized controlled) Follow up 28 days.
8.6 - Positive end-expiratory pressure

**Consensus Recommendation**

For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, consider using a higher PEEP strategy (PEEP > 10 cm H2O) over a lower PEEP strategy.

**Key Info**

**Benefits and harms**

While there is no current evidence for using a higher PEEP strategy in patients with COVID-19 and moderate to severe ARDS, a higher PEEP strategy is recommended for ventilated patients with moderate to severe ARDS of other aetiologies. A higher PEEP strategy may be associated potential harms, e.g. pneumothorax.

**Certainty of the Evidence**

No studies were identified in COVID-19 patients that address the question of lower versus higher PEEP strategy.

**Preference and values**

We have no systematically collected information regarding patients' preferences and values at this point.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit.
Rationale
While there is no current evidence for using a higher PEEP strategy in patients with COVID-19 and moderate to severe ARDS, a higher PEEP strategy is recommended for ventilated patients with moderate to severe ARDS of other aetiologies.

Adaptation
The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign [88].

8.7 - Prone positioning

Recommendation Strength Not Set
Positioning the patient in a face-down (prone) position may help to open up (recruit) collapsed alveoli and improve oxygen levels in the blood.

8.7.1 - Prone positioning for adults

Consensus Recommendation
For mechanically ventilated adults with COVID-19 and hypoxaemia despite optimising ventilation, consider prone positioning for more than 12 hours a day.

Current reports suggest prone ventilation is effective in improving hypoxia associated with COVID-19. This should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff, and that minimises the risk of adverse events, e.g. accidental extubation.

Key Info
Benefits and harms
While there is no current evidence for using prone positioning in patients with COVID-19, it is recommended for ventilated patients with moderate to severe ARDS of other aetiologies. In these patients it is known to have a survival benefit, but may increase the risk of harms from complications such as pressure injury, endotracheal tube obstruction or accidental extubation.
Adaptation

The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign [88]. Wording has been adapted for clarity and applicability to the Australian context [7].

Preference and values

We have no systematically collected information regarding patients’ preferences and values at this point.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Proning is associated with significant cost since additional staff are needed to move and monitor those in prone position. Healthcare workers must be effectively trained to facilitate safe practice.

Equity

There is the potential for inequity as some healthcare facilities may not have sufficient staff to offer prone positioning.

Acceptability

We have no systematically collected evidence regarding acceptability. Clear communication from health professionals regarding the possible benefits and harms of prone positioning is essential.

Feasibility

Prone positioning of mechanically ventilated patients is likely feasible if performed by trained personnel in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events, e.g., accidental extubation.

Consensus Recommendation

For adults with COVID-19 and respiratory symptoms who are receiving any form of supplemental oxygen therapy and have not yet been intubated, consider prone positioning. When positioning a patient in prone, ensure it is used with caution and close monitoring of the patient. Patients who are deteriorating should be considered for early endotracheal intubation and invasive mechanical ventilation.

Rationale

Prone positioning is used in people with severe hypoxaemic respiratory failure in the context of ARDS. In ventilated people with ARDS, prone positioning improves oxygenation and clinical outcomes. Prone positioning is thought to work by improving tidal ventilation, especially to dependent parts of the lung, enhancing ventilation and perfusion matching as well as favourably distributing the pleural pressures throughout the lung thus minimising further damage.
8.7.2 - Prone positioning for pregnant and postpartum women

Consensus Recommendation

For mechanically ventilated pregnant women with COVID-19 and hypoxaemia despite optimising ventilation, consider prone positioning for more than 12 hours a day.

Current reports suggest prone ventilation in adult patients is effective in improving hypoxia associated with COVID-19. This should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff, and that minimises the risk of adverse events, e.g. accidental extubation.

Proning of a pregnant woman should avoid abdominal compression and ensure a woman's hips and chest are supported. In the absence of specialised equipment, proning can be performed using pillows and blankets.

Proning can be challenging in late gestation and delivery of the baby may be warranted.

Key Info

Benefits and harms

The benefit of prone positioning in pregnant women with COVID-19 is unknown, but it may improve lung mechanics and gas exchange. However, it can be associated with harms such as hypoperfusion, compartment syndrome, pressure ulcers, airway swelling and peripheral arterial compression.

Certainty of the Evidence

No studies were identified in COVID-19 patients that address the interventions or outcomes of interest.

Preference and values

We have no systematically collected information regarding the preferences and values of pregnant and breastfeeding women with COVID-19 at this point.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Caring for pregnant women with COVID-19 (irrespective of prone positioning) requires greater resources than for women without COVID-19. Proning is associated with significant cost since additional staff are needed to move and monitor those in prone position. Healthcare workers must be effectively trained to facilitate safe practice.

Equity

There is the potential for inequity as some healthcare facilities may not have sufficient staff to offer prone positioning.

Acceptability

We have no systematically collected evidence regarding acceptability. Acceptability of prone positioning is expected to vary and individual preferences should be considered. Clear communication from health professionals regarding the possible benefits and harms of prone positioning is essential.

Feasibility

Important issues, or potential issues not investigated
Prone positioning may be less feasible later in pregnancy. Prone positioning of mechanically ventilated patients is likely feasible if performed by trained personnel in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events, e.g. accidental extubation.

Consensus Recommendation

For pregnant and postpartum women with COVID-19 and respiratory symptoms who are receiving any form of supplemental oxygen therapy and have not yet been intubated, consider prone positioning. When positioning a pregnant woman in prone, care should be taken to support the gravid uterus to reduce aorta-caval compression. Women who are deteriorating should be considered for early endotracheal intubation and invasive mechanical ventilation. Birth of the baby should be considered when it may enhance maternal resuscitation or be beneficial to the fetus.

Current reports suggest prone ventilation in adult patients is effective in improving hypoxia associated with COVID-19. This should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events, e.g. accidental extubation.

Proning of a pregnant woman should avoid abdominal compression and ensure a woman’s hips and chest are supported. In the absence of specialised equipment, it can be performed using pillows and blankets.

Proning can be challenging in late gestation and delivery of the baby may be warranted.

