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

NATIONAL
COVID-19
CLINICAL
EVIDENCE
TASKFORCE

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Disclaimer

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 or by emailing guidelines@covid19evidence.net.au.

These clinical guidelines are a general guide to appropriate practice, to be followed subject to the clinician's judgement and the patient's preference in each individual case. The guidelines are not intended to be proscriptive. They are designed to provide information to assist decision making and have been informed by the highest quality evidence available at the time of compilation. Accordingly, the parties involved in the development of these guidelines shall have no liability to any users of the information contained in this publication for any loss or damage, cost or expense incurred or arising from reliance on the information contained in this publication.

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1. Reading Guide

Info Box

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 As a result, recommendations based on current evidence are likely to become outdated quickly as new primary studies are published.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.

Only in research settings (Orange)
An “only in research settings” recommendation is given when there is insufficient evidence to determine if an intervention is either beneficial or harmful. When an “only in research” recommendation is given, the panel recommends that the intervention should only be considered in a randomised clinical trial with appropriate ethical approval. In any other circumstance, the intervention is not recommended.

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.

Evidence to decision: 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

Info Box

Novel coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since its identification in December 2019 and subsequent declaration as a Public Health Emergency of International Concern on 30 January 2020 *[1]*, the World Health Organization (WHO) estimates that almost 15 million direct and indirect deaths have occurred from SARS-CoV-2 globally in 2020 and 2021 *[459]*.

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 *[195]*.

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 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.

Recommendations within this guideline were developed in collaboration with the organisations listed below. All member organisations are part of the steering committee and formally endorse the guideline. The Steering Committee is governed by a consensus based decision-making process, for more details on the methods and processes of the Taskforce please see the Methods and processes section of this guideline.

- Cochrane Australia (Secretariat)
- Allied Health Professions Australia
- Australian Association of Gerontology
- Australian and New Zealand College of Anaesthetists
- Australian and New Zealand Intensive Care Society
- Australian and New Zealand Society for Geriatric Medicine
- Australian College of Critical Care Nurses
- Australian College of Midwives
- Australian College of Nursing
- Australian College of Neonatal Nurses
- Australian College of Rural and Remote Medicine
- Australian Primary Health Care Nurses Association
- Australian Resuscitation Council
- Australian Sleep Association
- Australian Society of Anaesthetists
- Australasian Association of Academic Primary Care
- Australasian College for Emergency Medicine
- Australasian College for Infection Prevention and Control
- Australasian College of Paramedicine
- Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine
- Australasian Society for Infectious Diseases
- Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists
- College of Emergency Nursing Australasia
- CRANAplus
- National Aboriginal Community Controlled Health Organisation
- Palliative Care Australia
- Rehabilitation Medicine Society of Australia and New Zealand
- Royal Australasian College of Physicians
- Royal Australasian College of Surgeons
- Royal Australian and New Zealand College of Obstetricians and Gynaecologists
- Royal Australian and New Zealand College of Psychiatrists
- Royal Australian College of General Practitioners
- Society of Hospital Pharmacists of Australia
- Thoracic Society of Australia and New Zealand
- Thrombosis and Haemostasis Society of Australia and New Zealand

Publication approval

Australian Government

National Health and Medical Research Council

Version 63 of these guideline recommendations were approved without exception by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 06 December 2022, under Section 14A of the National Health and Medical Research Council Act 1992.

Versions 20, 28, 36, 42, 48 and 57 of these guideline recommendations have all been approved by the NHMRC in full. In approving the guideline recommendations, NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of 5 years. To see the full version 57 click here.

NHMRC is satisfied that the guideline recommendations are systematically derived, based on the identification and synthesis of the best available scientific evidence, and developed for health professionals practising in an Australian health care setting.

This publication reflects the views of the authors and not necessarily the views of the Australian Government.

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 Taskforce will seek NHMRC approval of the guideline under section 14A of the *National Health and Medical Research Council Act 1992* on an ongoing basis as new recommendations are added or existing recommendations are changed. 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 info@clinicalevidence.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.

Consumer-centred care in the context of COVID-19

Consumer-centred care is the provision of health care that is respectful of, or responsive to, the needs, preferences and values of consumers. Consumer-centred care "*...redefines the relationships in health care by placing an emphasis on collaborating with people of all ages, at all levels of care, and in all health care settings*." *[5][12]*

Fast access to reliable healthcare advice

1. Effective treatment by trusted professionals
2. Continuity of care and smooth transitions

3. Involvement and support for family and carers
4. Clear information, communication and support for self care
5. Involvement in decisions and respect for preferences
6. Emotional support, empathy and respect
7. Attention to physical and environmental needs *[581]*

In the context of COVID-19, we need to acknowledge the barriers and inequities experienced by consumers. Groups who will face greater barriers and inequities than others include, but are not limited to people with: a disability or cognitive impairment, complex and chronic health needs, stigmatised health conditions and people from culturally or linguistically diverse backgrounds *[7]*.

The Australian Charter of Healthcare Rights (2nd edition) outlines the basic rights that patients and consumers are entitled to receive. These rights are particularly important in the current context. Rights of particular note include:

- access to healthcare services and treatment that meet needs
- safety through safe and high-quality health care in an environment that feels safe
- respect as an individual, with culture, identity, beliefs and choices recognised
- partnership through open and honest communication with healthcare providers
- information about their conditions and the possible benefits and risks of different tests and treatments, waiting times and costs and access to health information to support informed consent
- privacy and security of personal and health information maintained *[8]*

COVID-19 requires clinical responsiveness to new and emerging treatments, including a significant degree of uncertainty as new treatments emerge. However, consumer preferences and values must remain central in the provision of healthcare and be balanced with the needs of the health service and public health concerns. Health services remain responsible for ensuring that their work remains patient centred. In the context of COVID-19, key concepts include ensuring:

- equity in resource allocation and provision of care
- choice and agency of the consumer
- ethical provision of care at all times

Informed consent is a further component of consumer-centred care and underpins consideration of treatment options for COVID-19 by consumers, families and carers.

Informed consent
Informed consent forms an essential component of the moral right of individuals to autonomy over their own bodies *[9]*. Informed consent is generally understood to be a person's voluntary decision about their health care that is made with knowledge and understanding of the benefits and risks involved *[10][11]*.

In practical terms, informed consent is the process by which a healthcare professional provides appropriate information to a consumer about their treatment options, associated risks and benefits, fees, charges and possible additional costs, and supports them to make a decision about their care. From a legal perspective, informed consent should comply with jurisdictional legislation and best practice and is defined in terms of an agreement or process by which, having provided the relevant information, the rights of individuals to agree or to refuse treatment are upheld. This is particularly important where there are issues relating to impaired capacity of a person to consent *[10]*.

Consent processes help deliver services that are more closely aligned with the priorities and concerns of the community. This has a range of benefits, including improved health outcomes and a more efficient allocation of resources. In this way, informed consent processes are important in developing a genuinely consumer-focused health system.

For ethical decision-making, decisions about whether care is provided and in what form must be informed by the preferences of patients as well as clinical judgement *[9]*. Any changes affecting the existing plan or access to treatment must be considered with the patient, and the consented plan drafted and followed.

The *National Health and Medical Research Council (NHMRC) Guidelines: Communicating with Patients* addresses the content of information that should be provided, and states the patient needs to be advised of the possible or likely nature of the procedure or treatment [and] the proposed approach, including:

- what the proposed approach entails
- the expected benefits
- common side effects and material risks

- whether the procedure is conventional or experimental
- who will perform the procedure or treatment
- other options for management of the complaint
- the realistic expectations for the outcome of the procedure or treatment
- the time and cost involved, including any out-of-pocket expenses and any potential costs should further treatment be required *[13]*

These principles underpin the Australian Health Practitioner Regulation Agency (AHPRA) standards for healthcare professionals, including medical and allied health practitioners, and nurses and midwives to support informed consent by patients about their health care *[11]*.

While in the context of COVID-19, decisions may be being made at greater speed and in more resource-constrained environments than other health care environments, efforts must be made as far as practical to ensure that consumers are involved in their care.

In practical terms, informed consent processes should support the role of consumers as genuine partners in health care and promote consumer involvement in decision-making. Shared decision-making practices as between a treating team and consumer (patients as partners in care) should be standard practice. Consideration must be paid to people with complex communication needs, including those who communicate in ways other than speech and have limited capacity to make decisions about their health care. All consumers should be actively involved in decisions about their treatment and care to the extent they wish to be, and they should be supported to do so *[9]*.

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 are pregnant or breastfeeding and do not identify as women.

Note on caring for children and adolescents in the context of COVID-19
The Taskforce regards child- and family-centred care indispensable in managing the health and wellbeing of children and adolescents, and urges continuity of child-centred services, with a particular focus on equity of access. We support efforts to ensure children are able to remain in contact with parents, carers and families despite COVID-19 and recognise this may require specific attention to infection control management practices and may involve adjunctive use of technology such as video-calling. Health facilities should have plans to manage these issues for children and adolescents. We endorse the approach and goals established by the United Nations *Policy Brief: the impact of COVID-19 on children [4]*.

Child-centred services include among others: schooling, nutrition programs, maternal and newborn care, immunisation services, sexual and reproductive health services, HIV treatment, mental health and psychosocial services, birth registration, community-based child protection programs, out-of-home care, and case management for children requiring supplementary personalised care, including those living with long-term medical conditions, disabilities and victims of abuse or family violence *[4]*. Particularly relevant for the Australian context is to ensure continuity of Aboriginal and Torres Strait Islander child services.

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 Care of Older People and Palliative 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 with frailty or cognitive impairment and COVID-19*
  This population includes older people (usually over 65 years of age) 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

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- [Vancouver style] National Clinical Evidence Taskforce. Australian guidelines for the clinical care of people with COVID-19. 2023 [version 72]. Available from: https://clinicalevidence.net.au

3. Methods and processes

Info Box

Methods and processes
Information about the methods and processes used is described in the technical report and the search methods document.

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.

Scientific publications

- Weekly updates of national living evidence-based guidelines: Methods for the Australian Living Guidelines for Care of People with COVID-19. Tendal et al. **2020** *J Clin Epidemiol* doi: 10.1016/j.jclinepi.2020.11.005.
- Clinical care of pregnant and postpartum women with COVID-19: Living recommendations from the National COVID-19 Clinical Evidence Taskforce. Vogel et al. **2020** *ANZJOG* doi: 10.1111/ajo.13270.
- Clinical care of children and adolescents with COVID-19: recommendations from the National COVID-19 Clinical Evidence Taskforce. Fraile Navarro et al. **2021** *Med J Aust* doi: 10.5694/mja2.51305.
- Care of older people and people requiring palliative care with COVID-19: guidance from the Australian National COVID-19 Clinical Evidence Taskforce. Cheyne et al. **2021** *Med J Aust* doi: 10.5694/mja2.51353.
- Care for adults with COVID-19: living guidelines from the National COVID-19 Clinical Evidence Taskforce. White et al. **2022** *Med J Aust* doi: 10.5694/mja2.51718.
- Awareness, value and use of the Australian living guidelines for the clinical care of people with COVID-19: an impact evaluation. Millard et al. **2022** *J Clin Epidemiol* doi: 10.1016/j.jclinepi.2021.11.035.
- The Australian living guidelines for the clinical care of people with COVID-19: What worked, what didn't and why, a mixed methods process evaluation. Turner at al. **2022** *PLoS One* doi: 10.1371/journal.pone.0261479.
- Weekly updating of guideline recommendations was feasible: the Australian National COVID-19 Clinical Evidence Taskforce. Hewitt et al. **2023** *J Clin Epidemiol* doi: 10.1016/j.jclinepi.2023.02.019.

Conflicts of interest
Our policy for managing conflicts of interest and the template used for collecting the declarations of interest can be found on the website here and here. A summary of the declarations of interests can be found here.

Public consultation
We welcome feedback and suggestions. Comments can be submitted via the feedback function under each recommendation in MAGIC or by emailing info@clinicalevidence.net.au

4. Consumer-centred care in the context of COVID-19

Info Box

Consumer-centred care is the provision of health care that is respectful of, or responsive to, the needs, preferences and values of consumers. Consumer-centred care places an emphasis on collaboration with all patients at all levels of care and in all healthcare settings *[5][12]*.

The key principles of consumer-centred care are:

- Fast access to reliable healthcare advice
- Effective treatment by trusted professionals
- Continuity of care and smooth transitions
- Involvement and support for family and carers
- Clear information, communication and support for self care
- Involvement in decisions and respect for preferences
- Emotional support, empathy and respect
- Attention to physical and environmental needs *[581]*

Note on terminology

Following discussion with the COVID-19 Care Working Group, the term “healthcare decision-maker” has been used to refer to a person who has legal responsibility for making healthcare decisions on behalf of another person. Terminology for this role varies across Australia, including terms such as guardian (Myagedcare.gov.au), substitute decision-maker (Advance Care Planning Australia) or decision supporter (NDIS.gov.au).

The term “carers” has been used to refer to persons who provide unpaid care and support to family members and friends (Carers Australia).

We have not undertaken systematic reviews to inform the following good practice points as they are based on established principles and values that are important to consider when providing patient-centred care.

Good practice statement

Take the time to listen to the patient, validate their experience and offer information about the symptoms they are experiencing, including management options.

Good practice statement

Provide appropriate information to the patient, healthcare decision-maker or family/carers about treatment options, associated risks and benefits, fees, charges and possible additional costs.

Respect the patient’s, healthcare decision-maker’s or family/carer’s priorities and preferences, and practise shared decision-making when deciding on and communicating the care plan.

Enable and support patients to make informed decisions and manage their own care to the degree of their preference.

Use interpreters, where appropriate, to ensure effective communication with the patient, healthcare decision maker or family/carers.

Decisions around proceeding to more invasive forms of ventilation should be based on discussion, consideration of the patient’s expected short and long-term responses to more invasive forms of treatment and an advance care directive or plan if available.

Good practice statement

Ensure early and ongoing collaboration with the patient, their healthcare decision-maker or family/carers as appropriate, around goals of care, which may include active disease-directed care.

Good practice statement

Updated

Ensure cultural and spiritual/religious practices that are part of the person's wishes are identified, prioritised and observed/ facilitated, where possible. Where not possible, it is essential to communicate this with the patient, healthcare decision-maker or family/carers, as appropriate. [Taskforce / Vic Health / APHRA]

Good practice statement

Determine the most appropriate setting of care (and transition in or out of a hospital setting) by considering:

- clinical features
- the patient's preferences and, where appropriate, healthcare decision-maker's or family/carer's preferences
- the context in terms of rural or remote locations
- public health responses
- ability to monitor for clinical deterioration and the availability of rapid transfer to higher level of care.

Good practice statement

The impact of visiting restrictions should be considered when holding care planning discussions to enable patients, healthcare decision-maker and family/carers to share in decision-making. [Taskforce/*[582]*]

Good practice statement

When healthcare workers are wearing face masks, remember that those with sensory impairments may not be able to hear or use lip reading to assist in understanding. Consider the use of written communication tools (e.g., clipboards) in the room, or digital tools if outside the room without face masks (e.g., video tablets, two-way radios). [Taskforce/*[582]*]

Good practice statement

Respiratory distress and a diagnosis of COVID-19, or ongoing symptoms following COVID-19, will likely cause increased levels of anxiety and distress. There may be worsening of pre-existing mental health conditions.

Communicate with patients and support their mental wellbeing to help alleviate any anxiety or fear they may have about COVID-19 and post-COVID-19 conditions. [Taskforce / NICE]

Good practice statement

Consider the patient's physical, psychological and emotional complex needs in care and care planning, including the patient's complex symptom and functional needs, pain management, personal care and level of assistance required for activities.

Good practice statement

Healthcare workers should provide care that is within their expertise, knowledge and capabilities, and is the optimal care option for the patient. Seek specialist advice or multidisciplinary care arrangements where these would benefit the patient.

Use of virtual care, including telehealth, should be considered where appropriate.

5. Definition of disease severity

Info Box

The Primary and Chronic Care Panel and Acute and Critical Care Panel are responsible for defining disease severity for adults. The Paediatric and Adolescent Care Panel are responsible for defining disease severity for children and adolescents.

Definitions are subsequently reviewed by the Guidelines Leadership Group and approved by the Steering Committee prior to publication.

5.1 Definition of disease severity for adults

Consensus recommendation

Mild illness	An individual with no clinical features suggestive of moderate or more severe disease: • no OR mild symptoms and signs (fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, loss of taste and smell) • no new shortness of breath or difficulty breathing on exertion • no evidence of lower respiratory tract disease during clinical assessment or on imaging (if performed)
Moderate illness	A stable patient with evidence of lower respiratory tract disease: • during clinical assessment, such as ◦ oxygen saturation 92–94% on room air at rest ◦ desaturation or breathlessness with mild exertion • or on imaging
Severe illness	A patient with signs of moderate disease who is deteriorating OR A patient meeting any of the following criteria: • respiratory rate ≥ 30 breaths/min • oxygen saturation < 92% on room air at rest or requiring oxygen • lung infiltrates > 50%
Critical illness	A patient meeting any of the following criteria: • Respiratory failure (defined as any of) ◦ severe respiratory failure (PaO_2/FiO_2 < 200) ◦ respiratory distress or acute respiratory distress syndrome (ARDS) ◦ deteriorating despite non-invasive forms of respiratory support (i.e. non-invasive ventilation [NIV], or high-flow nasal oxygen [HFNO]) ◦ requiring mechanical ventilation • hypotension or shock • impairment of consciousness • other organ failure

Adaptation

The definitions of disease severity are adapted from published definitions from China *[15]*, Italy *[16]* and Alfred Health (Melbourne) *[17]*.

5.2 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.

	Feeding / hydration / conscious state	**Respiratory / vital signs**	**Oxygen requirement**[1]
Mild illness	Normal or mildly reduced feeding	No or mild upper respiratory tract symptoms OR No or mild work of breathing	
Moderate illness	Poor feeding, unable to maintain hydration without nasogastric or intravenous (IV) fluids AND With normal conscious state	Moderate work of breathing OR Abnormal vital signs for age (tachycardia, tachypnoea) but does not persistently breach Early Warning System (e.g. Medical Emergency Team [MET]) Criteria[2] OR Brief self-resolving apnoea (infants)	Individuals requiring low-flow oxygen and/or with chest x-ray changes due to COVID-19 without other severe features
Severe illness	Poor feeding, unable to maintain hydration without nasogastric or IV fluids OR Drowsy / tired but easily rousable	Moderate-severe work of breathing OR Abnormal vital signs for age (tachycardia, tachypnoea) with breaches of Early Warning System (e.g. Medical Emergency Team [MET]) Criteria OR Apnoea needing support / stimulation (infants)	Requires high-flow oxygen[3] or non-invasive ventilation
Critical illness	Poor feeding, unable to maintain hydration without nasogastric or IV fluids OR Altered conscious state / unconscious	Unable to maintain breathing or prevent apnoea without advanced modes of support OR Abnormal vital signs for age with persistent breaches of Early Warning System (e.g. Medical Emergency Team [MET]) Criteria OR Haemodynamically unstable without inotropic or vasopressor support OR Other organ failure	Requires advanced modes of support to maintain oxygenation. Intubation and mechanical ventilation OR Extracorporeal membrane oxygenation (ECMO)

[1] Oxygen saturation target should be modified for patients with cyanotic heart disease.

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

Note: comorbidities (e.g. preterm infants, oncology, immunocompromised, etc.) may increase the risk of more severe disease.

6. Monitoring and markers of clinical deterioration

Info Box

The Primary and Chronic Care Panel is responsible for developing recommendations specific to monitoring and markers of clinical deterioration.

Recommendations are subsequently reviewed by the Guidelines Leadership Group and approved by the Steering Committee prior to publication. In addition, all recommendations are reviewed by the Consumer Panel to establish acceptability to the patient population for which they are relevant.

6.1 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 *[195]*, National Institute for the Infectious Diseases (Italy) *[16]* and Surviving Sepsis Campaign *[193]*. Wording has been adapted for clarity and applicability to the Australian context.

6.2 Pulse oximeters

6.2.1 Pulse oximeters for adults

Consensus recommendation

In adults with risk factors for deterioration, who are being cared for at home, consider offering pulse oximetry to monitor oxygen saturation.

Additional information

For guidance on when to escalate care, please refer to the Pathways to Care Flowchart.

Risk factors for deterioration include:*

- *Older age, e.g. over 50 years for Aboriginal and Torres Strait Islander people, or otherwise over 65 years*
- *No vaccine dose or SARS-CoV-2 infection in the past 6 months*
- *Pregnant*
- *Comorbidities:*
  - *lung disease, including chronic obstructive pulmonary disease (COPD), asthma or bronchiectasis*
  - *cardiovascular disease, including hypertension*
  - *obesity (BMI > 30 kg/m2)*
  - *diabetes*
  - *renal failure*
  - *immunocompromising conditions (** see below)*
- *Concerns about personal safety or access to care*

There is no current evidence that supports the benefit of pulse oximetry compared with a home monitoring program in adults with COVID-19 who are receiving care at home. We are aware of a randomised controlled trial [456] that found no difference in days alive and out of hospital (at 30 days) in people who received pulse oximetry along with a text message based remote-monitoring program compared with the remote-monitoring program alone.

Be aware that different pulse oximeters have different specifications, and that some can under or overestimate readings, especially if the saturation level is borderline. Overestimation has been reported in people with darker skin.

The RACGP has developed supporting materials to assist the care of people with COVID-19 at home. Please refer to Managing COVID-19 at home with assistance from your general practice.