Key Info

Benefits and harms

The benefit of prone positioning in pregnant women with COVID-19 is unknown, but it may improve lung mechanics and gas exchange. However, it can be associated with harms such as hypoperfusion, compartment syndrome, pressure ulcers, airway swelling and peripheral arterial compression.

Certainty of the Evidence

No studies were identified in COVID-19 patients that address the interventions or outcomes of interest.

Preference and values

We have no systematically collected information regarding the preferences and values of pregnant and breastfeeding women with COVID-19 at this point.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Caring for pregnant women with COVID-19 (irrespective of prone positioning) requires greater resources than for women without COVID-19. Proning is associated with significant cost since additional staff are needed to move and monitor those in prone position. Healthcare workers must be effectively trained to facilitate safe practice.

Equity

There is the potential for inequity as some healthcare facilities may not have sufficient staff to offer prone positioning.
8.8 - Recruitment manoeuvres

Patients receiving respiratory support are at an increased risk of lung injury. Recruitment manoeuvres are used to open up ('recruit') collapsed alveoli and are a common element of an 'open lung approach' to protect the lungs during mechanical ventilation. The manoeuvres use a sustained increase in airway pressure to re-open collapsed alveoli.

Types of manoeuvres include: prolonged high continuous positive airway pressure; progressive incremental increases in positive end-expiratory pressure at a constant driving pressure (incremental PEEP, stepwise or staircase); and high driving pressures.

Consensus Recommendation

For mechanically ventilated adults with COVID-19 and hypoxaemia despite optimising ventilation, consider using recruitment manoeuvres.

If recruitment manoeuvres are used, do not use staircase or stepwise (incremental PEEP) recruitment manoeuvres.

Key Info

Benefits and harms

Recruitment manoeuvres may benefit mechanically ventilated patients with COVID-19 by opening collapsed lung units during mechanical ventilation. However, they may also be associated with harms, such as increased risk of barotrauma and transient hypotension.

Certainty of the Evidence

No studies were identified in COVID-19 patients that compare recruitment manoeuvres to no recruitment manoeuvres or variations on recruitment manoeuvres.

Preference and values

We have no systematically collected information regarding patients' preferences and values at this point.
Adaptation
The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign [88]. Wording has been adapted for clarity and applicability to the Australian context.

8.9 - Extracorporeal membrane oxygenation

Recommendation Strength Not Set
Extracorporeal membrane oxygenation (ECMO) is a form of life support that removes blood from the body via large cannulae, oxygenates and removes carbon dioxide from the blood external to the patient, and then returns the blood to the body.

Venovenous (VV) ECMO provides oxygenation support for the lungs only, while venoarterial (VA) ECMO supports the heart and lungs.

8.9.1 - ECMO for adults

Consensus Recommendation
In mechanically ventilated adults with COVID-19 and refractory respiratory failure (despite optimising ventilation, including proning), consider using venovenous extracorporeal membrane oxygenation (VV ECMO) if available, or referring the patient to an ECMO centre.

Due to the resource-intensive nature of ECMO and the need for experienced centres, healthcare workers and infrastructure, ECMO should only be considered in selected patients with COVID-19 and severe ARDS.

Key Info
Benefits and harms Small net benefit, or little difference between alternatives
ECMO is only used as a form of life support in selected patients who are severely ill, and aims to increase oxygenation and reduce ventilator-induced lung injuries. However, it may be associated with a risk of serious side effects, such as major bleeding, disseminated intravascular coagulation and injuries from cannulation.

**Certainty of the Evidence**

No studies were identified in COVID-19 patients that compare ECMO to no ECMO.

**Preference and values**

We have no systematically collected information regarding patients’ preferences and values at this point. However, the serious risk of side effects may be unacceptable for some patients and their families.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. ECMO is resource-intensive and requires experienced centres, healthcare workers and infrastructure.

**Equity**

Due to the resource-intensive nature of ECMO there may be issues with inequity as only certain centres will have the ability to offer ECMO or ECMO retrieval. ECMO will only be considered in selected patients who are likely to have access to appropriate centres.

**Acceptability**

There may be important issues with acceptability. The intervention could be considered less acceptable due to its possible harms and some may not consider its benefits worth the risk.

**Feasibility**

Due to the resource-intensive nature of ECMO there are likely to be feasibility issues. ECMO is likely to only be feasible in a limited number of centres.

**Adaptation**

The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign [88]. Wording has been adapted for clarity and applicability to the Australian context.
8.9.2 - ECMO for pregnant and postpartum women

**Consensus Recommendation**

Consider referral to an ECMO centre for venovenous ECMO in mechanically ventilated pregnant women with COVID-19 and refractory respiratory failure (despite optimising ventilation, including proning). Delivery of the baby prior to ECMO to enhance maternal resuscitation should be considered on a case-by-case basis.

Due to the resource-intensive nature of ECMO and the need for experienced centres, healthcare workers and infrastructure, ECMO should only be considered in selected pregnant women with COVID-19 and severe ARDS.

The decision on whether to use ECMO should be taken in consultation with the woman's family, as well as obstetric and intensive care specialists. Key considerations include gestational age, fetal viability, fetal well-being and the risks and benefits to mother and baby.

Early referral to an ECMO centre is preferred.

As pregnant and postpartum women may have haemostatic alterations, anticoagulation regimens may need to be modified appropriately.

**Key Info**

**Benefits and harms**

The benefit of ECMO in pregnant women with COVID-19 is unclear. ECMO is only used as a form of life support in selected patients who are severely ill, and aims to increase oxygenation and reduce ventilator-induced lung injuries. However, it may be associated with an increased risk of serious side effects, such as major bleeding and injuries from cannulation. The need for anticoagulation and risk of bleeding concomitant to the use of ECMO needs to be considered carefully in pregnant women, given that this therapy may not be effectively administered without anticoagulation and it increases the risk of bleeding in pregnant women.

**Certainty of the Evidence**

No studies were identified in COVID-19 patients that compared ECMO to no ECMO.