** Evidence enabling us to rank risk factors in order of priority is not yet available.*

*** Immunocompromising conditions:*

- *Primary or acquired immunodeficiency:*
  - *haematological neoplasms: leukaemias, lymphomas, myelodysplastic syndromes*
  - *post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months)*
  - *immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency*
- *Other significantly immunocompromising conditions:*
  - *immunosuppressive therapy (current or recent)*
  - *chemotherapy or radiotherapy*
  - *high-dose corticosteroids (≥ 20 mg of prednisone per day, or equivalent) for ≥ 14 days*
  - *all biologics and most disease-modifying anti-rheumatic drugs (DMARDs)*

6.2.2 Pulse oximeters for children and adolescents

Consensus recommendation

Children and adolescents with asymptomatic or mild COVID-19 do not routinely require peripheral oxygen saturation monitoring. However, children and adolescents at high risk of deterioration who are being cared for at home should be offered monitoring of peripheral oxygen saturation with pulse oximetry, if age-appropriate oximeters and training can be provided, and an appropriate pathway for escalation.

Additional information

For guidance on definitions of disease severity for children and adolescents, including peripheral oxygen saturation thresholds, please refer to the specific section in the guideline.

Based on international cohorts [370] potential factors to consider in children or adolescents with mild COVID-19 at high risk of progression may include:*

- *Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions*
- *Severe asthma*
- *Obesity (above the 95th percentile on BMI for age growth chart)*

The use of pulse oximetry in children or adolescents to assist in assessing and monitoring the severity of respiratory symptoms and to detect early deterioration should always be in conjunction with clinical assessment of disease severity. Home pulse oximetry should only be used if patient's, healthcare decision-maker or family/carers have received education on how to self-monitor and when to call a GP or triple 0.

Only age-appropriate pulse oximeters should be used in children. Be aware that different pulse oximeters have different specifications, and that some can under or overestimate readings, especially if the saturation level is borderline. Overestimation has been reported in people with darker skin.

** Evidence enabling us to rank risk factors in order of priority is not yet available.*

7. Drug treatments

Info Box

Several classes of therapies have been investigated to determine their effectiveness in treating COVID-19. These include, but are not limited to, antivirals (remdesivir, lopinavir-ritonavir), antimalarials (hydroxychloroquine, chloroquine), interleukin receptor agonists (tocilizumab, anakinra), corticosteroids (dexamethasone) and convalescent plasma. The Taskforce is continually monitoring new research for randomised trials that evaluate any drug 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), evidence now supports the use of several treatments for individuals with COVID-19, and several treatments have also proven to be ineffective.

The drug class for the treatments being investigated are listed below:

- Antiandrogens
- Antineoplastics
- Antiparasitic, antifungals and other anti-infective agents
- Antihypertensives
- Antithrombotic, antiplatelets and related therapies
- Antivirals
- Human and blood derived products
- Immunomodulating drugs
- Interferons
- Other antibody related therapies
- Other therapies
- Vitamins, supplements and co-factors

The Drug Treatment Panel is responsible for developing recommendations specific to drug treatments for adults. The Pregnancy and Perinatal Care Panel and Paediatric and Adolescent Care Panel are responsible for developing recommendations specific to pregnant and breastfeeding women and children and adolescents, respectively.

Recommendations are subsequently reviewed by the Guidelines Leadership Group and approved by the Steering Committee prior to publication. In addition, all recommendations are reviewed by the Consumer Panel to establish acceptability to the patient population for which they are relevant.

7.1 Recommended drug treatments

7.1.1 Casirivimab plus imdevimab (Ronapreve)

7.1.1.1 Casirivimab plus imdevimab (Ronapreve) for adults

Not recommended

Do not use casirivimab plus imdevimab in **seropositive** adults hospitalised with moderate-to-critical COVID-19.

Additional information

In patients hospitalised with moderate-to-critical COVID-19 who are seropositive (detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab (Ronapreve) probably has little impact on risk of death, the need for invasive mechanical ventilation and discharge from hospital. Because of this, the Taskforce recommends against the use of casirivimab plus imdevimab in hospitalised patients who are seropositive.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

General adult population
Evidence indicates no difference between casirivimab plus imdevimab and standard care in incidence of death, requirement of mechanical ventilation or duration of hospital stay. There was no adverse event data reported within the RECOVERY trial, however data from studies focused on asymptomatic and mild outpatients suggests that casirivimab plus imdevimab has an acceptable safety profile.

Certainty of the Evidence

Moderate

Certainty of the evidence is moderate for all-cause mortality, mechanical ventilation and discharge from hospital due to serious imprecision (reliance on a single study).

Values and preferences

Substantial variability is expected or uncertain

General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this 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.

Resources

No important issues with the recommended alternative

As casirivimab plus imdevimab is not recommended in seropositive patients there are no resource considerations.

Equity

No important issues with the recommended alternative

As casirivimab plus imdevimab is not recommended in seropositive patients there are no equity considerations.

Acceptability

No important issues with the recommended alternative

As casirivimab plus imdevimab is not recommended in seropositive patients there are no acceptability considerations.

Feasibility

No important issues with the recommended alternative

As casirivimab plus imdevimab is not recommended in seropositive patients there are no feasibility considerations.

Rationale

Based on the available evidence, casirivimab plus imdevimab is no more effective than standard care in treating SARS-CoV-2 seronegative patients with COVID-19. We therefore recommend that casirivimab plus imdevimab should not be used.

Clinical Question/ PICO

Population: Patients hospitalised with COVID-19
Intervention: Casirivimab plus imdevimab
Comparator: Standard care

Summary

Evidence indicates a reduction in death in seronegative patients hospitalised with mild-to-critical COVID-19.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial (RECOVERY) that compared casirivimab plus imdevimab with standard care in 9785 patients hospitalised with moderate-to-critical COVID-19, a third of whom were seronegative at baseline *[415]*, and one randomised trial that compared casirivimab plus imdevimab with placebo in 1336 patients hospitalised with mild-to-moderate COVID-19, approximately half of whom were seronegative at baseline *[520]*.

Study characteristics
Median age of participants was 62 years in both studies. Women comprised 37% of participants in RECOVERY and 47% in Somersan-Karakaya et al. Within RECOVERY, patients received a single intravenously administered 8000 mg dose of Ronapreve (4000 mg casirivimab plus 4000 mg imdevimab) or standard care. Twelve children (12–18 years) were included in RECOVERY but data were not reported separately. In Somersan-Karakaya et al patients received a single intravenously administered dose of 8000 mg Ronapreve (4000 mg casirivimab plus 4000 mg imdevimab), 2400 mg REGEN-COV (1200 mg casirivimab plus 1200 mg imdevimab) or placebo. Children were ineligible for inclusion. Pregnant and breastfeeding women were ineligible in both trials.

Both trials separated results based on serostatus at baseline (patients with SARS-CoV-2 neutralising antibodies versus those without antibodies). To determine whether subgrouping based on serostatus was appropriate, we undertook an ICEMAN analysis, with the results confirming the appropriateness of this approach. The full ICEMAN analysis can be found here.

What are the main results?
Results demonstrate that casirivimab plus imdevimab reduces death in seronegative patients (50 fewer per 1000; RR 0.82, CI 95% 0.73 to 0.91; 3673 patients in 2 studies). Casirivimab plus imdevimab probably has little impact on the need for mechanical ventilation, however it may increase discharge from hospital and reduce hospital length of stay.

For seropositive patients results indicate no difference in incidence of death, number of patients requiring invasive mechanical ventilation and discharge from hospital.

The Taskforce notes that in RECOVERY, treatment of participants occurred after sera were collected but before determination of their serostatus. The results in RECOVERY may therefore overestimate the effectiveness of casirivimab plus imdevimab in seronegative patients if serological testing results in substantial delays in administration.

Our confidence in the results

In seronegative patients certainty of the evidence is high for all-cause mortality, moderate for mechanical ventilation due to serious imprecision (reliance on a single study), and low for discharge from hospital and duration of hospital stay due to very serious imprecision (reliance on a single study and wide confidence intervals).

In seropositive patients certainty of the evidence is high for all-cause mortality, and moderate for mechanical ventilation and discharge from hospital due to serious imprecision (reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
Although the Therapeutic Goods Administration has provisionally approved the use of casirivimab plus imdevimab in patients with mild-to-moderate COVID-19 who have one or more risk factors for disease progression, as of 19 November 2021 it is not approved for use in hospitalised patients.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality [All patients] Within 28 days of commencing treatment 9 Critical	Relative risk 0.81 (CI 95% 0.56 — 1.17) Based on data from 10,982 participants in 2 studies. [1] (Randomized controlled)	201 per 1000 Difference:	163 per 1000 **38 fewer per 1000** (CI 95% 88 fewer — 34 more)	**High**	Casirivimab plus imdevimab decreases all-cause mortality
Invasive mechanical ventilation [All patients] Within 28 days of commencing treatment 9 Critical	Relative risk 1 (CI 95% 0.89 — 1.13) Based on data from 9,198 participants in 1 studies. [2] (Randomized controlled)	105 per 1000 Difference:	105 per 1000 **0 fewer per 1000** (CI 95% 12 fewer — 14 more)	**Moderate** Due to serious imprecision [3]	Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [all patients].
Discharged from hospital [All patients] Within 28 days of commencing treatment 6 Important	Relative risk 1.01 (CI 95% 0.98 — 1.04) Based on data from 9,785 participants in 1 studies. [4] (Randomized controlled)	690 per 1000 Difference:	697 per 1000 **7 more per 1000** (CI 95% 14 fewer — 28 more)	**Moderate** Due to serious imprecision [5]	Casirivimab plus imdevimab probably has little impact on discharge from hospital [total]
Discharged from hospital [All patients] Within 28 days of commencing treatment	Relative risk 1.03 (CI 95% 0.98 — 1.08) Based on data from 10,982 participants in 2 studies. [6] (Randomized	701 per 1000 Difference:	722 per 1000 **21 more per 1000** (CI 95% 14	**High**	Casirivimab plus imdevimab increases discharged from hospital

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important	controlled)		fewer — 56 more)		
All-cause mortality [seronegative] Within 28 days of commencing treatment 9 Critical	Relative risk 0.64 (CI 95% 0.36 — 1.15) Based on data from 3,673 participants in 2 studies. [7] (Randomized controlled)	**283** per 1000 Difference:	**181** per 1000 **102 fewer per 1000** (CI 95% 181 fewer — 42 more)	**Moderate** Due to serious imprecision [8]	Casirivimab plus imdevimab decreases all-cause mortality [seronegative]
Invasive mechanical ventilation [seronegative] Within 28 days of commencing treatment 9 Critical	Relative risk 0.88 (CI 95% 0.73 — 1.06) Based on data from 3,083 participants in 1 studies. [9] (Randomized controlled)	**135** per 1000 Difference:	**119** per 1000 **16 fewer per 1000** (CI 95% 36 fewer — 8 more)	**Moderate** Due to serious imprecision [10]	Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [seronegative patients].
Discharged from hospital [seropositive] Within 28 days of commencing treatment 6 Important	Relative risk 0.98 (CI 95% 0.95 — 1.01) Based on data from 6,632 participants in 1 studies. [11] (Randomized controlled)	**740** per 1000 Difference:	**725** per 1000 **15 fewer per 1000** (CI 95% 37 fewer — 7 more)	**High**	Casirivimab plus imdevimab probably has little impact on discharged from hospital [seropositive]
Discharged from hospital [seronegative] Within 28 days of commencing treatment 6 Important	Relative risk 1.11 (CI 95% 1.06 — 1.16) Based on data from 3,673 participants in 2 studies. [12] (Randomized controlled)	**600** per 1000 Difference:	**666** per 1000 **66 more per 1000** (CI 95% 36 more — 96 more)	**Moderate** Due to serious imprecision [13]	Casirivimab plus imdevimab probably increases discharged from hospital [seronegative]
All-cause mortality [seropositive] Within 28 days of commencing treatment 9 Critical	Relative risk 1.01 (CI 95% 0.91 — 1.12) Based on data from 7,202 participants in 2 studies. [14] (Randomized controlled)	**163** per 1000 Difference:	**165** per 1000 **2 more per 1000** (CI 95% 15 fewer — 20 more)	**High**	Casirivimab plus imdevimab has little or no difference on all-cause mortality [seropositive]

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Invasive mechanical ventilation [seropositive] Within 28 days of commencing treatment 9 Critical	Relative risk 1.08 (CI 95% 0.92 — 1.26) Based on data from 6,702 participants in 1 studies. [15] (Randomized controlled)	83 per 1000 Difference:	90 per 1000 **7 more per 1000** (CI 95% 7 fewer — 22 more)	**Moderate** Due to serious imprecision [16]	Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [seropositive patients].
Discharged from hospital [seropositive] Within 28 days of commencing treatment 6 Important	Relative risk 0.98 (CI 95% 0.95 — 1.01) Based on data from 6,632 participants in 1 studies. [17] (Randomized controlled)	740 per 1000 Difference:	725 per 1000 **15 fewer per 1000** (CI 95% 37 fewer — 7 more)	**Moderate** Due to serious imprecision [18]	Casirivimab plus imdevimab probably has little impact on discharge from hospital [seropositive patients].
Serious Adverse Events Within 28 days of commencing treatment 6 Important	Relative risk 0.85 (CI 95% 0.71 — 1.03) Based on data from 1,410 participants in 1 studies. [19] (Randomized controlled)	279 per 1000 Difference:	237 per 1000 **42 fewer per 1000** (CI 95% 81 fewer — 8 more)	**Low** Due to very serious imprecision [20]	Casirivimab plus imdevimab may decrease new serious adverse events
Duration of hospital stay [All patients] Days 6 Important	Lower better Based on data from 9,785 participants in 1 studies. [21] (Randomized controlled)	10 (Median)	10 (Median) CI 95%	**Moderate** Due to serious imprecision [22]	Casirivimab plus imdevimab probably has little impact on duration of hospital stay [all patients].
Duration of hospital stay [seronegative] Days 6 Important	Lower better Based on data from 3,153 participants in 1 studies. [23] (Randomized controlled)	17 (Median)	13 (Median) CI 95%	**Low** Due to very serious imprecision [24]	Casirivimab plus imdevimab may decrease duration of hospital stay [seronegative patients].

Attached Images

Consensus recommendation

Do not routinely use casirivimab plus imdevimab (Ronapreve) for the treatment of COVID-19.

The Taskforce has previously recommended the use of casirivimab plus imdevimab (Ronapreve) for the treatment of individuals with COVID-19. Recommendations for individuals not requiring hospitalisation were based on three studies that included 6622 participants with mild COVID-19 [320][367][400], which demonstrated a benefit with regards to hospitalisation and adverse events. Recommendations for hospitalised individuals were based on two studies that included 10982 participants with moderate to severe COVID-19 [415][520], which demonstrated a benefit with regards to all-cause mortality at 28 days and serious adverse events.

All clinical trials that contributed data to the analyses were conducted before the emergence of Omicron as the dominant variant. Since the development of the initial recommendations, a significant body of in vitro evidence has emerged demonstrating a significant reduction in activity of casirivimab plus imdevimab (Ronapreve) against the Omicron BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that casirivimab plus imdevimab (Ronapreve) is effective in treating individuals with currently circulating variants of COVID-19.

Clinical Question/ PICO

Population: Outpatients with mild COVID-19
Intervention: Casirivimab plus imdevimab
Comparator: Placebo

Summary

There remains significant uncertainty whether casirivimab plus imdevimab is more effective and safer than standard care in treating patients with mild or asymptomatic COVID-19.

What is the evidence informing this recommendation?
Evidence comes from three randomised trials that compared casirivimab plus imdevimab with placebo in 4856 adult outpatients with mild COVID-19 *[320][367]* and 207 asymptomatic outpatients *[400]*. Two trials are linked—one presents results from the phase I-II portion *[320]* and the second from the phase III portion of the study *[367]*. The third study included asymptomatic patients who had close contacts with confirmed COVID-19 individuals *[400]*.

Publication status
One study is only available as a preprint (Weinreich et al. posted to medRxiv on 12 June 2021 *[320]*) and has therefore not been peer reviewed.

Study characteristics
Median age of participants ranged from 41 to 50 years and the proportion of women ranged from 51 to 55%. Patients in the phase I and II portions of the study by Weinreich et al. received a dose of either 2400 mg or 8000 mg REGEN-COV (1:1 casirivimab:imdevimab). The larger phase III portion randomised patients to receive either one 2400 mg or one 8000 mg dose, revising their protocol midway to include one 1200 mg or 2400 mg dose. In O'Brien et al. patients received a single dose of 1200 mg. Pregnant and breastfeeding patients were ineligible.

Equity, diversity and inclusion

The characteristics of trial participants related to equity, diversity and inclusion (see technical report) were reported in minimal detail in the included studies. Ethnicity was reported in one study. As a result, the specific population(s) to whom this data directly applies is unclear.

None of these trials were conducted in Australia. This participant data comes from the United Kingdom.

The Taskforce will continue to extract and identify characteristics relevant to equity, diversity and inclusion where available.

What are the main results?
Casirivimab plus imdevimab decreases the incidence of adverse events (RR 0.74, CI 95% 0.64 to 0.86; 5842 patients in 2 studies) and serious adverse events (RR 0.34, CI 95% 0.25 to 0.48; 6622 patients in 3 studies), and

probably decreases hospitalisation (RR 0.30, CI 95% 0.20 to 0.44; 4261 patients in 2 studies). We are unsure if casirivimab plus imdevimab has an impact on death, mechanical ventilation, ICU admission or discontinuation due to adverse events.

Our confidence in the results
Certainty of the evidence is low for the critical outcomes of death and mechanical ventilation due to very serious imprecision (few events and reliance on a single study). Certainty is high for adverse events and serious adverse events, moderate for hospitalisation due to serious imprecision (majority of data comes from a single study) and low for discontinuation due to adverse events and ICU admission due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The Taskforce notes that as of 15 October 2021, the Therapeutic Goods Administration has provisionally approved the use of casirivimab plus imdevimab in **patients with mild-to-moderate COVID-19** who have one or more risk factors for disease progression.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.2 (CI 95% 0.04 — 1.02) Based on data from 4,057 participants in 1 studies. [1] (Randomized controlled)	4 per 1000 Difference:	1 per 1000 **3 fewer per 1000** (CI 95% 4 fewer — 0 fewer)	**Low** Due to very serious imprecision [2]	Casirivimab plus imdevimab may have little imapct on death (10 events).
Mechanical ventilation Within 28 days of commencing treatment 9 Critical	Relative risk 0.21 (CI 95% 0.04 — 1.06) Based on data from 3,432 participants in 1 studies. [3] (Randomized controlled)	4 per 1000 Difference:	1 per 1000 **3 fewer per 1000** (CI 95% 4 fewer — 0 fewer)	**Low** Due to very serious imprecision [4]	Casirivimab plus imdevimab may have little impact on mechanical ventilation (8 events).
ICU admission Within 28 days of commencing treatment 6 Important	Relative risk 0.32 (CI 95% 0.14 — 0.71) Based on data from 3,432 participants in 1 studies. [5] (Randomized controlled)	13 per 1000 Difference:	4 per 1000 **9 fewer per 1000** (CI 95% 11 fewer — 4 fewer)	**Low** Due to very serious imprecision [6]	Casirivimab plus imdevimab may have little impact on ICU admission (27 events).
Adverse events End of follow-up 6 Important	Relative risk 0.74 (CI 95% 0.64 — 0.86) Based on data from 5,842 participants in 2 studies. [7] (Randomized controlled)	132 per 1000 Difference:	98 per 1000 **34 fewer per 1000** (CI 95% 48	**High**	Casirivimab plus imdevimab may decrease adverse events slightly (602 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
			fewer — 18 fewer)		
Serious adverse event End of follow-up 6 Important	Relative risk 0.34 (CI 95% 0.25 — 0.48) Based on data from 6,622 participants in 3 studies. [8] (Randomized controlled)	37 per 1000 Difference:	13 per 1000 **24 fewer per 1000** (CI 95% 28 fewer — 19 fewer)	**High**	Casirivimab plus imdevimab may have little impact on serious adverse events (140 events).
Discontinuation due to adverse event During treatment 6 Important	Based on data from 780 participants in 1 studies. [9] (Randomized controlled)			**Low** Due to very serious imprecision [10]	We are uncertain whether casirivimab plus imdevimab increases or decreases discontinuation due to adverse events (1 event).
Hospitalisation Within 28 days of commencing treatment 6 Important	Relative risk 0.3 (CI 95% 0.2 — 0.44) Based on data from 4,261 participants in 2 studies. [11] (Randomized controlled)	45 per 1000 Difference:	14 per 1000 **31 fewer per 1000** (CI 95% 36 fewer — 25 fewer)	**Moderate** Due to serious imprecision [12]	Casirivimab plus imdevimab probably decreases hospitalisation slightly

Attached Images

7.1.1.2 Casirivimab plus imdevimab (Ronapreve) for pregnant or breastfeeding women

Consensus recommendation

Do not routinely use casirivimab plus imdevimab (Ronapreve) in pregnant or breastfeeding women with COVID-19.

The Taskforce has previously recommended the use of casirivimab plus imdevimab (Ronapreve) for the treatment of pregnant or breastfeeding women with COVID-19 with one or more risk factors for disease progression who are hospitalised with moderate to critical illness and who do not require oxygen. Recommendations for individuals not requiring hospitalisation were based on three studies that included 6622 participants with mild COVID-19 [320][367][400], which demonstrated a benefit with regards to hospitalisation and adverse events. Recommendations for hospitalised individuals were based on two studies that included 10982 participants with moderate to severe COVID-19 [415][520], which demonstrated a benefit with regards all-cause mortality at 28 days and serious adverse events. These studies did not include pregnant or breastfeeding women.

All clinical trials that contributed data to the analyses were conducted before the emergence of Omicron as the dominant variant. Since the development of the initial recommendations, a significant body of in vitro evidence has emerged demonstrating a significant reduction in activity of casirivimab plus imdevimab (Ronapreve) against the Omicron BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that casirivimab plus imdevimab (Ronapreve) is effective in treating pregnant or breastfeeding women with currently circulating variants of COVID-19.

Clinical Question/ PICO

Population: Outpatients with mild COVID-19
Intervention: Casirivimab plus imdevimab
Comparator: Placebo

Summary

There remains significant uncertainty whether casirivimab plus imdevimab is more effective and safer than standard care in treating patients with mild or asymptomatic COVID-19.

What is the evidence informing this recommendation?
Evidence comes from three randomised trials that compared casirivimab plus imdevimab with placebo in 4856 adult outpatients with mild COVID-19 *[320][367]* and 207 asymptomatic outpatients *[400]*. Two trials are linked—one presents results from the phase I-II portion *[320]* and the second from the phase III portion of the study *[367]*. The third study included asymptomatic patients who had close contacts with confirmed COVID-19 individuals *[400]*.

Publication status
One study is only available as a preprint (Weinreich et al. posted to medRxiv on 12 June 2021 *[320]*) and has therefore not been peer reviewed.

Study characteristics
Median age of participants ranged from 41 to 50 years and the proportion of women ranged from 51 to 55%. Patients in the phase I and II portions of the study by Weinreich et al. received a dose of either 2400 mg or 8000 mg REGEN-COV (1:1 casirivimab:imdevimab). The larger phase III portion randomised patients to receive either one 2400 mg or one 8000 mg dose, revising their protocol midway to include one 1200 mg or 2400 mg dose. In O'Brien et al. patients received a single dose of 1200 mg. Pregnant and breastfeeding patients were ineligible.

Equity, diversity and inclusion

The characteristics of trial participants related to equity, diversity and inclusion (see technical report) were reported in minimal detail in the included studies. Ethnicity was reported in one study. As a result, the specific population(s) to whom this data directly applies is unclear.

None of these trials were conducted in Australia. This participant data comes from the United Kingdom.

The Taskforce will continue to extract and identify characteristics relevant to equity, diversity and inclusion where available.

What are the main results?
Casirivimab plus imdevimab decreases the incidence of adverse events (RR 0.74, CI 95% 0.64 to 0.86; 5842 patients in 2 studies) and serious adverse events (RR 0.34, CI 95% 0.25 to 0.48; 6622 patients in 3 studies), and probably decreases hospitalisation (RR 0.30, CI 95% 0.20 to 0.44; 4261 patients in 2 studies). We are unsure if casirivimab plus imdevimab has an impact on death, mechanical ventilation, ICU admission or discontinuation due to adverse events.

Our confidence in the results
Certainty of the evidence is low for the critical outcomes of death and mechanical ventilation due to very serious imprecision (few events and reliance on a single study). Certainty is high for adverse events and serious adverse events, moderate for hospitalisation due to serious imprecision (majority of data comes from a single study) and low for discontinuation due to adverse events and ICU admission due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The Taskforce notes that as of 15 October 2021, the Therapeutic Goods Administration has provisionally approved the use of casirivimab plus imdevimab in **patients with mild-to-moderate COVID-19** who have one or more risk factors for disease progression.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.2 (CI 95% 0.04 — 1.02) Based on data from 4,057 participants in 1 studies. [1] (Randomized controlled)	4 per 1000 Difference:	1 per 1000 **3 fewer per 1000** (CI 95% 4 fewer — 0 fewer)	**Low** Due to very serious imprecision [2]	Casirivimab plus imdevimab may have little imapct on death (10 events).
Mechanical ventilation Within 28 days of commencing treatment 9 Critical	Relative risk 0.21 (CI 95% 0.04 — 1.06) Based on data from 3,432 participants in 1 studies. [3] (Randomized controlled)	4 per 1000 Difference:	1 per 1000 **3 fewer per 1000** (CI 95% 4 fewer — 0 fewer)	**Low** Due to very serious imprecision [4]	Casirivimab plus imdevimab may have little impact on mechanical ventilation (8 events).
ICU admission Within 28 days of commencing treatment 6 Important	Relative risk 0.32 (CI 95% 0.14 — 0.71) Based on data from 3,432 participants in 1 studies. [5] (Randomized controlled)	13 per 1000 Difference:	4 per 1000 **9 fewer per 1000** (CI 95% 11 fewer — 4 fewer)	**Low** Due to very serious imprecision [6]	Casirivimab plus imdevimab may have little impact on ICU admission (27 events).
Adverse events	Relative risk 0.74 (CI 95% 0.64 — 0.86) Based on data from	132 per 1000	98 per 1000	**High**	Casirivimab plus imdevimab may decrease adverse

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
End of follow-up 6 Important	5,842 participants in 2 studies. [7] (Randomized controlled)	Difference:	**34 fewer per 1000** (CI 95% 48 fewer — 18 fewer)		events slightly (602 events).
Serious adverse event End of follow-up 6 Important	Relative risk 0.34 (CI 95% 0.25 — 0.48) Based on data from 6,622 participants in 3 studies. [8] (Randomized controlled)	37 per 1000 Difference:	13 per 1000 **24 fewer per 1000** (CI 95% 28 fewer — 19 fewer)	**High**	Casirivimab plus imdevimab may have little impact on serious adverse events (140 events).
Discontinuation due to adverse event During treatment 6 Important	Based on data from 780 participants in 1 studies. [9] (Randomized controlled)			**Low** Due to very serious imprecision [10]	We are uncertain whether casirivimab plus imdevimab increases or decreases discontinuation due to adverse events (1 event).
Hospitalisation Within 28 days of commencing treatment 6 Important	Relative risk 0.3 (CI 95% 0.2 — 0.44) Based on data from 4,261 participants in 2 studies. [11] (Randomized controlled)	45 per 1000 Difference:	14 per 1000 **31 fewer per 1000** (CI 95% 36 fewer — 25 fewer)	**Moderate** Due to serious imprecision [12]	Casirivimab plus imdevimab probably decreases hospitalisation slightly

Attached Images

Not recommended

Do not use casirivimab plus imdevimab in **seropositive** pregnant or breastfeeding women who are hospitalised with moderate-to-critical COVID-19.

Additional information

In patients hospitalised with moderate-to-critical COVID-19 who are seropositive (detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab (Ronapreve) probably has little impact on risk of death, the need for invasive mechanical ventilation and discharge from hospital. Because of this, the Taskforce recommends against the use of casirivimab plus imdevimab in hospitalised patients who are seropositive.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Clinical Question/ PICO

Population: Patients hospitalised with COVID-19
Intervention: Casirivimab plus imdevimab
Comparator: Standard care

Summary

Evidence indicates a reduction in death in seronegative patients hospitalised with mild-to-critical COVID-19.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial (RECOVERY) that compared casirivimab plus imdevimab with standard care in 9785 patients hospitalised with moderate-to-critical COVID-19, a third of whom were seronegative at baseline *[415]*, and one randomised trial that compared casirivimab plus imdevimab with placebo in 1336 patients hospitalised with mild-to-moderate COVID-19, approximately half of whom were seronegative at baseline *[520]*.

Study characteristics
Median age of participants was 62 years in both studies. Women comprised 37% of participants in RECOVERY and 47% in Somersan-Karakaya et al. Within RECOVERY, patients received a single intravenously administered 8000 mg dose of Ronapreve (4000 mg casirivimab plus 4000 mg imdevimab) or standard care. Twelve children (12–18 years) were included in RECOVERY but data were not reported separately. In Somersan-Karakaya et al patients received a single intravenously administered dose of 8000 mg Ronapreve (4000 mg casirivimab plus 4000 mg imdevimab), 2400 mg REGEN-COV (1200 mg casirivimab plus 1200 mg imdevimab) or placebo. Children were ineligible for inclusion. Pregnant and breastfeeding women were ineligible in both trials.

Both trials separated results based on serostatus at baseline (patients with SARS-CoV-2 neutralising antibodies versus those without antibodies). To determine whether subgrouping based on serostatus was appropriate, we undertook an ICEMAN analysis, with the results confirming the appropriateness of this approach. The full ICEMAN analysis can be found here.

What are the main results?
Results demonstrate that casirivimab plus imdevimab reduces death in seronegative patients (50 fewer per 1000; RR 0.82, CI 95% 0.73 to 0.91; 3673 patients in 2 studies). Casirivimab plus imdevimab probably has little impact on the need for mechanical ventilation, however it may increase discharge from hospital and reduce hospital length of stay.

For seropositive patients results indicate no difference in incidence of death, number of patients requiring invasive mechanical ventilation and discharge from hospital.

The Taskforce notes that in RECOVERY, treatment of participants occurred after sera were collected but before determination of their serostatus. The results in RECOVERY may therefore overestimate the effectiveness of casirivimab plus imdevimab in seronegative patients if serological testing results in substantial delays in administration.

Our confidence in the results
In seronegative patients certainty of the evidence is high for all-cause mortality, moderate for mechanical ventilation due to serious imprecision (reliance on a single study), and low for discharge from hospital and duration of hospital stay due to very serious imprecision (reliance on a single study and wide confidence intervals).

In seropositive patients certainty of the evidence is high for all-cause mortality, and moderate for mechanical ventilation and discharge from hospital due to serious imprecision (reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
Although the Therapeutic Goods Administration has provisionally approved the use of casirivimab plus imdevimab in patients with mild-to-moderate COVID-19 who have one or more risk factors for disease progression, as of 19 November 2021 it is not approved for use in hospitalised patients.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality [All patients] Within 28 days of commencing treatment 9 Critical	Relative risk 0.81 (CI 95% 0.56 — 1.17) Based on data from 10,982 participants in 2 studies. [1] (Randomized controlled)	201 per 1000 Difference:	163 per 1000 **38 fewer per 1000** (CI 95% 88 fewer — 34 more)	**High**	Casirivimab plus imdevimab decreases all-cause mortality
Invasive mechanical ventilation [All patients] Within 28 days of commencing treatment 9 Critical	Relative risk 1 (CI 95% 0.89 — 1.13) Based on data from 9,198 participants in 1 studies. [2] (Randomized controlled)	105 per 1000 Difference:	105 per 1000 **0 fewer per 1000** (CI 95% 12 fewer — 14 more)	**Moderate** Due to serious imprecision [3]	Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [all patients].
Discharged from hospital [All patients] Within 28 days of commencing treatment 6 Important	Relative risk 1.01 (CI 95% 0.98 — 1.04) Based on data from 9,785 participants in 1 studies. [4] (Randomized controlled)	690 per 1000 Difference:	697 per 1000 **7 more per 1000** (CI 95% 14 fewer — 28 more)	**Moderate** Due to serious imprecision [5]	Casirivimab plus imdevimab probably has little impact on discharge from hospital [total]
Discharged from hospital [All patients] Within 28 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.98 — 1.08) Based on data from 10,982 participants in 2 studies. [6] (Randomized controlled)	701 per 1000 Difference:	722 per 1000 **21 more per 1000** (CI 95% 14 fewer — 56 more)	**High**	Casirivimab plus imdevimab increases discharged from hospital
All-cause mortality [seronegative] Within 28 days of commencing treatment 9 Critical	Relative risk 0.64 (CI 95% 0.36 — 1.15) Based on data from 3,673 participants in 2 studies. [7] (Randomized controlled)	283 per 1000 Difference:	181 per 1000 **102 fewer per 1000** (CI 95% 181 fewer — 42 more)	**Moderate** Due to serious imprecision [8]	Casirivimab plus imdevimab decreases all-cause mortality [seronegative]
Invasive mechanical ventilation [seronegative]	Relative risk 0.88 (CI 95% 0.73 — 1.06) Based on data from 3,083 participants in 1	135 per 1000 Difference:	119 per 1000 **16 fewer per**	**Moderate** Due to serious imprecision [10]	Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Within 28 days of commencing treatment 9 Critical	studies. [9] (Randomized controlled)		**1000** (CI 95% 36 fewer — 8 more)		[seronegative patients].
Discharged from hospital [seropositive] Within 28 days of commencing treatment 6 Important	Relative risk 0.98 (CI 95% 0.95 — 1.01) Based on data from 6,632 participants in 1 studies. [11] (Randomized controlled)	740 per 1000 Difference:	725 per 1000 **15 fewer per 1000** (CI 95% 37 fewer — 7 more)	**High**	Casirivimab plus imdevimab probably has little impact on discharged from hospital [seropositive]
Discharged from hospital [seronegative] Within 28 days of commencing treatment 6 Important	Relative risk 1.11 (CI 95% 1.06 — 1.16) Based on data from 3,673 participants in 2 studies. [12] (Randomized controlled)	600 per 1000 Difference:	666 per 1000 **66 more per 1000** (CI 95% 36 more — 96 more)	**Moderate** Due to serious imprecision [13]	Casirivimab plus imdevimab probably increases discharged from hospital [seronegative]
All-cause mortality [seropositive] Within 28 days of commencing treatment 9 Critical	Relative risk 1.01 (CI 95% 0.91 — 1.12) Based on data from 7,202 participants in 2 studies. [14] (Randomized controlled)	163 per 1000 Difference:	165 per 1000 **2 more per 1000** (CI 95% 15 fewer — 20 more)	**High**	Casirivimab plus imdevimab has little or no difference on all-cause mortality [seropositive]
Invasive mechanical ventilation [seropositive] Within 28 days of commencing treatment 9 Critical	Relative risk 1.08 (CI 95% 0.92 — 1.26) Based on data from 6,702 participants in 1 studies. [15] (Randomized controlled)	83 per 1000 Difference:	90 per 1000 **7 more per 1000** (CI 95% 7 fewer — 22 more)	**Moderate** Due to serious imprecision [16]	Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [seropositive patients].
Discharged from hospital [seropositive] Within 28 days of commencing treatment 6 Important	Relative risk 0.98 (CI 95% 0.95 — 1.01) Based on data from 6,632 participants in 1 studies. [17] (Randomized controlled)	740 per 1000 Difference:	725 per 1000 **15 fewer per 1000** (CI 95% 37 fewer — 7 more)	**Moderate** Due to serious imprecision [18]	Casirivimab plus imdevimab probably has little impact on discharge from hospital [seropositive patients].

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Serious Adverse Events Within 28 days of commencing treatment 6 Important	Relative risk 0.85 (CI 95% 0.71 — 1.03) Based on data from 1,410 participants in 1 studies. [19] (Randomized controlled)	279 per 1000 Difference:	237 per 1000 **42 fewer per 1000** (CI 95% 81 fewer — 8 more)	**Low** Due to very serious imprecision [20]	Casirivimab plus imdevimab may decrease new serious adverse events
Duration of hospital stay [All patients] Days 6 Important	Lower better Based on data from 9,785 participants in 1 studies. [21] (Randomized controlled)	10 (Median)	10 (Median) CI 95%	**Moderate** Due to serious imprecision [22]	Casirivimab plus imdevimab probably has little impact on duration of hospital stay [all patients].
Duration of hospital stay [seronegative] Days 6 Important	Lower better Based on data from 3,153 participants in 1 studies. [23] (Randomized controlled)	17 (Median)	13 (Median) CI 95%	**Low** Due to very serious imprecision [24]	Casirivimab plus imdevimab may decrease duration of hospital stay [seronegative patients].

Attached Images

7.1.1.3 Casirivimab plus imdevimab (Ronapreve) for children and adolescents

Consensus recommendation

Do not routinely use casirivimab plus imdevimab (Ronapreve) in children and adolescents with COVID-19.

The Taskforce has previously only recommended the use of casirivimab plus imdevimab (Ronapreve) in exceptional circumstances for seronegative children and adolescents aged 12 years and over and weighing at least 40 kg who are at high risk of disease progression. Recommendations were based on indirect evidence from three studies of 6622 non-hospitalised participants with mild COVID-19 [320][367][400] that excluded children and adolescents, but which demonstrated a benefit with regards to hospitalisation and adverse events. Recommendations for hospitalised children and adolescents were based on two studies that included 10982 participants with moderate to severe COVID-19 [415][520], which demonstrated a benefit with regards to all-cause mortality at 28 days and serious adverse events.

All clinical trials that contributed data to the analyses were conducted before the emergence of Omicron as the dominant variant. Since the development of the initial recommendations, a significant body of in vitro evidence has emerged demonstrating a significant reduction in activity of casirivimab plus imdevimab (Ronapreve) against the Omicron BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that casirivimab plus imdevimab (Ronapreve) is effective in treating children and adolescents with currently circulating variants of COVID-19.

Clinical Question/ PICO

Population: Outpatients with mild COVID-19
Intervention: Casirivimab plus imdevimab
Comparator: Placebo

Summary

There remains significant uncertainty whether casirivimab plus imdevimab is more effective and safer than standard care in treating patients with mild or asymptomatic COVID-19.

What is the evidence informing this recommendation?
Evidence comes from three randomised trials that compared casirivimab plus imdevimab with placebo in 4856 adult outpatients with mild COVID-19 *[320][367]* and 207 asymptomatic outpatients *[400]*. Two trials are linked—one presents results from the phase I-II portion *[320]* and the second from the phase III portion of the study *[367]*. The third study included asymptomatic patients who had close contacts with confirmed COVID-19 individuals *[400]*.

Publication status
One study is only available as a preprint (Weinreich et al. posted to medRxiv on 12 June 2021 *[320]*) and has therefore not been peer reviewed.

Study characteristics
Median age of participants ranged from 41 to 50 years and the proportion of women ranged from 51 to 55%. Patients in the phase I and II portions of the study by Weinreich et al. received a dose of either 2400 mg or 8000 mg REGEN-COV (1:1 casirivimab:imdevimab). The larger phase III portion randomised patients to receive either one 2400 mg or one 8000 mg dose, revising their protocol midway to include one 1200 mg or 2400 mg dose. In O'Brien et al. patients received a single dose of 1200 mg. Pregnant and breastfeeding patients were ineligible.

Equity, diversity and inclusion

The characteristics of trial participants related to equity, diversity and inclusion (see technical report) were reported in minimal detail in the included studies. Ethnicity was reported in one study. As a result, the specific population(s) to whom this data directly applies is unclear.

None of these trials were conducted in Australia. This participant data comes from the United Kingdom.

The Taskforce will continue to extract and identify characteristics relevant to equity, diversity and inclusion where available.

What are the main results?
Casirivimab plus imdevimab decreases the incidence of adverse events (RR 0.74, CI 95% 0.64 to 0.86; 5842 patients in 2 studies) and serious adverse events (RR 0.34, CI 95% 0.25 to 0.48; 6622 patients in 3 studies), and probably decreases hospitalisation (RR 0.30, CI 95% 0.20 to 0.44; 4261 patients in 2 studies). We are unsure if casirivimab plus imdevimab has an impact on death, mechanical ventilation, ICU admission or discontinuation due to adverse events.

Our confidence in the results
Certainty of the evidence is low for the critical outcomes of death and mechanical ventilation due to very serious imprecision (few events and reliance on a single study). Certainty is high for adverse events and serious adverse events, moderate for hospitalisation due to serious imprecision (majority of data comes from a single study) and low for discontinuation due to adverse events and ICU admission due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The Taskforce notes that as of 15 October 2021, the Therapeutic Goods Administration has provisionally approved the use of casirivimab plus imdevimab in **patients with mild-to-moderate COVID-19** who have one or more risk factors for disease progression.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.2 (CI 95% 0.04 — 1.02) Based on data from 4,057 participants in 1 studies. [1] (Randomized controlled)	4 per 1000 Difference:	1 per 1000 **3 fewer per 1000** (CI 95% 4 fewer — 0 fewer)	**Low** Due to very serious imprecision [2]	Casirivimab plus imdevimab may have little imapct on death (10 events).
Mechanical ventilation Within 28 days of commencing treatment 9 Critical	Relative risk 0.21 (CI 95% 0.04 — 1.06) Based on data from 3,432 participants in 1 studies. [3] (Randomized controlled)	4 per 1000 Difference:	1 per 1000 **3 fewer per 1000** (CI 95% 4 fewer — 0 fewer)	**Low** Due to very serious imprecision [4]	Casirivimab plus imdevimab may have little impact on mechanical ventilation (8 events).
ICU admission Within 28 days of commencing treatment 6 Important	Relative risk 0.32 (CI 95% 0.14 — 0.71) Based on data from 3,432 participants in 1 studies. [5] (Randomized controlled)	13 per 1000 Difference:	4 per 1000 **9 fewer per 1000** (CI 95% 11 fewer — 4 fewer)	**Low** Due to very serious imprecision [6]	Casirivimab plus imdevimab may have little impact on ICU admission (27 events).
Adverse events End of follow-up	Relative risk 0.74 (CI 95% 0.64 — 0.86) Based on data from 5,842 participants in 2	132 per 1000	98 per 1000	**High**	Casirivimab plus imdevimab may decrease adverse events slightly (602

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important	studies. [7] (Randomized controlled)	Difference:	**34 fewer per 1000** (CI 95% 48 fewer — 18 fewer)		events).
Serious adverse event End of follow-up 6 Important	Relative risk 0.34 (CI 95% 0.25 — 0.48) Based on data from 6,622 participants in 3 studies. [8] (Randomized controlled)	37 per 1000 Difference:	13 per 1000 **24 fewer per 1000** (CI 95% 28 fewer — 19 fewer)	**High**	Casirivimab plus imdevimab may have little impact on serious adverse events (140 events).
Discontinuation due to adverse event During treatment 6 Important	Based on data from 780 participants in 1 studies. [9] (Randomized controlled)			**Low** Due to very serious imprecision [10]	We are uncertain whether casirivimab plus imdevimab increases or decreases discontinuation due to adverse events (1 event).
Hospitalisation Within 28 days of commencing treatment 6 Important	Relative risk 0.3 (CI 95% 0.2 — 0.44) Based on data from 4,261 participants in 2 studies. [11] (Randomized controlled)	45 per 1000 Difference:	14 per 1000 **31 fewer per 1000** (CI 95% 36 fewer — 25 fewer)	**Moderate** Due to serious imprecision [12]	Casirivimab plus imdevimab probably decreases hospitalisation slightly

Attached Images

Only in research settings

Do not use casirivimab plus imdevimab in children under 12 years of age without risk factors for deterioration who have **mild or asymptomatic COVID-19** outside of randomised trials with appropriate ethical approval.