**Preference and values**

We have no systematically collected information regarding patients' preferences and values at this point. However, the serious risk of side effects may be unacceptable for some patients and their families.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. ECMO is resource-intensive and requires experienced centres, healthcare workers and infrastructure.

**Equity**

Due to the resource-intensive nature of ECMO there may be issues with inequity as only certain centres will have the ability to offer ECMO and it will only be considered in selected patients who are likely to have access to these centres.

**Acceptability**

There may be important issues with acceptability. The intervention could be considered less acceptable due to its possible harms and some may not consider its benefits worth the risk.
Rationale
ECMO is only used as a form of life support in those who are severely ill with refractory respiratory failure (despite optimising ventilation, including proning) and aims to increase oxygenation and reduce ventilator-induced lung injuries. It is recommended as a therapy for selected patients with severe ARDS of other aetiologies.

Feasibility

Due to the resource-intensive nature of ECMO there are likely to be feasibility issues. ECMO is likely to only be feasible in a limited number of centres.
9 - Steroids for people with asthma or COPD and COVID-19

9.1 - Steroids for people with asthma or COPD and COVID-19

**Consensus Recommendation**

Use inhaled or oral steroids for the management of people with co-existing asthma or COPD and COVID-19 as you would normally for viral exacerbation of asthma or COPD. Do not use a nebuliser.

**Key Info**

**Benefits and harms**

<table>
<thead>
<tr>
<th>Substantial net benefits of the recommended alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stopping long-term inhaled or oral corticosteroids suddenly can lead to exacerbation of symptoms of asthma and COPD or risk of relative adrenal insufficiency. There is currently no evidence specific to patients with COVID-19 and asthma or COPD.</td>
</tr>
</tbody>
</table>

**Certainty of the Evidence**

<table>
<thead>
<tr>
<th>No substantial variability expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no available evidence about outcomes for inhaled or oral corticosteroids for patients with COVID-19 and asthma or COPD.</td>
</tr>
</tbody>
</table>

**Preference and values**

<table>
<thead>
<tr>
<th>No important issues with the recommended alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>We have no systematically collected information regarding patients' preferences and values. The panel believes that, while there is uncertainty about the benefit to harm ratio regarding the use of corticosteroids for COVID-19, there are likely harms associated with an exacerbation of asthma or COPD, as well as harms associated with a sudden stopping of corticosteroids, and thus patients may prefer to take steroids as prescribed.</td>
</tr>
</tbody>
</table>

**Resources and other considerations**

<table>
<thead>
<tr>
<th>No important issues with the recommended alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>We have no systematically collected information regarding cost-benefit. Continued use of inhaled or oral corticosteroids as per usual care is unlikely to have an impact on availability of these drugs.</td>
</tr>
</tbody>
</table>

**Equity**

<table>
<thead>
<tr>
<th>No important issues with the recommended alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are no identified equity issues.</td>
</tr>
</tbody>
</table>

**Acceptability**

<table>
<thead>
<tr>
<th>No important issues with the recommended alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>The treatment is likely to be acceptable to both patients and clinicians.</td>
</tr>
</tbody>
</table>

**Feasibility**

<table>
<thead>
<tr>
<th>No important issues with the recommended alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are likely no important feasibility issues as the recommendation reflects usual care.</td>
</tr>
</tbody>
</table>

**Rationale**

Oral steroids and continuation of inhaled steroids reduce harms in patients experiencing exacerbations of asthma or COPD or and are considered usual care. There is currently no evidence to indicate that it is necessary to deviate from usual care.
Adaptation
The recommendation is adapted from published recommendations from three clinical guidelines, Australian Asthma Handbook, NICE [NG168] and NICE [NG 166]. Wording has been adapted for clarity and applicability to the Australian context.

Clinical Question/ PICO

| Population: | People with asthma or COPD and COVID-19 |
| Intervention: | Corticosteroids |
| Comparator: | Standard care |

Summary
For patients with severe asthma, the Australian Asthma Handbook recommends that clinicians "administer or prescribe systemic (oral) corticosteroids to manage severe flare-ups or acute asthma as indicated, following recommendations based on age-group" but to be cautious using corticosteroids when acute viral infection is suspected or confirmed (e.g. avoid use for mild flare-ups) [114]. This recommendation is in concordance with NICE NG166, which recommends that patients who develop symptoms and signs of an asthma exacerbation should follow their personalised asthma action plan and start a course of oral corticosteroids if clinically indicated [116].

For patients with asthma who are receiving inhaled steroids, the Australian Asthma Handbook also advises patients “to continue taking inhaled corticosteroids during the COVID-19 pandemic”. It reminds clinicians to “warn patients that stopping their preventer increases the risk of severe asthma flare-ups, including those triggered by viral respiratory infections”. This recommendation is in concordance with NICE NG166, which recommends that patients continue using oral or inhaled steroids and to avoid stopping oral or inhaled steroids.

For patients with COPD, NICE NG168 recommends that patients who are having an exacerbation for COPD start a course of oral corticosteroids and/or antibiotics if oral corticosteroids and/or antibiotics are clinically indicated [115]. Oral corticosteroids are not recommended for symptoms of COVID-19 alone (e.g. fever, dry cough or myalgia).

The recommendations take into consideration potential harms with starting oral corticosteroids (particularly at high doses for a prolonged period) and harms associated with withholding corticosteroids suddenly.

According to the Therapeutic Goods Administration, starting oral corticosteroids (prednisolone or dexamethasone) can lead to disturbed endocrine function, ophthalmological conditions and adrenal suppression [117][118].

Abrupt withdrawal of corticosteroids can lead to acute adrenal insufficiency or exacerbation of symptoms of asthma or COPD.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Standard care</td>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>See summary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## 10 - Anticoagulants

### 10.1 - Venous thromboembolism (VTE) prophylaxis

**Consensus Recommendation**

Use prophylactic doses of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) in adults with moderate COVID-19 or other indications, unless there is a contraindication, such as risk for major bleeding. Where severe acute kidney disease is present, unfractionated heparin or renally adjusted doses of LMWH may be used (e.g. enoxaparin 20 mg once daily or dalteparin 2500 IU once daily).