Additional information

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Clinical Question/ PICO

Population: Outpatients with mild COVID-19

Intervention: Casirivimab plus imdevimab
Comparator: Placebo

Summary

There remains significant uncertainty whether casirivimab plus imdevimab is more effective and safer than standard care in treating patients with mild or asymptomatic COVID-19.

What is the evidence informing this recommendation?
Evidence comes from three randomised trials that compared casirivimab plus imdevimab with placebo in 4856 adult outpatients with mild COVID-19 *[320][367]* and 207 asymptomatic outpatients *[400]*. Two trials are linked—one presents results from the phase I-II portion *[320]* and the second from the phase III portion of the study *[367]*. The third study included asymptomatic patients who had close contacts with confirmed COVID-19 individuals *[400]*.

Publication status
One study is only available as a preprint (Weinreich et al. posted to medRxiv on 12 June 2021 *[320]*) and has therefore not been peer reviewed.

Study characteristics
Median age of participants ranged from 41 to 50 years and the proportion of women ranged from 51 to 55%. Patients in the phase I and II portions of the study by Weinreich et al. received a dose of either 2400 mg or 8000 mg REGEN-COV (1:1 casirivimab:imdevimab). The larger phase III portion randomised patients to receive either one 2400 mg or one 8000 mg dose, revising their protocol midway to include one 1200 mg or 2400 mg dose. In O'Brien et al. patients received a single dose of 1200 mg. Pregnant and breastfeeding patients were ineligible.

Equity, diversity and inclusion

The characteristics of trial participants related to equity, diversity and inclusion (see technical report) were reported in minimal detail in the included studies. Ethnicity was reported in one study. As a result, the specific population(s) to whom this data directly applies is unclear.

None of these trials were conducted in Australia. This participant data comes from the United Kingdom.

The Taskforce will continue to extract and identify characteristics relevant to equity, diversity and inclusion where available.

What are the main results?
Casirivimab plus imdevimab decreases the incidence of adverse events (RR 0.74, CI 95% 0.64 to 0.86; 5842 patients in 2 studies) and serious adverse events (RR 0.34, CI 95% 0.25 to 0.48; 6622 patients in 3 studies), and probably decreases hospitalisation (RR 0.30, CI 95% 0.20 to 0.44; 4261 patients in 2 studies). We are unsure if casirivimab plus imdevimab has an impact on death, mechanical ventilation, ICU admission or discontinuation due to adverse events.

Our confidence in the results
Certainty of the evidence is low for the critical outcomes of death and mechanical ventilation due to very serious imprecision (few events and reliance on a single study). Certainty is high for adverse events and serious adverse events, moderate for hospitalisation due to serious imprecision (majority of data comes from a single study) and low for discontinuation due to adverse events and ICU admission due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The Taskforce notes that as of 15 October 2021, the Therapeutic Goods Administration has provisionally approved the use of casirivimab plus imdevimab in **patients with mild-to-moderate COVID-19** who have one or more risk factors for disease progression.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.2 (CI 95% 0.04 — 1.02) Based on data from 4,057 participants in 1 studies. [1] (Randomized controlled)	4 per 1000 Difference:	1 per 1000 **3 fewer per 1000** (CI 95% 4 fewer — 0 fewer)	**Low** Due to very serious imprecision [2]	Casirivimab plus imdevimab may have little imapct on death (10 events).
Mechanical ventilation Within 28 days of commencing treatment 9 Critical	Relative risk 0.21 (CI 95% 0.04 — 1.06) Based on data from 3,432 participants in 1 studies. [3] (Randomized controlled)	4 per 1000 Difference:	1 per 1000 **3 fewer per 1000** (CI 95% 4 fewer — 0 fewer)	**Low** Due to very serious imprecision [4]	Casirivimab plus imdevimab may have little impact on mechanical ventilation (8 events).
ICU admission Within 28 days of commencing treatment 6 Important	Relative risk 0.32 (CI 95% 0.14 — 0.71) Based on data from 3,432 participants in 1 studies. [5] (Randomized controlled)	13 per 1000 Difference:	4 per 1000 **9 fewer per 1000** (CI 95% 11 fewer — 4 fewer)	**Low** Due to very serious imprecision [6]	Casirivimab plus imdevimab may have little impact on ICU admission (27 events).
Adverse events End of follow-up 6 Important	Relative risk 0.74 (CI 95% 0.64 — 0.86) Based on data from 5,842 participants in 2 studies. [7] (Randomized controlled)	132 per 1000 Difference:	98 per 1000 **34 fewer per 1000** (CI 95% 48 fewer — 18 fewer)	**High**	Casirivimab plus imdevimab may decrease adverse events slightly (602 events).
Serious adverse event End of follow-up 6 Important	Relative risk 0.34 (CI 95% 0.25 — 0.48) Based on data from 6,622 participants in 3 studies. [8] (Randomized controlled)	37 per 1000 Difference:	13 per 1000 **24 fewer per 1000** (CI 95% 28 fewer — 19 fewer)	**High**	Casirivimab plus imdevimab may have little impact on serious adverse events (140 events).
Discontinuation due to adverse event During treatment 6 Important	Based on data from 780 participants in 1 studies. [9] (Randomized controlled)			**Low** Due to very serious imprecision [10]	We are uncertain whether casirivimab plus imdevimab increases or decreases discontinuation due to adverse events (1 event).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Hospitalisation Within 28 days of commencing treatment 6 Important	Relative risk 0.3 (CI 95% 0.2 — 0.44) Based on data from 4,261 participants in 2 studies. [11] (Randomized controlled)	45 per 1000 Difference:	14 per 1000 **31 fewer per 1000** (CI 95% 36 fewer — 25 fewer)	**Moderate** Due to serious imprecision [12]	Casirivimab plus imdevimab probably decreases hospitalisation slightly

Attached Images

Clinical Question/ PICO

Population: Patients hospitalised with COVID-19
Intervention: Casirivimab plus imdevimab
Comparator: Standard care

Summary

Evidence indicates a reduction in death in seronegative patients hospitalised with mild-to-critical COVID-19.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial (RECOVERY) that compared casirivimab plus imdevimab with standard care in 9785 patients hospitalised with moderate-to-critical COVID-19, a third of whom were seronegative at baseline *[415]*, and one randomised trial that compared casirivimab plus imdevimab with placebo in 1336 patients hospitalised with mild-to-moderate COVID-19, approximately half of whom were seronegative at baseline *[520]*.

Study characteristics
Median age of participants was 62 years in both studies. Women comprised 37% of participants in RECOVERY and 47% in Somersan-Karakaya et al. Within RECOVERY, patients received a single intravenously administered 8000 mg dose of Ronapreve (4000 mg casirivimab plus 4000 mg imdevimab) or standard care. Twelve children (12–18 years) were included in RECOVERY but data were not reported separately. In Somersan-Karakaya et al patients received a single intravenously administered dose of 8000 mg Ronapreve (4000 mg casirivimab plus 4000 mg imdevimab), 2400 mg REGEN-COV (1200 mg casirivimab plus 1200 mg imdevimab) or placebo. Children were ineligible for inclusion. Pregnant and breastfeeding women were ineligible in both trials.

Both trials separated results based on serostatus at baseline (patients with SARS-CoV-2 neutralising antibodies versus those without antibodies). To determine whether subgrouping based on serostatus was appropriate, we undertook an ICEMAN analysis, with the results confirming the appropriateness of this approach. The full ICEMAN analysis can be found here.

What are the main results?
Results demonstrate that casirivimab plus imdevimab reduces death in seronegative patients (50 fewer per 1000; RR 0.82, CI 95% 0.73 to 0.91; 3673 patients in 2 studies). Casirivimab plus imdevimab probably has little impact on the need for mechanical ventilation, however it may increase discharge from hospital and reduce hospital length of stay.

For seropositive patients results indicate no difference in incidence of death, number of patients requiring invasive mechanical ventilation and discharge from hospital.

The Taskforce notes that in RECOVERY, treatment of participants occurred after sera were collected but before determination of their serostatus. The results in RECOVERY may therefore overestimate the effectiveness of casirivimab plus imdevimab in seronegative patients if serological testing results in substantial delays in

administration.

Our confidence in the results
In seronegative patients certainty of the evidence is high for all-cause mortality, moderate for mechanical ventilation due to serious imprecision (reliance on a single study), and low for discharge from hospital and duration of hospital stay due to very serious imprecision (reliance on a single study and wide confidence intervals).

In seropositive patients certainty of the evidence is high for all-cause mortality, and moderate for mechanical ventilation and discharge from hospital due to serious imprecision (reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
Although the Therapeutic Goods Administration has provisionally approved the use of casirivimab plus imdevimab in patients with mild-to-moderate COVID-19 who have one or more risk factors for disease progression, as of 19 November 2021 it is not approved for use in hospitalised patients.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality [All patients] Within 28 days of commencing treatment 9 Critical	Relative risk 0.81 (CI 95% 0.56 — 1.17) Based on data from 10,982 participants in 2 studies. [1] (Randomized controlled)	201 per 1000 Difference:	163 per 1000 **38 fewer per 1000** (CI 95% 88 fewer — 34 more)	**High**	Casirivimab plus imdevimab decreases all-cause mortality
Invasive mechanical ventilation [All patients] Within 28 days of commencing treatment 9 Critical	Relative risk 1 (CI 95% 0.89 — 1.13) Based on data from 9,198 participants in 1 studies. [2] (Randomized controlled)	105 per 1000 Difference:	105 per 1000 **0 fewer per 1000** (CI 95% 12 fewer — 14 more)	**Moderate** Due to serious imprecision [3]	Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [all patients].
Discharged from hospital [All patients] Within 28 days of commencing treatment 6 Important	Relative risk 1.01 (CI 95% 0.98 — 1.04) Based on data from 9,785 participants in 1 studies. [4] (Randomized controlled)	690 per 1000 Difference:	697 per 1000 **7 more per 1000** (CI 95% 14 fewer — 28 more)	**Moderate** Due to serious imprecision [5]	Casirivimab plus imdevimab probably has little impact on discharge from hospital [total]
Discharged from hospital [All patients]	Relative risk 1.03 (CI 95% 0.98 — 1.08) Based on data from	701 per 1000	722 per 1000	**High**	Casirivimab plus imdevimab increases discharged from

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Within 28 days of commencing treatment 6 Important	10,982 participants in 2 studies. [6] (Randomized controlled)	Difference:	**21 more per 1000** (CI 95% 14 fewer — 56 more)		hospital
All-cause mortality [seronegative] Within 28 days of commencing treatment 9 Critical	Relative risk 0.64 (CI 95% 0.36 — 1.15) Based on data from 3,673 participants in 2 studies. [7] (Randomized controlled)	283 per 1000 Difference:	181 per 1000 **102 fewer per 1000** (CI 95% 181 fewer — 42 more)	**Moderate** Due to serious imprecision [8]	Casirivimab plus imdevimab decreases all-cause mortality [seronegative]
Invasive mechanical ventilation [seronegative] Within 28 days of commencing treatment 9 Critical	Relative risk 0.88 (CI 95% 0.73 — 1.06) Based on data from 3,083 participants in 1 studies. [9] (Randomized controlled)	135 per 1000 Difference:	119 per 1000 **16 fewer per 1000** (CI 95% 36 fewer — 8 more)	**Moderate** Due to serious imprecision [10]	Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [seronegative patients].
Discharged from hospital [seropositive] Within 28 days of commencing treatment 6 Important	Relative risk 0.98 (CI 95% 0.95 — 1.01) Based on data from 6,632 participants in 1 studies. [11] (Randomized controlled)	740 per 1000 Difference:	725 per 1000 **15 fewer per 1000** (CI 95% 37 fewer — 7 more)	**High**	Casirivimab plus imdevimab probably has little impact on discharged from hospital [seropositive]
Discharged from hospital [seronegative] Within 28 days of commencing treatment 6 Important	Relative risk 1.11 (CI 95% 1.06 — 1.16) Based on data from 3,673 participants in 2 studies. [12] (Randomized controlled)	600 per 1000 Difference:	666 per 1000 **66 more per 1000** (CI 95% 36 more — 96 more)	**Moderate** Due to serious imprecision [13]	Casirivimab plus imdevimab probably increases discharged from hospital [seronegative]
All-cause mortality [seropositive] Within 28 days of commencing treatment 9 Critical	Relative risk 1.01 (CI 95% 0.91 — 1.12) Based on data from 7,202 participants in 2 studies. [14] (Randomized controlled)	163 per 1000 Difference:	165 per 1000 **2 more per 1000** (CI 95% 15 fewer — 20 more)	**High**	Casirivimab plus imdevimab has little or no difference on all-cause mortality [seropositive]

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Invasive mechanical ventilation [seropositive] Within 28 days of commencing treatment 9 Critical	Relative risk 1.08 (CI 95% 0.92 — 1.26) Based on data from 6,702 participants in 1 studies. [15] (Randomized controlled)	83 per 1000 Difference:	90 per 1000 **7 more per 1000** (CI 95% 7 fewer — 22 more)	**Moderate** Due to serious imprecision [16]	Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [seropositive patients].
Discharged from hospital [seropositive] Within 28 days of commencing treatment 6 Important	Relative risk 0.98 (CI 95% 0.95 — 1.01) Based on data from 6,632 participants in 1 studies. [17] (Randomized controlled)	740 per 1000 Difference:	725 per 1000 **15 fewer per 1000** (CI 95% 37 fewer — 7 more)	**Moderate** Due to serious imprecision [18]	Casirivimab plus imdevimab probably has little impact on discharge from hospital [seropositive patients].
Serious Adverse Events Within 28 days of commencing treatment 6 Important	Relative risk 0.85 (CI 95% 0.71 — 1.03) Based on data from 1,410 participants in 1 studies. [19] (Randomized controlled)	279 per 1000 Difference:	237 per 1000 **42 fewer per 1000** (CI 95% 81 fewer — 8 more)	**Low** Due to very serious imprecision [20]	Casirivimab plus imdevimab may decrease new serious adverse events
Duration of hospital stay [All patients] Days 6 Important	Lower better Based on data from 9,785 participants in 1 studies. [21] (Randomized controlled)	10 (Median)	10 (Median) CI 95%	**Moderate** Due to serious imprecision [22]	Casirivimab plus imdevimab probably has little impact on duration of hospital stay [all patients].
Duration of hospital stay [seronegative] Days 6 Important	Lower better Based on data from 3,153 participants in 1 studies. [23] (Randomized controlled)	17 (Median)	13 (Median) CI 95%	**Low** Due to very serious imprecision [24]	Casirivimab plus imdevimab may decrease duration of hospital stay [seronegative patients].

Attached Images

Not recommended

Do not use casirivimab plus imdevimab in **seropositive** children and adolescents hospitalised with moderate-to-critical COVID-19.

Additional information

In patients hospitalised with moderate-to-critical COVID-19 who are seropositive (detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab (Ronapreve) probably has little impact on risk of death, the need for invasive mechanical ventilation and discharge from hospital. Because of this, the Taskforce recommends against the use of casirivimab plus imdevimab in hospitalised patients who are seropositive.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Clinical Question/ PICO

Population: Patients hospitalised with COVID-19
Intervention: Casirivimab plus imdevimab
Comparator: Standard care

Summary

Evidence indicates a reduction in death in seronegative patients hospitalised with mild-to-critical COVID-19.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial (RECOVERY) that compared casirivimab plus imdevimab with standard care in 9785 patients hospitalised with moderate-to-critical COVID-19, a third of whom were seronegative at baseline *[415]*, and one randomised trial that compared casirivimab plus imdevimab with placebo in 1336 patients hospitalised with mild-to-moderate COVID-19, approximately half of whom were seronegative at baseline *[520]*.

Study characteristics
Median age of participants was 62 years in both studies. Women comprised 37% of participants in RECOVERY and 47% in Somersan-Karakaya et al. Within RECOVERY, patients received a single intravenously administered 8000 mg dose of Ronapreve (4000 mg casirivimab plus 4000 mg imdevimab) or standard care. Twelve children (12–18 years) were included in RECOVERY but data were not reported separately. In Somersan-Karakaya et al patients received a single intravenously administered dose of 8000 mg Ronapreve (4000 mg casirivimab plus 4000 mg imdevimab), 2400 mg REGEN-COV (1200 mg casirivimab plus 1200 mg imdevimab) or placebo. Children were ineligible for inclusion. Pregnant and breastfeeding women were ineligible in both trials.

Both trials separated results based on serostatus at baseline (patients with SARS-CoV-2 neutralising antibodies versus those without antibodies). To determine whether subgrouping based on serostatus was appropriate, we undertook an ICEMAN analysis, with the results confirming the appropriateness of this approach. The full ICEMAN analysis can be found here.

What are the main results?
Results demonstrate that casirivimab plus imdevimab reduces death in seronegative patients (50 fewer per 1000; RR 0.82, CI 95% 0.73 to 0.91; 3673 patients in 2 studies). Casirivimab plus imdevimab probably has little impact on the need for mechanical ventilation, however it may increase discharge from hospital and reduce hospital length of stay.

For seropositive patients results indicate no difference in incidence of death, number of patients requiring invasive mechanical ventilation and discharge from hospital.

The Taskforce notes that in RECOVERY, treatment of participants occurred after sera were collected but before determination of their serostatus. The results in RECOVERY may therefore overestimate the effectiveness of casirivimab plus imdevimab in seronegative patients if serological testing results in substantial delays in administration.

Our confidence in the results
In seronegative patients certainty of the evidence is high for all-cause mortality, moderate for mechanical ventilation due to serious imprecision (reliance on a single study), and low for discharge from hospital and duration of hospital stay due to very serious imprecision (reliance on a single study and wide confidence intervals).

In seropositive patients certainty of the evidence is high for all-cause mortality, and moderate for mechanical ventilation and discharge from hospital due to serious imprecision (reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
Although the Therapeutic Goods Administration has provisionally approved the use of casirivimab plus imdevimab in patients with mild-to-moderate COVID-19 who have one or more risk factors for disease progression, as of 19 November 2021 it is not approved for use in hospitalised patients.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality [All patients] Within 28 days of commencing treatment 9 Critical	Relative risk 0.81 (CI 95% 0.56 — 1.17) Based on data from 10,982 participants in 2 studies. [1] (Randomized controlled)	201 per 1000 Difference:	163 per 1000 **38 fewer per 1000** (CI 95% 88 fewer — 34 more)	**High**	Casirivimab plus imdevimab decreases all-cause mortality
Invasive mechanical ventilation [All patients] Within 28 days of commencing treatment 9 Critical	Relative risk 1 (CI 95% 0.89 — 1.13) Based on data from 9,198 participants in 1 studies. [2] (Randomized controlled)	105 per 1000 Difference:	105 per 1000 **0 fewer per 1000** (CI 95% 12 fewer — 14 more)	**Moderate** Due to serious imprecision [3]	Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [all patients].
Discharged from hospital [All patients] Within 28 days of commencing treatment 6 Important	Relative risk 1.01 (CI 95% 0.98 — 1.04) Based on data from 9,785 participants in 1 studies. [4] (Randomized controlled)	690 per 1000 Difference:	697 per 1000 **7 more per 1000** (CI 95% 14 fewer — 28 more)	**Moderate** Due to serious imprecision [5]	Casirivimab plus imdevimab probably has little impact on discharge from hospital [total]
Discharged from hospital [All patients] Within 28 days	Relative risk 1.03 (CI 95% 0.98 — 1.08) Based on data from 10,982 participants in	701 per 1000 Difference:	722 per 1000 **21 more per**	**High**	Casirivimab plus imdevimab increases discharged from hospital

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
of commencing treatment 6 Important	2 studies. [6] (Randomized controlled)		**1000** (CI 95% 14 fewer — 56 more)		
All-cause mortality [seronegative] Within 28 days of commencing treatment 9 Critical	Relative risk 0.64 (CI 95% 0.36 — 1.15) Based on data from 3,673 participants in 2 studies. [7] (Randomized controlled)	**283** per 1000 Difference:	**181** per 1000 **102 fewer per 1000** (CI 95% 181 fewer — 42 more)	**Moderate** Due to serious imprecision [8]	Casirivimab plus imdevimab decreases all-cause mortality [seronegative]
Invasive mechanical ventilation [seronegative] Within 28 days of commencing treatment 9 Critical	Relative risk 0.88 (CI 95% 0.73 — 1.06) Based on data from 3,083 participants in 1 studies. [9] (Randomized controlled)	**135** per 1000 Difference:	**119** per 1000 **16 fewer per 1000** (CI 95% 36 fewer — 8 more)	**Moderate** Due to serious imprecision [10]	Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [seronegative patients].
Discharged from hospital [seropositive] Within 28 days of commencing treatment 6 Important	Relative risk 0.98 (CI 95% 0.95 — 1.01) Based on data from 6,632 participants in 1 studies. [11] (Randomized controlled)	**740** per 1000 Difference:	**725** per 1000 **15 fewer per 1000** (CI 95% 37 fewer — 7 more)	**High**	Casirivimab plus imdevimab probably has little impact on discharged from hospital [seropositive]
Discharged from hospital [seronegative] Within 28 days of commencing treatment 6 Important	Relative risk 1.11 (CI 95% 1.06 — 1.16) Based on data from 3,673 participants in 2 studies. [12] (Randomized controlled)	**600** per 1000 Difference:	**666** per 1000 **66 more per 1000** (CI 95% 36 more — 96 more)	**Moderate** Due to serious imprecision [13]	Casirivimab plus imdevimab probably increases discharged from hospital [seronegative]
All-cause mortality [seropositive] Within 28 days of commencing treatment 9 Critical	Relative risk 1.01 (CI 95% 0.91 — 1.12) Based on data from 7,202 participants in 2 studies. [14] (Randomized controlled)	**163** per 1000 Difference:	**165** per 1000 **2 more per 1000** (CI 95% 15 fewer — 20 more)	**High**	Casirivimab plus imdevimab has little or no difference on all-cause mortality [seropositive]

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** REGEN-COV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Invasive mechanical ventilation [seropositive] Within 28 days of commencing treatment 9 Critical	Relative risk 1.08 (CI 95% 0.92 — 1.26) Based on data from 6,702 participants in 1 studies. [15] (Randomized controlled)	83 per 1000 Difference:	90 per 1000 **7 more per 1000** (CI 95% 7 fewer — 22 more)	**Moderate** Due to serious imprecision [16]	Casirivimab plus imdevimab probably has little impact on invasive mechanical ventilation [seropositive patients].
Discharged from hospital [seropositive] Within 28 days of commencing treatment 6 Important	Relative risk 0.98 (CI 95% 0.95 — 1.01) Based on data from 6,632 participants in 1 studies. [17] (Randomized controlled)	740 per 1000 Difference:	725 per 1000 **15 fewer per 1000** (CI 95% 37 fewer — 7 more)	**Moderate** Due to serious imprecision [18]	Casirivimab plus imdevimab probably has little impact on discharge from hospital [seropositive patients].
Serious Adverse Events Within 28 days of commencing treatment 6 Important	Relative risk 0.85 (CI 95% 0.71 — 1.03) Based on data from 1,410 participants in 1 studies. [19] (Randomized controlled)	279 per 1000 Difference:	237 per 1000 **42 fewer per 1000** (CI 95% 81 fewer — 8 more)	**Low** Due to very serious imprecision [20]	Casirivimab plus imdevimab may decrease new serious adverse events
Duration of hospital stay [All patients] Days 6 Important	Lower better Based on data from 9,785 participants in 1 studies. [21] (Randomized controlled)	10 (Median)	10 (Median) CI 95%	**Moderate** Due to serious imprecision [22]	Casirivimab plus imdevimab probably has little impact on duration of hospital stay [all patients].
Duration of hospital stay [seronegative] Days 6 Important	Lower better Based on data from 3,153 participants in 1 studies. [23] (Randomized controlled)	17 (Median)	13 (Median) CI 95%	**Low** Due to very serious imprecision [24]	Casirivimab plus imdevimab may decrease duration of hospital stay [seronegative patients].