### Key Info

**Benefits and harms**

There is uncertainty around benefits and harms for patients with COVID-19, but the benefits as well as harms associated with the use of LMW heparin and other anticoagulants are well-known in other patient groups.

**Certainty of the Evidence**

There is no available evidence regarding outcomes for the use of LMW heparin or other anticoagulants in patients with COVID-19.

**Preference and values**

We have no systematically collected information regarding patients’ preferences and values. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients may prefer to wait while other patients may be more willing to take risks.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the potential impact on reduced access to these treatments by patients currently using them for other indications.

**Equity**

There are no identified equity issues.

**Acceptability**

Treatment is probably acceptable to both patients and clinicians. However, we have no systematically collected evidence regarding acceptability.

**Feasibility**

There are no identified feasibility issues.

**Rationale**

The panel believes that the benefits of pharmacologic prophylaxis among medically ill patients outweigh potential harm, such as bleeding caused by this prophylaxis. The panel believes that this will also apply to patients with COVID-19 and therefore...
recommend pharmacologic prophylaxis.

**Adaptation**

The recommendation for use of DVT prophylaxis is adapted from published recommendations by the International Society on Thrombosis and Haemostasis [119], University of Miami [120] and British Haematological Society [121]. Wording has been adapted for clarity and applicability to the Australian context.

**Clinical Question/ PICO**

**Population:** People with moderate COVID-19  
**Intervention:** DVT prophylaxis  
**Comparator:** Standard care

**Summary**

At present there are no randomised trials that have investigated the benefits of using anticoagulants in patients with moderate COVID-19. There is variability in existing COVID-19 specific recommendations regarding the use of anticoagulants in COVID-19 patients, such that the use of anticoagulants should be considered in all patients [119][120], all immobilised or severely ill patients [121] or used based on best existing data and best current local practices [122].

Heparin is contraindicated in individuals with ulcerative conditions showing a tendency to haemorrhage (e.g. gastrointestinal ulcer, ulcerative colitis), cerebral haemorrhage, severe thrombocytopaenia or other severe coagulation disorders, and individuals with an uncontrollable active bleeding state. The use of heparin can result in side effects such as haemorrhage, thrombocytopaenia, skin necrosis or irritation at the injection site, and suppression of aldosterone synthesis with hyperkalaemia and/or metabolic acidosis [123][124].

**Outcome Timeframe**

<table>
<thead>
<tr>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>See summary</strong></td>
<td>Relative risk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative risk: CI 95%

**10.2 - Increased-dose venous thromboembolism (VTE) prophylaxis**

**Consensus Recommendation**

Consider using increased prophylactic dosing of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg twice daily or dalteparin 5000 IU twice daily) in adults with severe or critical COVID-19 or other indications, unless there is a contraindication, such as risk for major bleeding or platelet count < 30 x 10^9/L. Where severe acute kidney disease is present (creatinine clearance < 30 mL/min), unfractionated heparin or renal adjusted doses of LMWH may be used (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily).
Key Info

<table>
<thead>
<tr>
<th>Benefits and harms</th>
<th>Substantial net benefits of the recommended alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is uncertainty around the benefits and harms for patients with COVID-19. However, there are well-known benefits as well as harms associated with the use of LMW heparin and other anticoagulants in other patient groups.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Certainty of the Evidence</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>There is currently no evidence relating to increased prophylactic doses of anticoagulants in patients with COVID-19.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preference and values</th>
<th>No substantial variability expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>We have no systematically collected information regarding patients’ preferences and values. Since there is uncertainty regarding the benefit to harm ratio, some patients may prefer to wait while other patients may be more willing to take risks.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resources and other considerations</th>
<th>Important issues, or potential issues not investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the potential impact on reduced access to treatments by patients currently using them for other indications.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Equity</th>
<th>No Important issues with the recommended alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are no identified equity issues.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acceptability</th>
<th>Important issues, or potential issues not investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment is probably acceptable to both patients and clinicians, however, we have no systematically collected evidence regarding acceptability.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feasibility</th>
<th>No Important issues with the recommended alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are no identified feasibility issues.</td>
<td></td>
</tr>
</tbody>
</table>

Rationale

Conventional prophylactic doses of anticoagulants seem less effective in preventing VTE in severe or critically ill COVID-19 patients. It is unclear whether higher doses will improve outcomes but the risk-benefit ratio seems acceptable.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with severe or critical COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Increased-dose thromboprophylaxis</td>
</tr>
<tr>
<td>Comparator</td>
<td>Conventional treatment</td>
</tr>
</tbody>
</table>

Summary

There are no randomised trials comparing increased-dose thromboprophylaxis to conventional treatment in patients with COVID-19 but there are observational studies. Ten studies have reported on the prevalence of venous thromboembolic
(VTE) events in patients with critical or severe COVID-19, ranging from 3.3% to 69% (see Table).

<table>
<thead>
<tr>
<th>Study</th>
<th>Severity of Illness</th>
<th>VTE events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goyal 2020 [71]</td>
<td>Moderate / Critical</td>
<td>13/393 (3.3%)*</td>
</tr>
<tr>
<td>Lodigani 2020 [63]</td>
<td>Severe / Critical</td>
<td>28/362 (7.7%)</td>
</tr>
<tr>
<td>Helms 2020 [67]</td>
<td>Severe / Critical</td>
<td>28/150 (18.7%)</td>
</tr>
<tr>
<td>Middeldorp 2020 [62]</td>
<td>Severe / Critical</td>
<td>39/198 (20%)</td>
</tr>
<tr>
<td>Poissy 2020 [61]</td>
<td>Severe / Critical</td>
<td>22/107 (20.6%)</td>
</tr>
<tr>
<td>Cui 2020 [66]</td>
<td>Severe / Critical</td>
<td>20/81 (25%)</td>
</tr>
<tr>
<td>Klok 2020 [65]</td>
<td>Severe / Critical</td>
<td>75/184 (40.8%)</td>
</tr>
<tr>
<td>Zhang 2020 [68]</td>
<td>Critical</td>
<td>66/143 (46.1%)</td>
</tr>
<tr>
<td>Wichmann 2020 [60]</td>
<td>Critical</td>
<td>7/12 (58%)</td>
</tr>
<tr>
<td>Llitjos 2020 [64]</td>
<td>Severe / Critical</td>
<td>18/26 (69%)</td>
</tr>
</tbody>
</table>

*prevalence was 7.7% and 1.1% in patients receiving and not receiving mechanical ventilation, respectively.

Eight studies were assessed as moderate risk of bias due to low external validity—cohort not representative of the target population and lack of random selection/census. One was at high risk of bias [60] and one was unclear due to limited reporting of methods [71].

One study reported outcomes in patients with moderate to critical COVID-19 who received systemic anticoagulants versus those who did not [70]. Mortality was similar between the groups (22.5% systemic vs 22.8% control). Although more patients receiving systemic anticoagulants required mechanical ventilation (29.8% vs 8.1%), mortality was lower in this group (29.1% vs 62.7%). Major bleeding events were slightly higher in the control group (3.0% vs 1.9%).

A meta-analysis on platelet count in patients with COVID-19 included nine studies (1779 participants) [69]. Platelet count was significantly lower in patients with more severe compared to less severe COVID-19 (mean -31 x 109/L), with the lowest platelet counts linked to mortality (mean -48 x 109/L). The authors concluded that low platelet count is associated with increased risk of severe disease and mortality in patients with COVID-19.
11 - ACEIs/ARBs in patients with COVID-19

11.1 - ACEIs/ARBs in patients with COVID-19

**Strong Recommendation**

In patients with COVID-19 who are receiving ACEIs/ARBs, there is currently no evidence to deviate from usual care and these medications should be continued unless contraindicated.

Stopping these medications abruptly can lead to acute heart failure or unstable blood pressure.

---

**Key Info**

**Benefits and harms**

- Stopping ACEI/ARB medication could lead to acute heart failure or unstable blood pressure. There is currently no randomised trial evidence specific to patients with COVID-19 and the use of ACEIs/ARBs.

**Certainty of the Evidence**

- While there are no randomised trials of ACEIs/ARBs in patients with COVID-19, there are observational studies that seek to determine if there is an association between ACEIs/ARBs and diagnosis of COVID-19 or mortality for patients with a diagnosis of COVID-19.

**Preference and values**

- We have no systematically collected information regarding patients’ preferences and values. The panel believes that, while there is uncertainty about the benefit to harm ratio regarding the use of ACEIs/ARBs in patients with COVID-19, there are likely harms associated with stopping ACEIs/ARBs. The panel believes that most patients would prefer to continue their current medication although some may want to discuss benefits and risks of discontinuing treatment.

**Resources and other considerations**

- We have no systematically collected information regarding cost-benefit. Continued use of ACEIs/ARBs as per usual care is unlikely to have an impact on availability of these drugs.

**Equity**

- There are no identified equity issues.

**Acceptability**

- Continued concomitant ACEI/ARB medication is likely to be acceptable to both patients and clinicians.

**Feasibility**

- There are likely no important feasibility issues as the recommendation reflects usual care.

**Rationale**

ACEIs/ARBs for people with hypertension, where indicated, are considered usual care. There is currently no evidence to indicate that it is necessary to deviate from usual care. Stopping these medications abruptly can lead to acute heart failure or unstable blood pressure.
**Adaptation**

This recommendation is adapted from published recommendations from numerous Australian and international guidelines and position statements\[137\]|\[138\]|\[139\]|\[140\]|\[141\]|\[142\]|\[143\]|\[144\]|\[145\]|\[146\]|\[147\]|\[148\]|\[149\]|\[150\]. Wording has been adapted for clarity and applicability to the Australian context.

**Clinical Question/ PICO**

- **Population:** People with COVID-19 who are taking ACEIs/ARBs
- **Intervention:** Continued use of concomitant ACEIs/ARBs
- **Comparator:** Stopping concomitant ACEIs/ARBs

**Summary**

At present, no randomised trials have investigated the benefits of continuing or stopping ACEIs/ARBs in patients with COVID-19. There is, however, unanimous international consensus that ACEI or ARB medications should be continued in patients with COVID-19.

Systematic reviews of observational studies provide further support for the continuation of ACEIs/ARBs in patients with COVID-19\[151\]|\[152\]. These reviews conclude that continued use of ACEIs/ARBs was unlikely to be associated with an increased risk of disease severity or mortality in patients with COVID-19. The conclusions are based on very low certainty evidence due to serious risk of bias, serious imprecision and inconsistency in findings between studies.

Despite the very low certainty evidence that continued use of concomitant ACEIs/ARBs increases or decreases mortality or disease severity in patients with COVID-19, there is high certainty evidence of harm if ACEIs/ARBs are stopped abruptly in patients who are already receiving them. Stopping these medications could lead to acute heart failure or unstable blood pressure. For this reason the recommendation is designated as 'Strong' in favour of continuation.
<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td>Odds Ratio 0.88 (CI 95% 0.68 - 1.14) Based on data from 2,412 patients in 4 studies. ¹ (Observational (non-randomized))</td>
<td><strong>287</strong> per 1000: 262 per 1000 <strong>Difference: 25 fewer per 1000</strong> 72 fewer - 28 more</td>
<td>Very Low Due to serious risk of bias, inconsistency and very serious imprecision ²</td>
<td>We are uncertain whether continued use of concomitant ACEIs/ ARBs increases or decreases mortality in patients with COVID-19.</td>
</tr>
<tr>
<td><strong>Risk of severe or lethal COVID-19</strong></td>
<td>Odds Ratio 1 (CI 95% 0.84 - 1.18) Based on data from 11,334 patients in 5 studies. ³ (Observational (non-randomized))</td>
<td><strong>309</strong> per 1000: 309 per 1000 <strong>Difference: 0 fewer per 1000</strong> ( CI 95% 36 fewer - 36 more )</td>
<td>Very Low Due to serious risk of bias, inconsistency, indirectness and imprecision ⁴</td>
<td>We are uncertain whether continued use of concomitant ACEIs/ ARBs increases or decreases the risk of mortality or progression to severe COVID-19.</td>
</tr>
<tr>
<td><strong>Severity (narrative analysis)</strong></td>
<td>Based on data from 23,565 patients in 13 studies. ⁵</td>
<td>Continued use of ACEIs/ARBs in patients with COVID-19 does not appear to increase the likelihood of more severe COVID-19 illness.</td>
<td>Very Low Due to serious risk of bias and imprecision ⁶</td>
<td>We are uncertain whether continued use of concomitant ACEIs/ ARBs increases or decreases the risk of progression to severe COVID-19.</td>
</tr>
</tbody>
</table>