Attached Images

7.1.2 Corticosteroids (inhaled)

7.1.2.1 Corticosteroids (inhaled) for adults

Conditional recommendation

Consider using inhaled corticosteroids (budesonide or ciclesonide) within 14 days of symptom onset in adults with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression.

Additional information

In adults with confirmed COVID-19 who do not require oxygen, inhaled corticosteroids probably reduce hospitalisation. In individuals who are subsequently hospitalised due to disease progression, inhaled corticosteroids probably decrease the requirement for supplemental oxygen if taken within 14 days of onset of symptoms.

Five trials provide evidence for inhaled corticosteroids in the treatment of COVID-19, three comparing ciclesonide with standard care, and two comparing budesonide with standard care or placebo. Results are primarily based on the PRINCIPLE trial [359] in which adults were treated with inhaled budesonide (by breath-actuated inhaler) 800 µg twice daily for up to 14 days. Based on the inclusion criteria for this trial, risk factors for disease progression include age ≥ 65 years or ≥ 50 years with one or more of the following comorbidities:

- *Diabetes (not treated with insulin)*
- *Heart disease and/or hypertension*
- *Asthma or lung disease*
- *Weakened immune system due to a serious illness or medication (e.g. chemotherapy)*
- *Mild hepatic impairment*
- *Stroke or other neurological problem*

Approximately 11% and 1% of participants had received one or two doses of vaccine at enrolment, respectively, however results were not reported separately for this population.

Budesonide and ciclesonide are safe to use in pregnant and breastfeeding women.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Results show that inhaled corticosteroids probably reduces hospitalisation and decrease the requirement of supplemental oxygen in adult outpatients subsequently hospitalised with COVID-19. Based on current evidence, inhaled corticosteroids appear to have an acceptable safety profile when used to treat patients with COVID-19.

Certainty of the Evidence

Moderate

Certainty of the evidence is moderate for requirement of supplemental oxygen and hospitalisation (due to serious imprecision based on reliance on a single study), and low for all-cause mortality, invasive mechanical ventilation, ICU admission, serious adverse events and clinical recovery (due to very serious imprecision based on reliance on a single study, wide confidence intervals and/or few events).

Values and preferences

No substantial variability expected

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

Pregnant and breastfeeding women
We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. However, inhaled corticosteroids are used for other indications in pregnancy (such as asthma)

and no harm has been shown for women or their babies.

Children and adolescents
We have no systematically collected information regarding the preferences and values of the patient, healthcare decision-maker or family/carers ~~patients, parents, carers, families and guardians~~. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources

No important issues with the recommended alternative

Inhaled corticosteroids are widely available and affordable. Use of inhaled corticosteroids for the treatment of symptomatic COVID-19 in adults who do not require oxygen and who have one or more risk factors for disease progression is unlikely to have an impact on availability of these drugs for other indications

Equity

No important issues with the recommended alternative

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

Acceptability

No important issues with the recommended alternative

Although we have no systematically collected evidence regarding acceptability, inhaled corticosteroids are likely to be acceptable to both patients and clinicians.

Feasibility

No important issues with the recommended alternative

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

Inhaled budesonide (AstraZeneca Pty Ltd) is listed in the Australian Register of Therapeutic Goods for the treatment of non-COVID related conditions (*ARTG numbers: 80877, 80876, 80875;* AusPAR). As of 3 December 2021, budesonide is yet to be awarded provisional determination by the Therapeutic Goods Administration for the treatment of COVID-19.

Rationale

In adults who do not require oxygen, inhaled corticosteroids decrease the risk of hospitalisation and requirement of supplemental oxygen. Because of this, the Taskforce gives a conditional recommendation for inhaled corticosteroids both within and outside a randomised trial.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Inhaled corticosteroids
Comparator: Control

Summary

Evidence indicates a probable reduction in the need for supplemental oxygen in adults with symptomatic COVID-19 who do not require oxygen and have one or more risk factors for disease progression.

What is the evidence informing this recommendation?
Evidence comes from two randomised trials that compared inhaled budesonide with standard care in over 1900 adults in the community with mild COVID-19 *[157][359]* and three randomised trials that compared inhaled ciclesonide with standard care in over 600 adults with mild COVID-19 *[426][427][428]*. The vast majority of data comes from the PRINCIPLE trial, which included 1856 adults with symptomatic COVID-19 who had one or more risk factors for disease progression.

Study characteristics
Mean age of participants within the PRINCIPLE trial was ~64 years and 52% were women. The majority of patients had one or more comorbidities, including high blood pressure requiring medication (45%), diabetes (21%) and heart problems (16%).

What are the main results?
Inhaled corticosteroids probably decreases the requirement for supplemental oxygen (RR 0.69, CI 95% 0.49 to 0.98; 1559 patients from 1 study). Inhaled corticosteroids may improve clinical recovery and reduce hospitalisation, however we are unsure if budesonide has an impact on death, invasive mechanical ventilation, ICU admission or serious adverse events.

Our confidence in the results
Certainty of the evidence is moderate for requirement of supplemental oxygen (due to serious imprecision based on reliance on a single study), and low for all-cause mortality, invasive mechanical ventilation, hospitalisation, ICU admission, serious adverse events and clinical recovery (due to very serious imprecision based on reliance on a single study, wide confidence intervals and/or few events).

For children and adolescents, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included study).

Additional information
Common side effects and harms associated with budesonide are dysphonia, oropharyngeal candidiasis and bruising.

Inhaled budesonide and ciclesonide are safe to use in **pregnancy and during breastfeeding** but have not been tested in this population to treat COVID-19.

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Inhaled corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.61 (CI 95% 0.22 — 1.67) Based on data from 2,189 participants in 3 studies. [1] (Randomized controlled)	**9** per 1000 Difference:	**5** per 1000 **4 fewer per 1000** (CI 95% 7 fewer — 6 more)	**Moderate** Due to serious imprecision [2]	Inhaled corticosteroids probably have little impact on all-cause mortality (16 events).
All-cause mortality Within 14 days of commencing treatment 9 Critical	Based on data from 61 participants in 1 studies. [3]				No patients died.
Invasive mechanical	Relative risk 0.94 (CI 95% 0.44 — 1.98)	**18**	**17**	**Low** Due to very	Budesonide may have little impact on invasive

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Inhaled corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
ventilation Within 28 days of commencing treatment 9 Critical	Based on data from 1,560 participants in 1 studies. [4] (Randomized controlled)	per 1000 Difference:	per 1000 **1 fewer per 1000** (CI 95% 10 fewer — 18 more)	serious imprecision [5]	mechanical ventilation (27 events).
Supplemental oxygen Within 28 days of commencing treatment 6 Important	Relative risk 0.69 (CI 95% 0.49 — 0.98) Based on data from 1,559 participants in 1 studies. [6] (Randomized controlled)	93 per 1000 Difference:	64 per 1000 **29 fewer per 1000** (CI 95% 47 fewer — 2 fewer)	**Moderate** Due to serious imprecision [7]	Budesonide probably decreases supplemental oxygen slightly (123 events).
Hospitalisation End of follow-up 6 Important	Relative risk 0.64 (CI 95% 0.31 — 1.3) Based on data from 2,335 participants in 4 studies. [8] (Randomized controlled)	101 per 1000 Difference:	65 per 1000 **36 fewer per 1000** (CI 95% 70 fewer — 30 more)	**Moderate** Due to serious imprecision [9]	Inhaled corticosteroids probably decrease hospitalisation slightly (202 events).
ICU admission Within 28 days of commencing treatment 6 Important	Relative risk 0.48 (CI 95% 0.23 — 1.01) Based on data from 1,550 participants in 1 studies. [10] (Randomized controlled)	27 per 1000 Difference:	13 per 1000 **14 fewer per 1000** (CI 95% 21 fewer — 0 fewer)	**Low** Due to very serious imprecision [11]	Inhaled corticosteroids may have little impact on ICU admission (31 events).
ED visits or hospital admissions Within 28 days of commencing treatment 6 Important	Relative risk 0.19 (CI 95% 0.04 — 0.83) Based on data from 400 participants in 1 studies. [12] (Randomized controlled)	54 per 1000 Difference:	10 per 1000 **44 fewer per 1000** (CI 95% 52 fewer — 9 fewer)	**Low** Due to very serious imprecision [13]	Inhaled corticosteroids may decrease ED visits or hospital admissions slightly (13 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.51 (CI 95% 0.09 — 2.76) Based on data from 1,647 participants in 2 studies. [14] (Randomized controlled)	5 per 1000 Difference:	3 per 1000 **2 fewer per 1000** (CI 95% 5 fewer — 9 more)	**Moderate** Due to serious imprecision [15]	Inhaled corticosteroids probably have little impact on serious adverse events (6 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Inhaled corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Adverse events End of follow-up 6 Important	Relative risk 1.04 (CI 95% 0.58 — 1.88) Based on data from 603 participants in 2 studies. [16] (Randomized controlled)	146 per 1000 Difference:	152 per 1000 **6 more per 1000** (CI 95% 61 fewer — 128 more)	**Low** Due to serious inconsistency and serious imprecision [17]	Inhaled corticosteroids may have little or no difference on adverse events (89 events).
Clinical recovery Within 28 days of commencing treatment 6 Important	Relative risk 1.2 (CI 95% 1.1 — 1.32) Based on data from 1,586 participants in 1 studies. [18] (Randomized controlled)	488 per 1000 Difference:	586 per 1000 **98 more per 1000** (CI 95% 49 more — 156 more)	**Low** Due to serious risk of bias and serious imprecision [19]	Inhaled corticosteroids may improve clinical recovery (852 events).

Attached Images

7.1.2.2 Corticosteroids (inhaled) for children and adolescents

Conditional recommendation

Consider using inhaled corticosteroids (budesonide and ciclesonide) within 14 days of symptom onset for the treatment of symptomatic COVID-19 in children and adolescents who do not require oxygen and who have one or more risk factors for disease progression.

Additional information

In adults with confirmed COVID-19 who do not require oxygen, inhaled corticosteroids probably reduce hospitalisation. In adults who are subsequently hospitalised due to disease progression, inhaled corticosteroids probably decrease the requirement for supplemental oxygen if taken within 14 days of onset of symptoms.

Results are primarily based on the PRINCIPLE trial [359], in which adults were treated with inhaled budesonide (by breath-actuated inhaler) 800 µg twice daily for up to 14 days. No children or adolescents were included in the trial.

Based on international cohort studies [370], risk factors for disease severity in children include:

- *Paediatric Complex Chronic Conditions: congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions*
- *Severe asthma*
- *Obesity*

Approximately 11% and 1% of participants had received one or two doses of vaccine at enrolment, respectively, however results were not reported separately for this population.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Results show that inhaled corticosteroids probably reduces hospitalisation and decrease the requirement of supplemental oxygen in adult outpatients subsequently hospitalised with COVID-19. Based on current evidence, inhaled corticosteroids appear to have an acceptable safety profile when used to treat patients with COVID-19.

Certainty of the Evidence

Low

Certainty of the evidence is low for requirement of supplemental oxygen and hospitalisation (due to serious imprecision based on reliance on a single study, and indirectness), and very low for all-cause mortality, invasive mechanical ventilation, ICU admission, serious adverse events and clinical recovery (due to very serious imprecision based on reliance on a single study, indirectness, wide confidence intervals and/or few events).

Values and preferences

No substantial variability expected

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

Pregnant and breastfeeding women
We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. However, inhaled corticosteroids are used for other indications in pregnancy (such as asthma) and no harm has been shown for women or their babies.

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

families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources No important issues with the recommended alternative

Inhaled corticosteroids are widely available and affordable. Use of inhaled corticosteroids for the treatment of symptomatic COVID-19 in adults who do not require oxygen and who have one or more risk factors for disease progression is unlikely to have an impact on availability of these drugs for other indications

Equity No important issues with the recommended alternative

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

Acceptability No important issues with the recommended alternative

Although we have no systematically collected evidence regarding acceptability, inhaled corticosteroids are likely to be acceptable to both patients and clinicians.

Feasibility No important issues with the recommended alternative

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

Inhaled budesonide (AstraZeneca Pty Ltd) is listed in the Australian Register of Therapeutic Goods for the treatment of non-COVID related conditions (*ARTG numbers: 80877, 80876, 80875; AusPAR*). As of 3 December 2021, budesonide is yet to be awarded provisional determination by the Therapeutic Goods Administration for the treatment of COVID-19.

Rationale

In adults who do not require oxygen, inhaled corticosteroids decrease the risk of hospitalisation and requirement of supplemental oxygen. Because of this, the Taskforce gives a conditional recommendation for inhaled corticosteroids both within and outside a randomised trial.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Inhaled corticosteroids
Comparator: Control

Summary

Evidence indicates a probable reduction in the need for supplemental oxygen in adults with symptomatic COVID-19 who do not require oxygen and have one or more risk factors for disease progression.

What is the evidence informing this recommendation?
Evidence comes from two randomised trials that compared inhaled budesonide with standard care in over 1900 adults in the community with mild COVID-19 *[157][359]* and three randomised trials that compared inhaled ciclesonide with standard care in over 600 adults with mild COVID-19 *[426][427][428]*. The vast majority of data comes from the PRINCIPLE trial, which included 1856 adults with symptomatic COVID-19 who had one or more

risk factors for disease progression.

Study characteristics
Mean age of participants within the PRINCIPLE trial was ~64 years and 52% were women. The majority of patients had one or more comorbidities, including high blood pressure requiring medication (45%), diabetes (21%) and heart problems (16%).

What are the main results?
Inhaled corticosteroids probably decreases the requirement for supplemental oxygen (RR 0.69, CI 95% 0.49 to 0.98; 1559 patients from 1 study). Inhaled corticosteroids may improve clinical recovery and reduce hospitalisation, however we are unsure if budesonide has an impact on death, invasive mechanical ventilation, ICU admission or serious adverse events.

Our confidence in the results
Certainty of the evidence is moderate for requirement of supplemental oxygen (due to serious imprecision based on reliance on a single study), and low for all-cause mortality, invasive mechanical ventilation, hospitalisation, ICU admission, serious adverse events and clinical recovery (due to very serious imprecision based on reliance on a single study, wide confidence intervals and/or few events).

For children and adolescents, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included study).

Additional information
Common side effects and harms associated with budesonide are dysphonia, oropharyngeal candidiasis and bruising.

Inhaled budesonide and ciclesonide are safe to use in **pregnancy and during breastfeeding** but have not been tested in this population to treat COVID-19.

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Inhaled corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.61 (CI 95% 0.22 — 1.67) Based on data from 2,189 participants in 3 studies. [1] (Randomized controlled)	9 per 1000 Difference:	5 per 1000 **4 fewer per 1000** (CI 95% 7 fewer — 6 more)	**Moderate** Due to serious imprecision [2]	Inhaled corticosteroids probably have little impact on all-cause mortality (16 events).
All-cause mortality Within 14 days of commencing treatment 9 Critical	Based on data from 61 participants in 1 studies. [3]				No patients died.
Invasive mechanical ventilation Within 28 days of commencing treatment	Relative risk 0.94 (CI 95% 0.44 — 1.98) Based on data from 1,560 participants in 1 studies. [4] (Randomized controlled)	18 per 1000 Difference:	17 per 1000 **1 fewer per 1000** (CI 95% 10 fewer — 18 more	**Low** Due to very serious imprecision [5]	Budesonide may have little impact on invasive mechanical ventilation (27 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Inhaled corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical			)		
Supplemental oxygen Within 28 days of commencing treatment 6 Important	Relative risk 0.69 (CI 95% 0.49 — 0.98) Based on data from 1,559 participants in 1 studies. [6] (Randomized controlled)	93 per 1000 Difference:	64 per 1000 **29 fewer per 1000** (CI 95% 47 fewer — 2 fewer)	**Moderate** Due to serious imprecision [7]	Budesonide probably decreases supplemental oxygen slightly (123 events).
Hospitalisation End of follow-up 6 Important	Relative risk 0.64 (CI 95% 0.31 — 1.3) Based on data from 2,335 participants in 4 studies. [8] (Randomized controlled)	101 per 1000 Difference:	65 per 1000 **36 fewer per 1000** (CI 95% 70 fewer — 30 more)	**Moderate** Due to serious imprecision [9]	Inhaled corticosteroids probably decrease hospitalisation slightly (202 events).
ICU admission Within 28 days of commencing treatment 6 Important	Relative risk 0.48 (CI 95% 0.23 — 1.01) Based on data from 1,550 participants in 1 studies. [10] (Randomized controlled)	27 per 1000 Difference:	13 per 1000 **14 fewer per 1000** (CI 95% 21 fewer — 0 fewer)	**Low** Due to very serious imprecision [11]	Inhaled corticosteroids may have little impact on ICU admission (31 events).
ED visits or hospital admissions Within 28 days of commencing treatment 6 Important	Relative risk 0.19 (CI 95% 0.04 — 0.83) Based on data from 400 participants in 1 studies. [12] (Randomized controlled)	54 per 1000 Difference:	10 per 1000 **44 fewer per 1000** (CI 95% 52 fewer — 9 fewer)	**Low** Due to very serious imprecision [13]	Inhaled corticosteroids may decrease ED visits or hospital admissions slightly (13 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.51 (CI 95% 0.09 — 2.76) Based on data from 1,647 participants in 2 studies. [14] (Randomized controlled)	5 per 1000 Difference:	3 per 1000 **2 fewer per 1000** (CI 95% 5 fewer — 9 more)	**Moderate** Due to serious imprecision [15]	Inhaled corticosteroids probably have little impact on serious adverse events (6 events).
Adverse events End of follow-up	Relative risk 1.04 (CI 95% 0.58 — 1.88) Based on data from 603 participants in 2	146 per 1000 Difference:	152 per 1000 **6 more per 1000**	**Low** Due to serious inconsistency and serious	Inhaled corticosteroids may have little or no difference on adverse events (89 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Control	**Intervention** Inhaled corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important	studies. [16] (Randomized controlled)		(CI 95% 61 fewer — 128 more)	imprecision [17]	
Clinical recovery Within 28 days of commencing treatment 6 Important	Relative risk 1.2 (CI 95% 1.1 — 1.32) Based on data from 1,586 participants in 1 studies. [18] (Randomized controlled)	488 per 1000 Difference:	586 per 1000 **98 more per 1000** (CI 95% 49 more — 156 more)	**Low** Due to serious risk of bias and serious imprecision [19]	Inhaled corticosteroids may improve clinical recovery (852 events).

Attached Images

7.1.3 Corticosteroids (systemic)

7.1.3.1 Corticosteroids (systemic) for adults

Recommended

Use intravenous or oral dexamethasone for up to 10 days (or acceptable alternative regimen) in **adults with COVID-19 who require oxygen** (including mechanically ventilated patients).

Additional information

The suggested regimen of corticosteroid use is 6 mg of dexamethasone (oral or intravenous) daily for up to 10 days. In patients for whom dexamethasone is not available, acceptable alternative regimens include:

- *hydrocortisone: intravenous (50 mg), every 6 hours for up to 10 days*
- *prednisolone: oral (50 mg), daily for up to 10 days*
- *methylprednisolone may also be an acceptable alternative, however the most appropriate dosage is uncertain*

Five randomised trials have compared high dose (defined as ≥12mg dexamethasone daily or equivalent) versus low dose steroids. Although study populations were varied, there was no improvement in mortality with a higher dose of steroids, and a suggestion of harm. Based on the existing evidence, the Taskforce recommends 6 mg dexamethasone (or equivalent) per day for 10 days in line with the RECOVERY trial [38]. For those requiring mechanical ventilation/HFNO, uncertainty remains for high dose corticosteroids. Trials are still recruiting in this patient group.