2. **Risk of bias:** Serious. Selective outcome reporting, Missing intention-to-treat analysis. **Inconsistency:** Serious. The magnitude of statistical heterogeneity was high, with I²:24 %. **Indirectness:** Serious. Differences between the outcomes of interest and those reported (mortality was either reported alone or together with severe COVID-19). **Imprecision:** Very Serious. The review was limited only to studies where patient records included a diagnosis of hypertension. Other reviews have identified patients receiving ACEI/ARBs without confirming a diagnosis of hypertension..
4. **Risk of bias:** Serious. Selective outcome reporting, Missing intention-to-treat analysis. **Inconsistency:** Serious. The magnitude of statistical heterogeneity was high, with I²:50 %. **Imprecision:** Serious. The review was limited only to studies where patient records included a diagnosis of hypertension. Other reviews have identified patients receiving ACEI/ARBs without confirming a diagnosis of hypertension..
5. Systematic review [151].
6. **Risk of bias:** Serious. Missing intention-to-treat analysis, Selective outcome reporting. **Inconsistency:** No serious. **Indirectness:** No serious. **Imprecision:** Serious. No meta-analysis was possible. Publication bias: No serious.
12 - Pregnancy and perinatal care

Recommendation Strength Not Set

For recommendations on disease modifying treatments, chemoprophylaxis and respiratory support in pregnant or breastfeeding women please see sections above. We are continuously working on updating all recommendations to reflect special populations, including pregnant and breastfeeding women.

12.1 - Mode of birth

Weak Recommendation

For pregnant women with COVID-19, mode of birth should remain as per usual care.

There is currently no evidence to indicate that caesarean section for women with COVID-19 reduces the risk of vertical transmission to the newborn. Mode of birth should continue as per usual care. Respiratory deterioration due to COVID-19 may prompt urgent delivery on an individual basis.

Key Info

Benefits and harms

Evidence informing this recommendation comes from a systematic review of 49 studies comprising 655 women and 666 newborns, of whom 28 newborns (4.2%) had a COVID-19 infection. No cases of newborn COVID-19 infection met the criteria for confirmed vertical transmission, and newborn infections did not differ substantively by mode of birth (vaginal birth or caesarean section).

Certainty of the Evidence

Certainty of the evidence is very low due to reliance on case reports and case series. Evidence informing this recommendation comes from a systematic review estimating the risk of the newborn becoming infected with COVID-19 by mode of birth (vaginal or caesarean) in pregnant women with confirmed or suspected COVID-19 infection.

Preference and values

There is no systematically collected information regarding the preferences and values of pregnant women with COVID-19 at this point. Mode of birth should be individualised, based on clinical indications and taking into consideration individual preferences and values.

Resources and other considerations

We have no systematically collected evidence regarding cost-benefit. Caring for pregnant women with COVID-19 (regardless of mode of birth) requires greater resources than for women without COVID-19. The routine use of caesarean section for all pregnant women with COVID-19 would have additional resource implications.

Equity

For pregnant women with COVID-19, access to on-site paediatric support is needed at the time of birth. This may be more challenging for those women living in rural or remote areas.
**Rationale**

There is currently no evidence to indicate that caesarean section for pregnant women with COVID-19 reduces the risk of vertical transmission. Usual care practices regarding clinical indications for caesarean section should be used.

No cases of newborn COVID-19 infection met the criteria for confirmed vertical transmission, and newborn infections did not differ substantively by mode of birth (vaginal birth or caesarean section). Therefore, the benefits and harms of mode of birth should be considered as per usual care, taking into consideration relevant clinical indications and a woman’s individual preferences. However, clinical deterioration due to worsening COVID-19 may prompt urgent delivery of the baby.

**Acceptability**

Acceptability of different modes of birth by pregnant women is expected to vary and individual preferences should be taken into consideration. Clear communication from health professionals regarding the benefits and harms of different modes of birth is essential to aid discussion around individual preferences and acceptability.

**Feasibility**

There are no identified feasibility issues as the recommendation reflects usual care.

**Clinical Question/ PICO**

**Population:** Pregnant women with COVID-19  
**Intervention:** Caesarean section  
**Comparator:** Vaginal birth

**Summary**

Evidence informing this recommendation comes from a systematic review that estimated the risk of the newborn becoming infected with COVID-19 by mode of birth (vaginal or caesarean) [153]. The review included 49 case reports or case series comprising 666 newborns. Cases were only included where the mother either had confirmed COVID-19 (based on a positive swab) or a high clinical suspicion of COVID-19 where a swab had not been taken. The incidence of COVID-19 infection in newborns is given in the table below.

<table>
<thead>
<tr>
<th>Mode of birth</th>
<th>Total newborns*</th>
<th>Infected</th>
<th>Not infected</th>
<th>Not tested</th>
<th>Died</th>
<th>% Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal</td>
<td>292</td>
<td>8</td>
<td>261</td>
<td>21</td>
<td>7</td>
<td>2.7% (8/292)</td>
</tr>
<tr>
<td>Caesarean</td>
<td>374</td>
<td>20</td>
<td>313</td>
<td>26</td>
<td>1</td>
<td>5.3% (20/374)</td>
</tr>
</tbody>
</table>

*the review authors contacted the first author of the paper where there were missing newborn data (4 hospitals)

No cases of COVID-19 infection met the criteria for confirmed vertical transmission (positive PCR in umbilical cord blood, newborn blood collected within the first 12 hours of birth, or amniotic fluid collected prior to rupture of membranes). It was not possible to apply the classification developed by Shah et al [154] (confirmed, probable, possible, unlikely or not infected) due to lack of virological testing at birth or in first 12 hours of life.