It is unclear whether older people living with frailty or cognitive impairment, or those requiring palliative care were included in the studies on which this recommendation is based. Until further evidence in these populations is available, the Taskforce does not believe a different recommendation should apply, unless contraindicated.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

In patients receiving oxygen or invasive mechanical ventilation, death is reduced with corticosteroids. Although indirect evidence suggests that corticosteroids may increase the risk of hyperglycaemia, the panel believes the mortality benefit outweighs any potential harms associated with corticosteroid use.

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

Moderate

In patients with severe or critical illness, certainty of the evidence is moderate for all-cause mortality and serious adverse events (due to serious inconsistency in direction of effect), mechanical ventilation or death and discharge from hospital (due to serious imprecision).

For adverse events (gastrointestinal bleeding, super infections, hyperglycaemia, neuromuscular weakness and neuropsychiatric effects), evidence is generally low due to serious indirectness (evidence comes from non-COVID-19 patients) and serious imprecision.

Values and preferences

No substantial variability expected

We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that since there are mortality benefits most informed patients would agree with the recommendation and opt for corticosteroids.

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

No important issues with the recommended alternative

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

Equity

No important issues with the recommended alternative

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

Acceptability

No important issues with the recommended alternative

Although we have no systematically collected evidence regarding acceptability, corticosteroids are 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

No important issues with the recommended alternative

Intravenous dexamethasone (Pfizer Australia Pty Ltd; Alphapharm Pty Ltd) is listed in the Australian Register of Therapeutic Goods for the treatment of non-COVID related conditions (ARTG numbers 178774, 16374, 163200; (AusPAR). As of 3 December 2021, dexamethasone is yet to be awarded provisional determination by the Therapeutic Goods Administration for the treatment of COVID-19.

Corticosteroids are likely to be feasible because they are already widely used for other indications. There are no known issues with availability of these drugs.

Rationale

Due to a reduction in death, along with no important resource implications and the likely acceptability of these drugs, we recommend corticosteroids for adults with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

Clinical Question/ PICO

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

Summary

Evidence indicates that corticosteroids reduce deaths in patients with critical or severe COVID-19, but may increase deaths in patients with moderate COVID-19.

What is the evidence informing this recommendation?
Evidence comes from a meta-analysis and associated living guidance *[27]* of seven randomised trials of patients with critical COVID-19 *[31][32][33][34][36][37][315]*, one study of patients with moderate, severe or critical COVID-19 *[38]*, and one study of patients with severe COVID-19 *[39]*. Over 5700 patients are included in the meta-analysis. All trials compared corticosteroids plus standard care with standard care alone.

In addition, two meta-analyses of corticosteroids for other conditions—other coronavirus infections, influenza, community-acquired pneumonia, acute respiratory distress *[28]* and sepsis *[29]*—provided indirect evidence for serious adverse events.

We have found three new studies comparing corticosteroids with standard care (Corral-Gudino et al. (GLUCOCOVID) Wien Klin Wochenschr doi: 10.1007/s00508-020-01805-8, Tang et al. Respiration doi: 10.1159/000512063 and Jamaati et al. Eur J Pharmacol doi: 10.1016/j.ejphar.2021.173947). These studies are currently under review and, although not expected to change the recommendation, an updated recommendation will be included in a future version of the guideline.

Study characteristics
Three studies compared dexamethasone with standard care *[34][36][38]*, three compared hydrocortisone with standard care *[31][33][315]* and three compared methylprednisolone with standard care *[32][37][39]*.

Disease severity was reported independently for each trial. Definitions included patients who required mechanical ventilation or non-invasive ventilation, PaO2/FiO2 < 200, positive end-expiratory pressure (PEEP) ≥ 5 cmH2O, and the presence of pneumonia or infiltrates on chest imaging.

Mean or median age ranged from 57 to 67 years in the corticosteroid groups and from 60 to 66 years in the standard care groups. The proportion of women was 32% (range 13% to 43%) in the corticosteroid groups and 29% (range 21% to 36%) in the standard care groups.

What are the main results?
Compared with standard care, corticosteroids probably reduce death in patients with severe and critical COVID-19. For every 1000 patients given corticosteroids, 51 more are likely to survive compared with those receiving standard care (RR 0.84 CI 95% 0.73 to 0.98; 5789 patients in 9 studies). Corticosteroids in patients requiring oxygen also probably reduce the composite outcome of requirement for invasive mechanical ventilation or death, and time to discharge from hospital.

In patients who do not require oxygen, corticosteroids probably increase death (RR 1.27 CI 95% 1.00 to 1.61; 1535 patients in 1 study) and the composite outcome of invasive mechanical ventilation or death.

Indirect evidence of corticosteroid use in patients with other, similar indications possibly shows no difference in the incidence of gastrointestinal bleeding, super infections, neuromuscular weakness and neuropsychiatric effects. However, corticosteroid use was probably associated with an increase in hyperglycaemia (RR 1.16 CI 95% 1.08 to 1.25; 8938 patients in 8 studies).

Our confidence in the results
In patients with severe or critical illness, certainty of the evidence is moderate for all-cause mortality and serious adverse events (due to serious inconsistency in direction of effect) and invasive mechanical ventilation or death, and discharge from hospital (due to serious imprecision).

In patients with moderate illness, certainty is low for all outcomes (all-cause mortality, invasive mechanical ventilation or death and discharge from hospital) due to very serious imprecision (reliance on a single study and wide confidence intervals).

For adverse events (gastrointestinal bleeding, super infections, hyperglycaemia, neuromuscular weakness and neuropsychiatric effects), certainty is low due to serious indirectness (evidence from non-COVID-19 patients) and serious imprecision.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality [adults requiring oxygen] Within 28 days of commencing treatment 9 Critical	Relative risk 0.84 (CI 95% 0.73 — 0.98) Based on data from 5,789 participants in 9 studies. [1] (Randomized controlled)	316 per 1000 Difference:	265 per 1000 **51 fewer per 1000** (CI 95% 85 fewer — 6 fewer)	**Moderate** Due to some inconsistency [2]	Corticosteroids probably decrease death at day 28 in adults who require oxygen.
Serious adverse events [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 0.8 (CI 95% 0.53 — 1.19) Based on data from 696 participants in 6 studies. [3] (Randomized controlled)	234 per 1000 Difference:	187 per 1000 **47 fewer per 1000** (CI 95% 110 fewer — 44 more)	**Moderate** Due to serious inconsistency [4]	Corticosteroids probably have little impact on serious adverse events in adults who require oxygen.
Invasive mechanical ventilation or death [adults requiring oxygen] [5] Within 28 days of commencing treatment 9 Critical	Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 participants in 1 studies. [6] (Randomized controlled)	320 per 1000 Difference:	282 per 1000 **38 fewer per 1000** (CI 95% 67 fewer — 10 fewer)	**Moderate** Due to only one study [7]	Corticosteroids probably decrease invasive mechanical ventilation or death in adults who require oxygen.
Discharge from hospital [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 participants in 2 studies. [8] (Randomized controlled)	582 per 1000 Difference:	640 per 1000 **58 more per 1000** (CI 95% 35 more — 87 more)	**Moderate** Due to serious inconsistency [9]	Corticosteroids probably increases discharge from hospital in adults who require oxygen.
All-cause mortality [adults not requiring oxygen] Within 28 days of commencing treatment	Relative risk 1.27 (CI 95% 1 — 1.61) Based on data from 1,535 participants in 1 studies. [10] (Randomized controlled)	140 per 1000 Difference:	178 per 1000 **38 more per 1000** (CI 95% 0 fewer — 85 more)	**Moderate** Due to only one study [11]	Corticosteroids probably increase death in adults who do not require oxygen.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical					
Invasive mechanical ventilation or death [adults not requiring oxygen] Within 28 days of commencing treatment	Relative risk 1.25 (CI 95% 1 — 1.57) Based on data from 1,535 participants in 1 studies. [12] (Randomized controlled)	155 per 1000 Difference:	194 per 1000 **39 more per 1000** (CI 95% 0 fewer — 88 more)	**Moderate** Due to only one study [13]	Corticosteroids probably increase invasive mechanical ventilation or death in adults who do not require oxygen.
9 Critical					
Discharge from hospital [adults not requiring oxygen] Within 28 days of commencing treatment	Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 participants in 1 studies. [14] (Randomized controlled)	804 per 1000 Difference:	772 per 1000 **32 fewer per 1000** (CI 95% 80 fewer — 8 more)	**Moderate** Due to only one study [15]	Corticosteroids may have little impact on discharge from hospital in adults who do not require oxygen.
6 Important					
Gastrointestinal bleeding End of treatment	Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5,403 participants in 30 studies. [16]	48 per 1000 Difference:	51 per 1000 **3 more per 1000** (CI 95% 7 fewer — 16 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on gastrointestinal bleeding.
6 Important					
Super infections End of treatment	Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 participants in 32 studies. [17]	186 per 1000 Difference:	188 per 1000 **2 more per 1000** (CI 95% 19 fewer — 24 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on number of patients with super infections.
6 Important					
Hyperglycaemia End of treatment	Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 participants in 24 studies. [18]	286 per 1000 Difference:	332 per 1000 **46 more per 1000** (CI 95% 23 more — 72 more)	**Moderate** Due to serious indirectness	Corticosteroids probably increase the risk of hyperglycaemia.
Neuromuscular	Relative risk 1.09 (CI 95% 0.86 — 1.39)	69	75	**Low**	Corticosteroids may have little impact on

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
weakness End of treatment 6 Important	Based on data from 6,358 participants in 8 studies. [19]	per 1000 Difference:	per 1000 **6 more per 1000** (CI 95% 10 fewer — 27 more)	Due to serious indirectness and imprecision	neuromuscular weakness.
Neuropsychiatric effects End of treatment 6 Important	Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 participants in 7 studies. [20]	35 per 1000 Difference:	28 per 1000 **7 fewer per 1000** (CI 95% 21 fewer — 22 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuropsychiatric effects.

Attached Images

Conditional recommendation against

Do not routinely use dexamethasone (or other systemic corticosteroid) to treat COVID-19 in **adults who do not require oxygen**.

Additional information

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

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Important harms

In patients who do not require oxygen, death and risk of hypoglycaemia may be higher with dexamethasone and other corticosteroids.

Certainty of the Evidence

Low

In patients who do not require oxygen, certainty of the evidence is moderate for all outcomes (death, mechanical ventilation or death, and discharge from hospital) due to serious imprecision (reliance on a single study).

For adverse events (gastrointestinal bleeding, super infections, hyperglycaemia, neuromuscular weakness and neuropsychiatric effects), evidence is generally low due to serious indirectness (evidence comes from non-COVID-19 patients) and serious imprecision.

Values and preferences

We expect few to want the intervention

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

Based on the available evidence, the Consumer Panel believes that informed patients would not agree to this treatment for COVID-19.

Resources

No important issues with the recommended alternative

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

Equity

No important issues with the recommended alternative

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

Acceptability

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding acceptability.

Feasibility

No important issues with the recommended alternative

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

Rationale

Evidence suggests that dexamethasone in patients with COVID-19 who do not require oxygen may increase the risk of death. We therefore recommend against dexamethasone and other corticosteroids in this population unless there is an alternative evidence-based indication for its use.

Clinical Question/ PICO

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

Summary

Evidence indicates that corticosteroids reduce deaths in patients with critical or severe COVID-19, but may increase deaths in patients with moderate COVID-19.

What is the evidence informing this recommendation?
Evidence comes from a meta-analysis and associated living guidance *[27]* of seven randomised trials of patients with critical COVID-19 *[31][32][33][34][36][37][315]*, one study of patients with moderate, severe or critical COVID-19 *[38]*, and one study of patients with severe COVID-19 *[39]*. Over 5700 patients are included in the meta-analysis. All trials compared corticosteroids plus standard care with standard care alone.

In addition, two meta-analyses of corticosteroids for other conditions—other coronavirus infections, influenza, community-acquired pneumonia, acute respiratory distress *[28]* and sepsis *[29]*—provided indirect evidence for serious adverse events.

We have found three new studies comparing corticosteroids with standard care (Corral-Gudino et al. (GLUCOCOVID) Wien Klin Wochenschr doi: 10.1007/s00508-020-01805-8, Tang et al. Respiration doi: 10.1159/000512063 and Jamaati et al. Eur J Pharmacol doi: 10.1016/j.ejphar.2021.173947). These studies are currently under review and, although not expected to change the recommendation, an updated recommendation will be included in a future version of the guideline.

Study characteristics
Three studies compared dexamethasone with standard care *[34][36][38]*, three compared hydrocortisone with standard care *[31][33][315]* and three compared methylprednisolone with standard care *[32][37][39]*.

Disease severity was reported independently for each trial. Definitions included patients who required mechanical ventilation or non-invasive ventilation, PaO2/FiO2 < 200, positive end-expiratory pressure (PEEP) ≥ 5 cmH2O, and the presence of pneumonia or infiltrates on chest imaging.

Mean or median age ranged from 57 to 67 years in the corticosteroid groups and from 60 to 66 years in the standard care groups. The proportion of women was 32% (range 13% to 43%) in the corticosteroid groups and 29% (range 21% to 36%) in the standard care groups.

What are the main results?
Compared with standard care, corticosteroids probably reduce death in patients with severe and critical COVID-19. For every 1000 patients given corticosteroids, 51 more are likely to survive compared with those receiving standard care (RR 0.84 CI 95% 0.73 to 0.98; 5789 patients in 9 studies). Corticosteroids in patients requiring oxygen also probably reduce the composite outcome of requirement for invasive mechanical ventilation or death, and time to discharge from hospital.

In patients who do not require oxygen, corticosteroids probably increase death (RR 1.27 CI 95% 1.00 to 1.61; 1535 patients in 1 study) and the composite outcome of invasive mechanical ventilation or death.

Indirect evidence of corticosteroid use in patients with other, similar indications possibly shows no difference in the incidence of gastrointestinal bleeding, super infections, neuromuscular weakness and neuropsychiatric effects. However, corticosteroid use was probably associated with an increase in hyperglycaemia (RR 1.16 CI 95% 1.08 to 1.25; 8938 patients in 8 studies).

Our confidence in the results
In patients with severe or critical illness, certainty of the evidence is moderate for all-cause mortality and serious adverse events (due to serious inconsistency in direction of effect) and invasive mechanical ventilation or death, and discharge from hospital (due to serious imprecision).

In patients with moderate illness, certainty is low for all outcomes (all-cause mortality, invasive mechanical ventilation or death and discharge from hospital) due to very serious imprecision (reliance on a single study and wide confidence intervals).

For adverse events (gastrointestinal bleeding, super infections, hyperglycaemia, neuromuscular weakness and neuropsychiatric effects), certainty is low due to serious indirectness (evidence from non-COVID-19 patients) and serious imprecision.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality [adults requiring oxygen] Within 28 days of commencing treatment 9 Critical	Relative risk 0.84 (CI 95% 0.73 — 0.98) Based on data from 5,789 participants in 9 studies. [1] (Randomized controlled)	316 per 1000 Difference:	265 per 1000 **51 fewer per 1000** (CI 95% 85 fewer — 6 fewer)	**Moderate** Due to some inconsistency [2]	Corticosteroids probably decrease death at day 28 in adults who require oxygen.
Serious adverse events	Relative risk 0.8 (CI 95% 0.53 — 1.19)	234	187	**Moderate** Due to serious	Corticosteroids probably have little

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
[adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Based on data from 696 participants in 6 studies. [3] (Randomized controlled)	per 1000 Difference:	per 1000 **47 fewer per 1000** (CI 95% 110 fewer — 44 more)	inconsistency [4]	impact on serious adverse events in adults who require oxygen.
Invasive mechanical ventilation or death [adults requiring oxygen] [5] Within 28 days of commencing treatment 9 Critical	Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 participants in 1 studies. [6] (Randomized controlled)	320 per 1000 Difference:	282 per 1000 **38 fewer per 1000** (CI 95% 67 fewer — 10 fewer)	**Moderate** Due to only one study [7]	Corticosteroids probably decrease invasive mechanical ventilation or death in adults who require oxygen.
Discharge from hospital [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 participants in 2 studies. [8] (Randomized controlled)	582 per 1000 Difference:	640 per 1000 **58 more per 1000** (CI 95% 35 more — 87 more)	**Moderate** Due to serious inconsistency [9]	Corticosteroids probably increases discharge from hospital in adults who require oxygen.
All-cause mortality [adults not requiring oxygen] Within 28 days of commencing treatment 9 Critical	Relative risk 1.27 (CI 95% 1 — 1.61) Based on data from 1,535 participants in 1 studies. [10] (Randomized controlled)	140 per 1000 Difference:	178 per 1000 **38 more per 1000** (CI 95% 0 fewer — 85 more)	**Moderate** Due to only one study [11]	Corticosteroids probably increase death in adults who do not require oxygen.
Invasive mechanical ventilation or death [adults not requiring oxygen] Within 28 days of commencing treatment	Relative risk 1.25 (CI 95% 1 — 1.57) Based on data from 1,535 participants in 1 studies. [12] (Randomized controlled)	155 per 1000 Difference:	194 per 1000 **39 more per 1000** (CI 95% 0 fewer — 88 more)	**Moderate** Due to only one study [13]	Corticosteroids probably increase invasive mechanical ventilation or death in adults who do not require oxygen.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical					
Discharge from hospital [adults not requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 participants in 1 studies. [14] (Randomized controlled)	804 per 1000 Difference:	772 per 1000 **32 fewer per 1000** (CI 95% 80 fewer — 8 more)	**Moderate** Due to only one study [15]	Corticosteroids may have little impact on discharge from hospital in adults who do not require oxygen.
Gastrointestinal bleeding End of treatment 6 Important	Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5,403 participants in 30 studies. [16]	48 per 1000 Difference:	51 per 1000 **3 more per 1000** (CI 95% 7 fewer — 16 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on gastrointestinal bleeding.
Super infections End of treatment 6 Important	Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 participants in 32 studies. [17]	186 per 1000 Difference:	188 per 1000 **2 more per 1000** (CI 95% 19 fewer — 24 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on number of patients with super infections.
Hyperglycaemia End of treatment 6 Important	Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 participants in 24 studies. [18]	286 per 1000 Difference:	332 per 1000 **46 more per 1000** (CI 95% 23 more — 72 more)	**Moderate** Due to serious indirectness	Corticosteroids probably increase the risk of hyperglycaemia.
Neuromuscular weakness End of treatment 6 Important	Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 participants in 8 studies. [19]	69 per 1000 Difference:	75 per 1000 **6 more per 1000** (CI 95% 10 fewer — 27 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuromuscular weakness.
Neuropsychiatric effects End of treatment 6 Important	Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 participants in 7 studies. [20]	35 per 1000 Difference:	28 per 1000 **7 fewer per 1000**	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuropsychiatric effects.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
			(CI 95% 21 fewer — 22 more)		

Attached Images

7.1.3.2 Corticosteroids (systemic) for pregnant or breastfeeding women

Recommended

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

If steroids are indicated for fetal lung maturity in women at risk of preterm birth, a standard antenatal corticosteroid regimen should be used (e.g. intramuscular dexamethasone 6 mg every 12 hours for four doses), followed by 6 mg dexamethasone daily until 10 days has been reached.

If steroids are not indicated for fetal lung maturity, use dexamethasone 6 mg daily intravenously or orally for up to 10 days.

Additional information

The suggested regimen of corticosteroid use is 6 mg of dexamethasone (oral or intravenous) daily for up to 10 days. In patients for whom dexamethasone is not available, acceptable alternative regimens include:

- *hydrocortisone: intravenous (50 mg), every 6 hours for up to 10 days*
- *prednisolone: oral (50 mg), daily for up to 10 days*

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

In patients receiving oxygen or invasive mechanical ventilation, death is reduced with dexamethasone. Although indirect evidence suggests that corticosteroids may increase the risk of hyperglycaemia, the panel believes the mortality benefit outweighs any potential harms associated with corticosteroid use.

Dexamethasone is used for other clinical indications during pregnancy and is considered safe to use when indicated.

Certainty of the Evidence

Low

In patients with severe or critical illness, certainty of the evidence is low for all-cause mortality and serious adverse events (due to serious inconsistency in direction of effect and serious indirectness), mechanical ventilation or death and discharge from hospital (due to serious imprecision and serious indirectness).

For adverse events (gastrointestinal bleeding, super infections, hyperglycaemia, neuromuscular weakness and neuropsychiatric effects), evidence is generally low due to serious indirectness (evidence comes from non-COVID-19 patients) and serious imprecision.

Values and preferences

No substantial variability expected

We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women. The Consumer Panel believes that since there are mortality benefits most informed pregnant or breastfeeding women would agree with the recommendation and opt for corticosteroids.

Resources

No important issues with the recommended alternative

Corticosteroids are widely available and affordable. Use of corticosteroids in pregnant and breastfeeding women

with COVID-19 who are receiving supplementary oxygen or invasive ventilation is unlikely to have an impact on availability of these drugs for other indications.

Equity

No important issues with the recommended alternative

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

Acceptability

No important issues with the recommended alternative

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

Feasibility

No important issues with the recommended alternative

Intravenous dexamethasone (Pfizer Australia Pty Ltd; Alphapharm Pty Ltd) is listed in the Australian Register of Therapeutic Goods for the treatment of non-COVID related conditions (ARTG numbers 178774, 16374, 163200; (AusPAR). As of 3 December 2021, dexamethasone is yet to be awarded provisional determination by the Therapeutic Goods Administration for the treatment of COVID-19.

Corticosteroids are likely to be feasible because they are already widely used for other indications. There are no known issues with availability of these drugs.

Rationale

Due to a reduction in death, along with no important resource implications, and the likely acceptability of corticosteroids and applicability of the evidence to pregnant and breastfeeding women, we recommend corticosteroids for pregnant and breastfeeding women with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

The recommended corticosteroid regimen (dexamethasone 6 mg daily intravenously or orally) reflects the regimen used in the RECOVERY trial, which is the largest trial available and demonstrated a significant reduction in all-cause mortality. The acceptable alternative regimens (hydrocortisone, prednisolone) were informed by the range of corticosteroid regimens used in other available trials, as well as a pharmacological assessment to ensure that an alternative regimen has equivalent bioavailability.

Clinical Question/ PICO

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

Summary

Evidence indicates that corticosteroids reduce deaths in patients with critical or severe COVID-19, but may increase deaths in patients with moderate COVID-19.

What is the evidence informing this recommendation?
Evidence comes from a meta-analysis and associated living guidance *[27]* of seven randomised trials of patients with critical COVID-19 *[31][32][33][34][36][37][315]*, one study of patients with moderate, severe and critical COVID-19 *[38]* and one study of patients with severe COVID-19 *[39]*. Over 5700 patients are included in the meta-analysis. All trials compared corticosteroids plus standard care with standard care alone.

In addition, two meta-analyses of corticosteroids for other conditions—other coronavirus infections, influenza, community-acquired pneumonia, acute respiratory distress *[28]* and sepsis *[29]*—provided indirect evidence for serious adverse events.

Study characteristics
Three studies compared dexamethasone with standard care *[34][36][38]*, three compared hydrocortisone with standard care *[31][33][315]* and three compared methylprednisolone with standard care *[32][37][39]*.

Disease severity was reported independently for each trial. Definitions included patients who required mechanical ventilation or non-invasive ventilation (NIV), PaO2/FiO2 < 200, positive end-expiratory pressure (PEEP) ≥ 5 cmH2O, and the presence of pneumonia or infiltrates on chest imaging.

Mean or median age ranged from 57 to 67 years in the corticosteroid groups and from 60 to 66 years in the standard care groups. The proportion of women was 32% (range 13% to 43%) in the corticosteroid groups and 29% (range 21% to 36%) in the standard care groups.

What are the main results?
Compared with standard care, corticosteroids probably reduce death in patients with severe and critical COVID-19. For every 1000 patients given corticosteroids, 51 more are likely to survive compared with those receiving standard care (RR 0.84 CI 95% 0.73 to 0.98; 5789 patients in 9 studies). Corticosteroids in patients requiring oxygen also probably reduce the composite outcome of requirement for invasive mechanical ventilation or death, and time to discharge from hospital.

In patients who do not require oxygen, corticosteroids probably increase death (RR 1.27 CI 95% 1.00 to 1.61; 1535 patients in 1 study) and the composite outcome of invasive mechanical ventilation or death.

Indirect evidence of corticosteroid use in patients with other, similar indications shows no difference in the incidence of gastrointestinal bleeding, superinfections, neuromuscular weakness and neuropsychiatric effects. However, corticosteroid use was associated with an increase in hyperglycaemia (RR 1.16 CI 95% 1.08 to 1.25; 8938 patients in 8 studies).

Our confidence in the results
Certainty of the evidence for all outcomes is judged to be low for pregnant and breastfeeding women, and children and adolescents due to serious indirectness. This is in addition to concerns in the adult population about inconsistency in direction of effect and serious imprecision.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality [adults requiring oxygen] Within 28 days of commencing treatment 9 Critical	Relative risk 0.84 (CI 95% 0.73 — 0.98) Based on data from 5,789 participants in 9 studies. [1] (Randomized controlled)	316 per 1000 Difference:	265 per 1000 **51 fewer per 1000** (CI 95% 85 fewer — 6 fewer)	**Low** Due to serious inconsistency and serious indirectness [2]	Corticosteroids may decrease death at day 28 in patients who require oxygen.
Serious adverse events [adults requiring oxygen] Within 28 days of commencing	Relative risk 0.8 (CI 95% 0.53 — 1.19) Based on data from 696 participants in 6 studies. [3] (Randomized controlled)	234 per 1000 Difference:	187 per 1000 **47 fewer per 1000** (CI 95% 110	**Low** Due to serious inconsistency and indirectness [4]	Corticosteroids may have little impact on serious adverse events in patients who require oxygen.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
treatment 6 Important			fewer — 44 more)		
Invasive mechanical ventilation or death [adults requiring oxygen] [5] Within 28 days after commencing treatment 9 Critical	Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 participants in 1 studies. [6] (Randomized controlled)	**320** per 1000 Difference:	**282** per 1000 **38 fewer per 1000** (CI 95% 67 fewer — 10 fewer)	**Low** Due to only one study and serious indirectness [7]	Corticosteroids may decrease invasive mechanical ventilation or death in patients who require oxygen.
All-cause mortality [adults not requiring oxygen] Within 28 days after commencing treatment 9 Critical	Relative risk 1.27 (CI 95% 1 — 1.61) Based on data from 1,535 participants in 1 studies. [8] (Randomized controlled)	**140** per 1000 Difference:	**178** per 1000 **38 more per 1000** (CI 95% 0 fewer — 85 more)	**Low** Due to only one study and serious indirectness [9]	Corticosteroids may increase death in patients who do not require oxygen.
Invasive mechanical ventilation or death [adults not requiring oxygen] Within 28 days after commencing treatment 9 Critical	Relative risk 1.25 (CI 95% 1 — 1.57) Based on data from 1,535 participants in 1 studies. [10] (Randomized controlled)	**155** per 1000 Difference:	**194** per 1000 **39 more per 1000** (CI 95% 0 fewer — 88 more)	**Low** Due to only one study and serious indirectness [11]	Corticosteroids may increase invasive mechanical ventilation or death in patients who do not require oxygen.
Discharge from hospital [adults not requiring oxygen] Within 28 days after commencing treatment 6 Important	Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 participants in 1 studies. [12] (Randomized controlled)	**804** per 1000 Difference:	**772** per 1000 **32 fewer per 1000** (CI 95% 80 fewer — 8 more)	**Low** Due to only one study and serious indirectness [13]	Corticosteroids may have little impact on discharge from hospital in patients who do not require oxygen.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Gastrointestinal bleeding End of treatment 6 Important	Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5,403 participants in 30 studies. [14]	48 per 1000 Difference:	51 per 1000 **3 more per 1000** (CI 95% 7 fewer — 16 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on gastrointestinal bleeding.
Super infections End of treatment 6 Important	Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 participants in 32 studies. [15]	186 per 1000 Difference:	188 per 1000 **2 more per 1000** (CI 95% 19 fewer — 24 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on number of patients with super infections.
Hyperglycaemia End of treatment 6 Important	Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 participants in 24 studies. [16]	286 per 1000 Difference:	332 per 1000 **46 more per 1000** (CI 95% 23 more — 72 more)	**Moderate** Due to serious indirectness	Corticosteroids probably increase the risk of hyperglycaemia.
Neuromuscular weakness End of treatment 6 Important	Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 participants in 8 studies. [17]	69 per 1000 Difference:	75 per 1000 **6 more per 1000** (CI 95% 10 fewer — 27 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuromuscular weakness.
Neuropsychiatric effects End of treatment 6 Important	Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 participants in 7 studies. [18]	35 per 1000 Difference:	28 per 1000 **7 fewer per 1000** (CI 95% 21 fewer — 22 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuropsychiatric effects.
Discharge from hospital [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 participants in 2 studies. [19] (Randomized controlled)	582 per 1000 Difference:	640 per 1000 **58 more per 1000** (CI 95% 35 more — 87 more)	**Low** Due to serious inconsistency and serious indirectness [20]	Corticosteroids may increase discharge from hospital in patients who require oxygen.

Attached Images

Conditional recommendation against

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

Additional information

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

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Important harms

In pregnant or breastfeeding women who do not require oxygen, there may be more deaths with dexamethasone and other corticosteroids.

Certainty of the Evidence

Low

In pregnant or breastfeeding women who do not require oxygen, certainty of the evidence is judged to be low for all outcomes (mortality, mechanical ventilation or death, and discharge from hospital) due to serious imprecision (reliance on a single study and wide confidence intervals) and serious indirectness (results based on the general adult population).

For adverse events (gastrointestinal bleeding, super infections, hyperglycaemia, neuromuscular weakness and neuropsychiatric effects), evidence is generally low due to serious indirectness (evidence comes from non-COVID-19 patients) and serious imprecision.

Values and preferences

We expect few to want the intervention

We have no systematically collected information regarding preferences and values of pregnant or breastfeeding women. The Consumer Panel believes that most informed pregnant or breastfeeding women may prefer to wait until the available evidence is clearer, and would not agree to this treatment for COVID-19.

Resources

No important issues with the recommended alternative

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

Equity

No important issues with the recommended alternative

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

Acceptability

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding acceptability.

Feasibility No important issues with the recommended alternative

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 death. We therefore recommend against dexamethasone and other corticosteroids in this population unless there is an alternative evidence-based indication for their use.

Clinical Question/ PICO

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

Summary

Evidence indicates that corticosteroids reduce deaths in patients with critical or severe COVID-19, but may increase deaths in patients with moderate COVID-19.

What is the evidence informing this recommendation?
Evidence comes from a meta-analysis and associated living guidance *[27]* of seven randomised trials of patients with critical COVID-19 *[31][32][33][34][36][37][315]*, one study of patients with moderate, severe and critical COVID-19 *[38]* and one study of patients with severe COVID-19 *[39]*. Over 5700 patients are included in the meta-analysis. All trials compared corticosteroids plus standard care with standard care alone.

In addition, two meta-analyses of corticosteroids for other conditions—other coronavirus infections, influenza, community-acquired pneumonia, acute respiratory distress *[28]* and sepsis *[29]*—provided indirect evidence for serious adverse events.

Study characteristics
Three studies compared dexamethasone with standard care *[34][36][38]*, three compared hydrocortisone with standard care *[31][33][315]* and three compared methylprednisolone with standard care *[32][37][39]*.

Disease severity was reported independently for each trial. Definitions included patients who required mechanical ventilation or non-invasive ventilation (NIV), PaO2/FiO2 < 200, positive end-expiratory pressure (PEEP) ≥ 5 cmH2O, and the presence of pneumonia or infiltrates on chest imaging.

Mean or median age ranged from 57 to 67 years in the corticosteroid groups and from 60 to 66 years in the standard care groups. The proportion of women was 32% (range 13% to 43%) in the corticosteroid groups and 29% (range 21% to 36%) in the standard care groups.

What are the main results?
Compared with standard care, corticosteroids probably reduce death in patients with severe and critical COVID-19. For every 1000 patients given corticosteroids, 51 more are likely to survive compared with those receiving standard care (RR 0.84 CI 95% 0.73 to 0.98; 5789 patients in 9 studies). Corticosteroids in patients requiring oxygen also probably reduce the composite outcome of requirement for invasive mechanical ventilation or death, and time to discharge from hospital.

In patients who do not require oxygen, corticosteroids probably increase death (RR 1.27 CI 95% 1.00 to 1.61; 1535 patients in 1 study) and the composite outcome of invasive mechanical ventilation or death.

Indirect evidence of corticosteroid use in patients with other, similar indications shows no difference in the incidence of gastrointestinal bleeding, superinfections, neuromuscular weakness and neuropsychiatric effects. However, corticosteroid use was associated with an increase in hyperglycaemia (RR 1.16 CI 95% 1.08 to 1.25; 8938 patients in 8 studies).

Our confidence in the results
Certainty of the evidence for all outcomes is judged to be low for pregnant and breastfeeding women, and children and adolescents due to serious indirectness. This is in addition to concerns in the adult population about inconsistency in direction of effect and serious imprecision.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality [adults requiring oxygen] Within 28 days of commencing treatment 9 Critical	Relative risk 0.84 (CI 95% 0.73 — 0.98) Based on data from 5,789 participants in 9 studies. [1] (Randomized controlled)	316 per 1000 Difference:	265 per 1000 **51 fewer per 1000** (CI 95% 85 fewer — 6 fewer)	**Low** Due to serious inconsistency and serious indirectness [2]	Corticosteroids may decrease death at day 28 in patients who require oxygen.
Serious adverse events [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 0.8 (CI 95% 0.53 — 1.19) Based on data from 696 participants in 6 studies. [3] (Randomized controlled)	234 per 1000 Difference:	187 per 1000 **47 fewer per 1000** (CI 95% 110 fewer — 44 more)	**Low** Due to serious inconsistency and indirectness [4]	Corticosteroids may have little impact on serious adverse events in patients who require oxygen.
Invasive mechanical ventilation or death [adults requiring oxygen] [5] Within 28 days after commencing treatment 9 Critical	Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 participants in 1 studies. [6] (Randomized controlled)	320 per 1000 Difference:	282 per 1000 **38 fewer per 1000** (CI 95% 67 fewer — 10 fewer)	**Low** Due to only one study and serious indirectness [7]	Corticosteroids may decrease invasive mechanical ventilation or death in patients who require oxygen.
All-cause mortality [adults not requiring oxygen] Within 28 days after commencing treatment 9 Critical	Relative risk 1.27 (CI 95% 1 — 1.61) Based on data from 1,535 participants in 1 studies. [8] (Randomized controlled)	140 per 1000 Difference:	178 per 1000 **38 more per 1000** (CI 95% 0 fewer — 85 more)	**Low** Due to only one study and serious indirectness [9]	Corticosteroids may increase death in patients who do not require oxygen.
Invasive mechanical ventilation or death [adults not requiring	Relative risk 1.25 (CI 95% 1 — 1.57) Based on data from 1,535 participants in 1 studies. [10]	155 per 1000 Difference:	194 per 1000 **39 more per 1000**	**Low** Due to only one study and serious indirectness [11]	Corticosteroids may increase invasive mechanical ventilation or death in patients who do not require oxygen.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
oxygen] Within 28 days after commencing treatment 9 Critical	(Randomized controlled)		(CI 95% 0 fewer — 88 more)		
Discharge from hospital [adults not requiring oxygen] Within 28 days after commencing treatment 6 Important	Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 participants in 1 studies. [12] (Randomized controlled)	804 per 1000 Difference:	772 per 1000 **32 fewer per 1000** (CI 95% 80 fewer — 8 more)	**Low** Due to only one study and serious indirectness [13]	Corticosteroids may have little impact on discharge from hospital in patients who do not require oxygen.
Gastrointestinal bleeding End of treatment 6 Important	Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5,403 participants in 30 studies. [14]	48 per 1000 Difference:	51 per 1000 **3 more per 1000** (CI 95% 7 fewer — 16 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on gastrointestinal bleeding.
Super infections End of treatment 6 Important	Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 participants in 32 studies. [15]	186 per 1000 Difference:	188 per 1000 **2 more per 1000** (CI 95% 19 fewer — 24 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on number of patients with super infections.
Hyperglycaemia End of treatment 6 Important	Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 participants in 24 studies. [16]	286 per 1000 Difference:	332 per 1000 **46 more per 1000** (CI 95% 23 more — 72 more)	**Moderate** Due to serious indirectness	Corticosteroids probably increase the risk of hyperglycaemia.
Neuromuscular weakness End of treatment 6 Important	Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 participants in 8 studies. [17]	69 per 1000 Difference:	75 per 1000 **6 more per 1000** (CI 95% 10 fewer — 27 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuromuscular weakness.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Neuropsychiatric effects End of treatment 6 Important	Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 participants in 7 studies. [18]	35 per 1000 Difference:	28 per 1000 **7 fewer per 1000** (CI 95% 21 fewer — 22 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuropsychiatric effects.
Discharge from hospital [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 participants in 2 studies. [19] (Randomized controlled)	582 per 1000 Difference:	640 per 1000 **58 more per 1000** (CI 95% 35 more — 87 more)	**Low** Due to serious inconsistency and serious indirectness [20]	Corticosteroids may increase discharge from hospital in patients who require oxygen.

Attached Images

7.1.3.3 Corticosteroids (systemic) for children and adolescents

Conditional recommendation

Consider using dexamethasone daily intravenously or orally for up to 10 days (or acceptable alternative regimen) in **children and adolescents with acute COVID-19 who require oxygen** (including mechanically ventilated patients).

Additional information

A dose of 6 mg daily is recommended in adults. The RECOVERY trial protocol stated a dose of 0.15 mg/kg/day to a maximum of 6 mg/day for children but it is unclear whether any children were included in the trial. If dexamethasone is not available, an acceptable alternative regimen would be:

- *hydrocortisone: intravenous or intramuscular 1 mg/kg/dose, every 6 hours for up to 10 days (to a maximum dose of 50 mg every 6 hours)*
- *methylprednisolone may also be an acceptable alternative, however the most appropriate dosage is uncertain*

For specific recommendations on the use of corticosteroids for PIMS-TS see section.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

In patients receiving oxygen or invasive mechanical ventilation, death is reduced with corticosteroids. Although indirect evidence suggests that corticosteroids may increase the risk of hypoglycaemia, the panel believes the mortality benefit outweighs any potential harms associated with corticosteroid use.

Certainty of the Evidence

Low

In patients with severe or critical illness, certainty of the evidence is low for all-cause mortality and serious adverse events (due to serious inconsistency in direction of effect and serious indirectness), mechanical ventilation or death, and discharge from hospital (due to serious imprecision and serious indirectness).

For adverse events (gastrointestinal bleeding, super infections, hyperglycaemia, neuromuscular weakness and neuropsychiatric effects), evidence is generally low due to serious indirectness (evidence comes from non-COVID-19 patients) and serious imprecision.

Values and preferences

No substantial variability expected

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

The Consumer Panel believes that some informed patients (and their parents, carers, families or guardians) may prefer to wait until the available evidence is clearer, but most informed patients (and their parents, carers, families or guardians) would agree to this treatment for COVID-19.

Resources

No important issues with the recommended alternative

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

Equity

No important issues with the recommended alternative

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

Acceptability

No important issues with the recommended alternative

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

Feasibility

No important issues with the recommended alternative

Intravenous dexamethasone (Pfizer Australia Pty Ltd; Alphapharm Pty Ltd) is listed in the Australian Register of Therapeutic Goods for the treatment of non-COVID related conditions (ARTG numbers 178774, 16374, 163200; (AusPAR). As of 3 December 2021, dexamethasone is yet to be awarded provisional determination by the Therapeutic Goods Administration for the treatment of COVID-19.

Corticosteroids are likely to be feasible because they are already widely used for other indications. There are no known issues with availability of these drugs.

Rationale

Due to a reduction in death, along with no important resource implications and the likely acceptability of these drugs, we recommend considering using corticosteroids in children and adolescents 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: Corticosteroids
Comparator: Standard care

Summary

Evidence indicates that corticosteroids reduce deaths in patients with critical or severe COVID-19, but may increase deaths in patients with moderate COVID-19.

What is the evidence informing this recommendation?
Evidence comes from a meta-analysis and associated living guidance *[27]* of seven randomised trials of patients with critical COVID-19 *[31][32][33][34][36][37][315]*, one study of patients with moderate, severe and critical COVID-19 *[38]* and one study of patients with severe COVID-19 *[39]*. Over 5700 patients are included in the meta-analysis. All trials compared corticosteroids plus standard care with standard care alone.

In addition, two meta-analyses of corticosteroids for other conditions—other coronavirus infections, influenza, community-acquired pneumonia, acute respiratory distress *[28]* and sepsis *[29]*—provided indirect evidence for serious adverse events.

Study characteristics
Three studies compared dexamethasone with standard care *[34][36][38]*, three compared hydrocortisone with standard care *[31][33][315]* and three compared methylprednisolone with standard care *[32][37][39]*.

Disease severity was reported independently for each trial. Definitions included patients who required mechanical ventilation or non-invasive ventilation (NIV), PaO2/FiO2 < 200, positive end-expiratory pressure (PEEP) ≥ 5 cmH2O, and the presence of pneumonia or infiltrates on chest imaging.

Mean or median age ranged from 57 to 67 years in the corticosteroid groups and from 60 to 66 years in the standard care groups. The proportion of women was 32% (range 13% to 43%) in the corticosteroid groups and

29% (range 21% to 36%) in the standard care groups.

What are the main results?
Compared with standard care, corticosteroids probably reduce death in patients with severe and critical COVID-19. For every 1000 patients given corticosteroids, 51 more are likely to survive compared with those receiving standard care (RR 0.84 CI 95% 0.73 to 0.98; 5789 patients in 9 studies). Corticosteroids in patients requiring oxygen also probably reduce the composite outcome of requirement for invasive mechanical ventilation or death, and time to discharge from hospital.

In patients who do not require oxygen, corticosteroids probably increase death (RR 1.27 CI 95% 1.00 to 1.61; 1535 patients in 1 study) and the composite outcome of invasive mechanical ventilation or death.

Indirect evidence of corticosteroid use in patients with other, similar indications shows no difference in the incidence of gastrointestinal bleeding, superinfections, neuromuscular weakness and neuropsychiatric effects. However, corticosteroid use was associated with an increase in hyperglycaemia (RR 1.16 CI 95% 1.08 to 1.25; 8938 patients in 8 studies).