**Outcome Timeframe**

**Study results and measurements**

**Absolute effect estimates**

Vaginal birth  
Caesarean section

**Certainty of the Evidence**

(Season of evidence)

**Plain text summary**

**Number of infected newborns**

Based on data from 666 patients in 49 studies. See summary for details. No cases of COVID-19 infection met the criteria for confirmed vertical transmission. Number of Very Low  
Due to very serious risk of  
We are uncertain whether caesarean section increases or
12.2 - Breastfeeding

 Weak Recommendation

Breastfeeding is supported irrespective of the presence of COVID-19. However, women with COVID-19 who are breastfeeding should use infection prevention and control measures (mask and hand hygiene) while infectious.

There is currently no evidence to indicate that breastfeeding increases the risk of vertical transmission to the newborn. As there are substantial known benefits for breastfeeding, women should be supported to initiate or continue breastfeeding.

Key Info

**Benefits and harms**

Evidence informing this recommendation comes from a systematic review of 49 studies comprising 655 women and 666 newborns, of whom 28 newborns (4.2%) had COVID-19. Testing of breastmilk was not reported. Of the 28 newborns infected, seven were breastfed, three formula-fed and one was given expressed breastmilk. The method of infant feeding was not reported for 17 newborns.

**Certainty of the Evidence**

Certainty of the evidence is very low due to reliance on case reports and case series.

**Preference and values**

There is no systematically collected information regarding the preferences and values of pregnant women with COVID-19 at this point. Breastfeeding is an individual decision based on consideration of individual preferences and values.

**Resources and other considerations**

We have no systematically collected evidence regarding cost-benefit. However, there is not expected to be any substantial resource considerations for breastfeeding compared to not breastfeeding. Caring for pregnant women and newborns with COVID-19 (irrespective of breastfeeding) requires greater resources than for women and newborns without COVID-19.

**Equity**

No important issues with the recommended alternative
There is currently no evidence to indicate that breastfeeding affects the risk of vertical transmission of COVID-19. Usual care practices regarding breastfeeding of newborns should be used.

No cases of newborn COVID-19 infection met the criteria for confirmed vertical transmission, and newborn infections did not differ substantively for different feeding practices, though evidence is currently limited.

Breastfeeding should be considered as per usual care, taking into consideration relevant clinical situation and a woman’s individual preferences.

Acceptability

Acceptability of infant feeding practices by pregnant and postpartum women is expected to vary and individual preferences should be considered. Clear communication from health professionals regarding the benefits and harms of different feeding practices is essential to aid discussion around individual preferences and acceptability.

Feasibility

There are likely no important feasibility issues as the recommendation reflects usual care.

Rationale

There is currently no evidence to indicate that breastfeeding affects the risk of vertical transmission of COVID-19. Usual care practices regarding breastfeeding of newborns should be used.

No cases of newborn COVID-19 infection met the criteria for confirmed vertical transmission, and newborn infections did not differ substantively for different feeding practices, though evidence is currently limited.

Breastfeeding should be considered as per usual care, taking into consideration relevant clinical situation and a woman’s individual preferences.

Clinical Question/ PICO

<table>
<thead>
<tr>
<th>Population:</th>
<th>Pregnant women with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Exposure of a newborn to breastmilk from mothers with confirmed or suspected COVID-19</td>
</tr>
<tr>
<td>Comparator:</td>
<td>No exposure of a newborn to breastmilk from mothers with confirmed or suspected COVID-19</td>
</tr>
</tbody>
</table>

Summary

Evidence informing this recommendation comes from a systematic review whose primary purpose was to estimate the risk of the newborn becoming infected with COVID-19 by mode of birth (vaginal or caesarean) [153]. The review included 49 case reports or case series comprising 666 newborns. Cases were only included where the mother either had confirmed COVID-19 (based on a positive swab) or a high clinical suspicion of COVID-19 where a swab had not been taken. No testing of breastmilk was reported. Newborn infection status by feeding type was reported for 209 newborns (see table).

<table>
<thead>
<tr>
<th>Feeding type</th>
<th>Total newborns</th>
<th>Infected</th>
<th>Not infected</th>
<th>Not tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breastmilk</td>
<td>148</td>
<td>7</td>
<td>139</td>
<td>2</td>
</tr>
<tr>
<td>Expressed breastmilk</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Formula</td>
<td>56</td>
<td>3</td>
<td>39</td>
<td>14</td>
</tr>
</tbody>
</table>

A separate living systematic review has been commissioned by WHO to identify studies of mothers with suspected or confirmed COVID-19 whose breastmilk was tested for COVID-19. The review has not yet been published but a WHO scientific brief summarises the findings [155]. Evidence is derived from case series, case reports and family cluster reports.

Breastmilk samples were tested for 46 mothers with confirmed COVID-19. Although 13 infants had confirmed infection with COVID-19, only three samples tested positive for viral RNA particles by RT-PCR (not live virus). Of the three mothers with viral RNA particles in their breastmilk:
• 1 newborn was positive for COVID-19 (infection source unknown; feeding method not reported)
• 2 newborns were negative for COVID-19 (1 breastfed; 1 fed expressed breastmilk once viral RNA particles no longer detected)

The authors state that at present, data are not sufficient to conclude vertical transmission of COVID-19 through breastfeeding.

### Outcome Timeframe

<table>
<thead>
<tr>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of infected newborns</strong> 1</td>
<td>9 Critical</td>
<td>Based on data from 666 patients in 49 studies. 2</td>
<td>See summary for details. Included newborns who had confirmed postnatal infection of COVID-19 (28/666 newborns). Testing of breastmilk was not reported. Of the 28 newborns infected, seven were breastfed, three formula-fed and one was given expressed breastmilk. The method of feeding was not reported for 17 newborns.</td>
</tr>
</tbody>
</table>

1. Number of infected newborns within 30 days of breastfeeding or receiving expressed breastmilk
2. Systematic review [153].
3. **Risk of bias: Very Serious.** Evidence is derived from case studies and case reports.. **Inconsistency: Serious.** Variations in outcome definitions, disease severity of infected mothers and availability of different testing modalities.. **Indirectness: Serious.** Differences between the outcomes of interest and those reported. Testing of breast milk not reported.. **Imprecision: Serious.** Variations in outcome definitions, disease severity of infected mothers and availability of different testing modalities..

**Publication bias: No serious.**

### 12.3 - Rooming-in

**Weak Recommendation**

For women with COVID-19 who have given birth, support rooming-in of mother and newborn. However, women with COVID-19 should use infection prevention and control measures (mask and hand hygiene) while infectious.

There is currently no evidence to indicate that a woman with a known COVID-19 infection should be separated from her newborn to prevent transmission. As there are substantial known benefits for keeping mother and newborn together postpartum, women should be supported to be with their newborn as per usual care.

Women should be encouraged and supported in using good hand hygiene before and after handling their baby, and using a mask while in close contact with their baby. To the extent possible, women who are infectious should practice physical distancing when not feeding or caring for the baby.
There is currently no evidence to indicate that rooming-in affects the risk of vertical transmission of COVID-19. Usual care practices regarding rooming-in of newborns should be used.

No cases of newborn COVID-19 infection met the criteria for confirmed vertical transmission, and newborn infections did not differ substantively for different rooming-in practices, though evidence is currently limited.

Therefore, the use of rooming-in should be considered as per usual care, taking into consideration relevant clinical situation and a woman's individual preferences.

**Clinical Question/ PICO**

**Population:** Women with COVID-19 who have given birth

**Intervention:** Rooming-in
Comparator: No rooming-in

Summary
Evidence informing this recommendation comes from a systematic review that reported the number of newborns infected with COVID-19 whose mothers had confirmed or suspected COVID-19 [153]. The review included 49 case reports or case series comprising 666 newborns, of whom 28 had confirmed postnatal infection. Newborn infection status by rooming-in approach was reported for 159 newborns (see table).

<table>
<thead>
<tr>
<th>Rooming-in approach</th>
<th>Total newborns</th>
<th>Infected</th>
<th>Not infected</th>
<th>Not tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother-baby isolation</td>
<td>52</td>
<td>6</td>
<td>32</td>
<td>14</td>
</tr>
<tr>
<td>Rooming-in of mother and baby</td>
<td>107</td>
<td>6</td>
<td>100</td>
<td>1</td>
</tr>
</tbody>
</table>

Of the 28 newborns infected with COVID-19, six were isolated from their mother and six were cared for in the same room—for the remaining 16 newborns the approach taken was not reported. Overall, 52 newborns were isolated and 107 were cared for in the same room.

Outcome

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of infected newborns (^1) Within 30 days of exposure</td>
<td>Based on data from 666 patients in 49 studies.</td>
<td>See summary for details. Included newborns who had confirmed postnatal infection (28/666 newborns). Of the 28 newborns infected, six were kept isolated from their mother, six were cared for in the same room as their mother and for 16 newborns the approach taken was not reported.</td>
<td>Very Low Due to very serious risk of bias, and serious imprecision, indirectness and inconsistency (^2)</td>
<td>We are uncertain whether rooming-in increases or decreases the number of infected newborns.</td>
</tr>
</tbody>
</table>

1. Number of infected neonates within 30 days of breastfeeding or receiving expressed breast milk
2. **Risk of bias:** Very Serious. Evidence is derived from case studies and case reports. **Inconsistency:** Serious. Variations in outcome definitions, disease severity of infected mothers and availability of different testing modalities. **Indirectness:** Serious. Differences between the outcomes of interest and those reported. Testing of breast milk not reported. **Imprecision:** Serious. Variations in outcome definitions, disease severity of infected mothers and availability of different testing modalities. **Publication bias:** No serious.
### 13 - Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEIs</td>
<td>Angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td>ANZICS</td>
<td>Australian and New Zealand Intensive Care Society</td>
</tr>
<tr>
<td>APO</td>
<td>Acute pulmonary oedema</td>
</tr>
<tr>
<td>ARBs</td>
<td>Angiotensin receptor blockers</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>BiPAP</td>
<td>Bilevel positive airway pressure (a form of oxygen therapy)</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Coronavirus Disease 2019 (disease caused by the virus SARS-CoV-2)</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure (a form of oxygen therapy)</td>
</tr>
<tr>
<td>DMTs</td>
<td>Disease-modifying treatments</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td>ECMO</td>
<td>Extracorporeal membrane oxygenation (a form of oxygen therapy)</td>
</tr>
<tr>
<td>FiO2</td>
<td>Fraction of inspired oxygen</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of recommendations, assessment, development, and evaluation</td>
</tr>
<tr>
<td>HCP</td>
<td>Healthcare professionals</td>
</tr>
<tr>
<td>HFNC</td>
<td>High-flow nasal cannula (a form of oxygen therapy)</td>
</tr>
<tr>
<td>HFNO</td>
<td>High-flow nasal oxygen (a form of oxygen therapy)</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IU</td>
<td>International units</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NMBAs</td>
<td>Neuromuscular blocking agents</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low-molecular-weight heparin</td>
</tr>
<tr>
<td>NIV</td>
<td>Non-invasive ventilation (a form of oxygen therapy)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>MERS</td>
<td>Middle East respiratory syndrome</td>
</tr>
<tr>
<td>PaO2</td>
<td>Partial pressure of arterial oxygen</td>
</tr>
<tr>
<td>PEEP</td>
<td>Positive end-expiratory pressure (a form of oxygen therapy)</td>
</tr>
<tr>
<td>PPE</td>
<td>Personal protective equipment</td>
</tr>
<tr>
<td>RT-PCT</td>
<td>Reverse transcription-polymerase chain reaction</td>
</tr>
<tr>
<td>SARS</td>
<td>Severe acute respiratory syndrome</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>Severe acute respiratory syndrome coronavirus 2 (the virus that causes the disease COVID-19)</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous thromboembolism</td>
</tr>
<tr>
<td>VV ECMO</td>
<td>Venovenous extracorporeal membrane oxygenation (a form of oxygen therapy)</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
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