Our confidence in the results
Certainty of the evidence for all outcomes is judged to be low for pregnant and breastfeeding women, and children and adolescents due to serious indirectness. This is in addition to concerns in the adult population about inconsistency in direction of effect and serious imprecision.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality [adults requiring oxygen] Within 28 days of commencing treatment 9 Critical	Relative risk 0.84 (CI 95% 0.73 — 0.98) Based on data from 5,789 participants in 9 studies. [1] (Randomized controlled)	**316** per 1000 Difference:	**265** per 1000 **51 fewer per 1000** (CI 95% 85 fewer — 6 fewer)	**Low** Due to serious inconsistency and serious indirectness [2]	Corticosteroids may decrease death at day 28 in patients who require oxygen.
Serious adverse events [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 0.8 (CI 95% 0.53 — 1.19) Based on data from 696 participants in 6 studies. [3] (Randomized controlled)	**234** per 1000 Difference:	**187** per 1000 **47 fewer per 1000** (CI 95% 110 fewer — 44 more)	**Low** Due to serious inconsistency and indirectness [4]	Corticosteroids may have little impact on serious adverse events in patients who require oxygen.
Invasive mechanical ventilation or death [adults requiring oxygen] [5] Within 28 days after	Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 participants in 1 studies. [6] (Randomized controlled)	**320** per 1000 Difference:	**282** per 1000 **38 fewer per 1000** (CI 95% 67 fewer — 10 fewer)	**Low** Due to only one study and serious indirectness [7]	Corticosteroids may decrease invasive mechanical ventilation or death in patients who require oxygen.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
commencing treatment 9 Critical					
All-cause mortality [adults not requiring oxygen] Within 28 days after commencing treatment 9 Critical	Relative risk 1.27 (CI 95% 1 — 1.61) Based on data from 1,535 participants in 1 studies. [8] (Randomized controlled)	**140** per 1000 Difference:	**178** per 1000 **38 more per 1000** (CI 95% 0 fewer — 85 more)	**Low** Due to only one study and serious indirectness [9]	Corticosteroids may increase death in patients who do not require oxygen.
Invasive mechanical ventilation or death [adults not requiring oxygen] Within 28 days after commencing treatment 9 Critical	Relative risk 1.25 (CI 95% 1 — 1.57) Based on data from 1,535 participants in 1 studies. [10] (Randomized controlled)	**155** per 1000 Difference:	**194** per 1000 **39 more per 1000** (CI 95% 0 fewer — 88 more)	**Low** Due to only one study and serious indirectness [11]	Corticosteroids may increase invasive mechanical ventilation or death in patients who do not require oxygen.
Discharge from hospital [adults not requiring oxygen] Within 28 days after commencing treatment 6 Important	Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 participants in 1 studies. [12] (Randomized controlled)	**804** per 1000 Difference:	**772** per 1000 **32 fewer per 1000** (CI 95% 80 fewer — 8 more)	**Low** Due to only one study and serious indirectness [13]	Corticosteroids may have little impact on discharge from hospital in patients who do not require oxygen.
Gastrointestinal bleeding End of treatment 6 Important	Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5,403 participants in 30 studies. [14]	**48** per 1000 Difference:	**51** per 1000 **3 more per 1000** (CI 95% 7 fewer — 16 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on gastrointestinal bleeding.
Super infections End of treatment	Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 participants in	**186** per 1000	**188** per 1000	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on number of patients with super infections.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important	32 studies. [15]	Difference:	**2 more per 1000** (CI 95% 19 fewer — 24 more)		
Hyperglycaemia End of treatment 6 Important	Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 participants in 24 studies. [16]	286 per 1000 Difference:	332 per 1000 **46 more per 1000** (CI 95% 23 more — 72 more)	**Moderate** Due to serious indirectness	Corticosteroids probably increase the risk of hyperglycaemia.
Neuromuscular weakness End of treatment 6 Important	Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 participants in 8 studies. [17]	69 per 1000 Difference:	75 per 1000 **6 more per 1000** (CI 95% 10 fewer — 27 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuromuscular weakness.
Neuropsychiatric effects End of treatment 6 Important	Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 participants in 7 studies. [18]	35 per 1000 Difference:	28 per 1000 **7 fewer per 1000** (CI 95% 21 fewer — 22 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuropsychiatric effects.
Discharge from hospital [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 participants in 2 studies. [19] (Randomized controlled)	582 per 1000 Difference:	640 per 1000 **58 more per 1000** (CI 95% 35 more — 87 more)	**Low** Due to serious inconsistency and serious indirectness [20]	Corticosteroids may increase discharge from hospital in patients who require oxygen.

Attached Images

Conditional recommendation against

Do not routinely use dexamethasone (or other oral or parenteral steroids) to treat COVID-19 in **children and adolescents who do not require oxygen**.

Additional information

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

For specific recommendations on the use of corticosteroids for PIMS-TS see section.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Important harms

In adult patients who do not require oxygen, there may be more deaths with dexamethasone and other corticosteroids. It is unclear if any children were included in the trials, therefore there is uncertainty regarding the benefits in this population but there are known potential adverse effects.

Certainty of the Evidence

Low

In children and adolescents who do not require oxygen, certainty of the evidence is judged to be low for all outcomes (death, mechanical ventilation or death, and discharge from hospital) due to serious imprecision (reliance on a single study and wide confidence intervals) and serious indirectness (results based on the general adult population).

For adverse events (gastrointestinal bleeding, super infections, hyperglycaemia, neuromuscular weakness and neuropsychiatric effects), evidence is generally low due to serious indirectness (evidence comes from non-COVID-19 patients) and serious imprecision.

Values and preferences

We expect few to want the intervention

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

The Consumer Panel believes that most informed patients (and their parents, carers, families and guardians) may prefer to wait until the available evidence is clearer, and would not agree to this treatment for COVID-19.

Resources

No important issues with the recommended alternative

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

Equity

No important issues with the recommended alternative

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

Acceptability

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding acceptability.

Feasibility

No important issues with the recommended alternative

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

Rationale

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

Clinical Question/ PICO

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

Summary

Evidence indicates that corticosteroids reduce deaths in patients with critical or severe COVID-19, but may increase deaths in patients with moderate COVID-19.

What is the evidence informing this recommendation?
Evidence comes from a meta-analysis and associated living guidance *[27]* of seven randomised trials of patients with critical COVID-19 *[31][32][33][34][36][37][315]*, one study of patients with moderate, severe and critical COVID-19 *[38]* and one study of patients with severe COVID-19 *[39]*. Over 5700 patients are included in the meta-analysis. All trials compared corticosteroids plus standard care with standard care alone.

In addition, two meta-analyses of corticosteroids for other conditions—other coronavirus infections, influenza, community-acquired pneumonia, acute respiratory distress *[28]* and sepsis *[29]*—provided indirect evidence for serious adverse events.

Study characteristics
Three studies compared dexamethasone with standard care *[34][36][38]*, three compared hydrocortisone with standard care *[31][33][315]* and three compared methylprednisolone with standard care *[32][37][39]*.

Disease severity was reported independently for each trial. Definitions included patients who required mechanical ventilation or non-invasive ventilation (NIV), PaO2/FiO2 < 200, positive end-expiratory pressure (PEEP) ≥ 5 cmH2O, and the presence of pneumonia or infiltrates on chest imaging.

Mean or median age ranged from 57 to 67 years in the corticosteroid groups and from 60 to 66 years in the standard care groups. The proportion of women was 32% (range 13% to 43%) in the corticosteroid groups and 29% (range 21% to 36%) in the standard care groups.

What are the main results?
Compared with standard care, corticosteroids probably reduce death in patients with severe and critical COVID-19. For every 1000 patients given corticosteroids, 51 more are likely to survive compared with those receiving standard care (RR 0.84 CI 95% 0.73 to 0.98; 5789 patients in 9 studies). Corticosteroids in patients requiring oxygen also probably reduce the composite outcome of requirement for invasive mechanical ventilation or death, and time to discharge from hospital.

In patients who do not require oxygen, corticosteroids probably increase death (RR 1.27 CI 95% 1.00 to 1.61; 1535 patients in 1 study) and the composite outcome of invasive mechanical ventilation or death.

Indirect evidence of corticosteroid use in patients with other, similar indications shows no difference in the incidence of gastrointestinal bleeding, superinfections, neuromuscular weakness and neuropsychiatric effects. However, corticosteroid use was associated with an increase in hyperglycaemia (RR 1.16 CI 95% 1.08 to 1.25; 8938 patients in 8 studies).

Our confidence in the results
Certainty of the evidence for all outcomes is judged to be low for pregnant and breastfeeding women, and children and adolescents due to serious indirectness. This is in addition to concerns in the adult population about inconsistency in direction of effect and serious imprecision.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality [adults requiring oxygen] Within 28 days of commencing treatment 9 Critical	Relative risk 0.84 (CI 95% 0.73 — 0.98) Based on data from 5,789 participants in 9 studies. [1] (Randomized controlled)	316 per 1000 Difference:	265 per 1000 **51 fewer per 1000** (CI 95% 85 fewer — 6 fewer)	**Low** Due to serious inconsistency and serious indirectness [2]	Corticosteroids may decrease death at day 28 in patients who require oxygen.
Serious adverse events [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 0.8 (CI 95% 0.53 — 1.19) Based on data from 696 participants in 6 studies. [3] (Randomized controlled)	234 per 1000 Difference:	187 per 1000 **47 fewer per 1000** (CI 95% 110 fewer — 44 more)	**Low** Due to serious inconsistency and indirectness [4]	Corticosteroids may have little impact on serious adverse events in patients who require oxygen.
Invasive mechanical ventilation or death [adults requiring oxygen] [5] Within 28 days after commencing treatment 9 Critical	Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 participants in 1 studies. [6] (Randomized controlled)	320 per 1000 Difference:	282 per 1000 **38 fewer per 1000** (CI 95% 67 fewer — 10 fewer)	**Low** Due to only one study and serious indirectness [7]	Corticosteroids may decrease invasive mechanical ventilation or death in patients who require oxygen.
All-cause mortality [adults not requiring oxygen] Within 28 days after commencing treatment	Relative risk 1.27 (CI 95% 1 — 1.61) Based on data from 1,535 participants in 1 studies. [8] (Randomized controlled)	140 per 1000 Difference:	178 per 1000 **38 more per 1000** (CI 95% 0 fewer — 85 more)	**Low** Due to only one study and serious indirectness [9]	Corticosteroids may increase death in patients who do not require oxygen.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical **Invasive mechanical ventilation or death [adults not requiring oxygen]** Within 28 days after commencing treatment 9 Critical	Relative risk 1.25 (CI 95% 1 — 1.57) Based on data from 1,535 participants in 1 studies. [10] (Randomized controlled)	155 per 1000 Difference:	194 per 1000 **39 more per 1000** (CI 95% 0 fewer — 88 more)	**Low** Due to only one study and serious indirectness [11]	Corticosteroids may increase invasive mechanical ventilation or death in patients who do not require oxygen.
Discharge from hospital [adults not requiring oxygen] Within 28 days after commencing treatment 6 Important	Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 participants in 1 studies. [12] (Randomized controlled)	804 per 1000 Difference:	772 per 1000 **32 fewer per 1000** (CI 95% 80 fewer — 8 more)	**Low** Due to only one study and serious indirectness [13]	Corticosteroids may have little impact on discharge from hospital in patients who do not require oxygen.
Gastrointestinal bleeding End of treatment 6 Important	Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5,403 participants in 30 studies. [14]	48 per 1000 Difference:	51 per 1000 **3 more per 1000** (CI 95% 7 fewer — 16 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on gastrointestinal bleeding.
Super infections End of treatment 6 Important	Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 participants in 32 studies. [15]	186 per 1000 Difference:	188 per 1000 **2 more per 1000** (CI 95% 19 fewer — 24 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on number of patients with super infections.
Hyperglycaemia End of treatment 6 Important	Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 participants in 24 studies. [16]	286 per 1000 Difference:	332 per 1000 **46 more per 1000** (CI 95% 23 more — 72 more)	**Moderate** Due to serious indirectness	Corticosteroids probably increase the risk of hyperglycaemia.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Neuromuscular weakness End of treatment 6 Important	Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 participants in 8 studies. [17]	69 per 1000 Difference:	75 per 1000 **6 more per 1000** (CI 95% 10 fewer — 27 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuromuscular weakness.
Neuropsychiatric effects End of treatment 6 Important	Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 participants in 7 studies. [18]	35 per 1000 Difference:	28 per 1000 **7 fewer per 1000** (CI 95% 21 fewer — 22 more)	**Low** Due to serious indirectness and imprecision	Corticosteroids may have little impact on neuropsychiatric effects.
Discharge from hospital [adults requiring oxygen] Within 28 days of commencing treatment 6 Important	Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 participants in 2 studies. [19] (Randomized controlled)	582 per 1000 Difference:	640 per 1000 **58 more per 1000** (CI 95% 35 more — 87 more)	**Low** Due to serious inconsistency and serious indirectness [20]	Corticosteroids may increase discharge from hospital in patients who require oxygen.

Attached Images

7.1.4 Molnupiravir (Lagevrio)

7.1.4.1 Molnupiravir (Lagevrio) for adults

Conditional recommendation against

Do not routinely use molnupiravir for the treatment of COVID-19.

Additional information

Preliminary results of the PANORAMIC trial in 25,783 participants with the Omicron variant provide high certainty evidence that molnupiravir does not have an impact on the combined endpoint of hospitalisation and/or mortality in multiply-vaccinated adults with mild COVID-19 and one or more risk factors for disease progression.*

*Patients at the highest risk of adverse outcomes from COVID-19** were not the target population of the PANORAMIC trial (although some were included), as in the UK these patients had been advised to access treatment directly though COVID specialist clinics. Therefore, there is less evidence about the effect of molnupiravir in these highest risk patients, and in some settings such as residential aged care.*

Although evidence regarding the use of other treatments (such as nirmatrelvir plus ritonavir, and remdesivir) in the highest risk patients is also limited, current evidence provides greater certainty of clinical benefit for other antiviral agents in the broader population; therefore use of these other antivirals agents rather than molnupiravir is preferred. However, there may be specific circumstances for the highest risk patients, where all other treatment options are contraindicated or inappropriate, in which non-routine use of molnupiravir might be considered, in consultation with specialist clinicians where necessary.

For further information, refer to the rationale.

**Approximately 95% of participants had received three or more doses of SARS-CoV-2 vaccine prior to treatment and a high proportion had likely experienced previous infection.*

***Definition of highest risk (https://www.gov.uk/government/publications/highest-risk-patients-eligible-for-covid-19-treatments-guide-for-patients/highest-risk-patients-eligible-for-new-covid-19-treatments-a-guide-for-patients) includes people with Down syndrome, leukaemia or lymphoma, sickle cell disease, chronic kidney disease (CKD) stage 4 or 5, severe liver disease, organ or bone marrow transplant, advanced HIV disease, multiple sclerosis, motor neurone disease, Huntington's disease or myasthenia gravis, cerebral palsy, or a weakened immune system due to a medical treatment (including biological therapy, chemotherapy or radiotherapy).*

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Values and preferences

We expect few to want the intervention

The consumer panel believes that most people would choose not to take this treatment given the evidence from PANORAMIC showing lack of effect on mortality and hospitalisation, even where other treatments (such as Paxlovid and remdesivir) are unavailable or contraindicated. In the highest risk people for whom other treatments are not appropriate, considerations around whether to use molnupiravir should be undertaken in consultation with an individual's specialist treatment team and with the patient's informed consent.

The consumer panel is concerned that equitable access to and uptake of preferable treatment options may be affected by levels of engagement with and access to current, evidence-based health care, and by consumer health literacy.

Clinical Question/ PICO

Population: Molnupiravir for COVID-19
Intervention: Molnupiravir
Comparator: Usual care

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual care	**Intervention** Molnupiravir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of treatment 9 Critical	Relative risk 0.6 (CI 95% 0.14 — 2.51) Based on data from 25,054 participants in 1 studies. [1] (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	**High**	Molnupiravir has no impact on all-cause mortality (8 events).
Mortality or hospitalisation Within 28 days of treatment 6 Important	Relative risk 1.07 (CI 95% 0.81 — 1.41) Based on data from 25,054 participants in 1 studies. [2] (Randomized controlled)	8 per 1000 Difference:	9 per 1000 **1 more per 1000** (CI 95% 2 fewer — 3 more)	**High**	Molnupiravir has no impact on mortality or hospitalisation.
Hospitalisation Within 28 days of commencing treatment 6 Important	Relative risk 1.07 (CI 95% 0.81 — 1.41) Based on data from 25,054 participants in 1 studies. [3] (Randomized controlled)	8 per 1000 Difference:	9 per 1000 **1 more per 1000** (CI 95% 2 fewer — 3 more)	**High**	Molnupiravir has no impact on hospitalisation.
Serious Adverse Events Within 28 days of treatment 6 Important	Relative risk 1.13 (CI 95% 0.75 — 1.68) Based on data from 25,708 participants in 1 studies. [4] (Randomized controlled)	3 per 1000 Difference:	3 per 1000 **0 fewer per 1000** (CI 95% 1 fewer — 2 more)	**High**	Molnupiravir has no impact on serious adverse events.
First reported recovery Within 28 days of treatment 6 Important	Relative risk 1.14 (CI 95% 1.12 — 1.15) Based on data from 24,543 participants in 1 studies. [5] (Randomized controlled)	690 per 1000 Difference:	787 per 1000 **97 more per 1000** (CI 95% 83 more — 103 more)	**Low** Due to very serious risk of bias [6]	Molnupiravir may improve first reported recovery slightly

Attached Images

7.1.4.2 Molnupiravir (Lagevrio) for pregnant or breastfeeding women

Only in research settings

Do not use molnupiravir for the treatment of COVID-19 in pregnant or breastfeeding women outside of randomised trials with appropriate ethical approval.

Additional information

Currently, there is no direct evidence for the use of molnupiravir (Lagevrio) in pregnant or breastfeeding women. Trials are needed in special populations, including pregnant or breastfeeding women. Until further evidence is available, do not use molnupiravir for the treatment of COVID-19 in pregnant or breastfeeding women unless they are eligible to be enrolled in trials.

There are no clinical data on the use of molnupiravir in pregnant or breastfeeding women. It is unknown whether molnupiravir is present in human or animal milk, and the effects on the breastfed newborn/infant, or the effects on milk production. A risk to the newborn/infant cannot be excluded.

There are no clinical data on the effects of molnupiravir against the SARS-CoV-2 Omicron variant.

Animal reproductive studies indicate that molnupiravir may have embryo-fetal development effects at high doses, which could include embryofetal lethality, teratogenicity, and reduced fetal growth. Animal studies have also shown potential deleterious effects on cartilage and bone growth and it is unclear if these effects are reversible. (TGA Product Information)

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

7.1.4.3 Molnupiravir (Lagevrio) for children and adolescents

Only in research settings

Do not use molnupiravir for the treatment of COVID-19 in children and adolescents outside of randomised trials with appropriate ethical approval.

Additional information

Currently, there is no direct evidence for the use of molnupiravir (Lagevrio) in children and adolescents. Trials are needed in special populations, including children and adolescents. Until further evidence is available, do not routinely use molnupiravir for the treatment of COVID-19 in children and adolescents unless they are eligible to be enrolled in trials.

Animal studies have shown potential deleterious effects on cartilage and bone growth, and it is unclear if these effects are reversible.

Currently molnupiravir is not approved for use in people under 18 years of age.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Molnupiravir may decrease the incidence of hospitalisation or death, and probably has little impact on the incidence of adverse or serious adverse events. We are unsure if molnupiravir has an impact on mortality, discontinuation due to adverse events, and the composite outcome of hospitalisation or death within subgroups based on SARS-CoV-2 variant.

Studies in animal models suggest potential embryolethal and teratogenic effects and deleterious effects on cartilage and bone growth at very high doses.

Certainty of the Evidence

Low

Certainty of the evidence is low for the composite outcome of hospitalisation or death, adverse events and serious adverse events (due to reliance on a single study) and very low for all-cause mortality and discontinuation due to adverse events (due to reliance on a single study and few events). Certainty is low or very low for all subgroup analyses focused on SARS-CoV-2 variant.

Values and preferences

Substantial variability is expected or uncertain

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

Pregnant or breastfeeding patients
We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. Although there is uncertainty regarding the benefit to harm ratio for women and their babies, evidence demonstrates embryolethality and reduced fetal growth in rats when administered at seven and three times the therapeutic dose. As such, the panel believes most women would not opt for treatment.

Children and adolescents
We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources

Important issues, or potential issues not investigated

The limited availability of molnupiravir, as well as the cost of treatment, are limiting factors preventing widespread use of this treatment.

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity; however any limitations on availability and the significant cost of molnupiravir may affect equity based on geographic area and access to molnupiravir.

Acceptability

Important issues, or potential issues not investigated

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

Feasibility

Important issues, or potential issues not investigated

Oral molnupiravir (Lagevrio; Merck Sharp & Dohme) was granted provisional approval by the Therapeutic Goods Administration on 18 January 2022 for the treatment of COVID-19 under the Black Triangle Scheme. Currently molnupiravir is not approved for use in people under 18 years of age.

Implementability could be affected by limitations to supply, however the likelihood and effect of such limitations on treating patients with COVID-19 will be dependent on the prevalence of COVID-19.

Rationale

General adult population

In adult outpatients with mild COVID-19, molnupiravir probably reduces the risk of hospitalisation or death slightly. Because of this, the Taskforce gives a consensus recommendation for molnupiravir both within and outside a randomised trial, only where other treatments (such as sotrovimab or nirmatrelvir plus ritonavir) are not suitable or available.

7.1.5 Nirmatrelvir plus ritonavir (Paxlovid)

7.1.5.1 Nirmatrelvir plus ritonavir (Paxlovid) for adults

Conditional recommendation

Consider using nirmatrelvir plus ritonavir within 5 days of symptom onset in unvaccinated adults* with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression.

Within the patient population for which nirmatrelvir plus ritonavir is conditionally recommended for use (see Additional information), decisions about the appropriateness of treatment with nirmatrelvir plus ritonavir should be based on the individual's risk of severe disease, including their age, presence of multiple risk factors, and vaccination status (including number of doses and time since last dose/ or timing of most recent infection).

** Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial. The efficacy of nirmatrelvir plus ritonavir is unclear in individuals who have received any COVID-19 vaccine. See consensus recommendation for guidance on use of nirmatrelvir plus ritonavir in vaccinated adults or in immunocompromised patients regardless of vaccination status.*

Additional information

In adults with confirmed COVID-19 who do not require oxygen, nirmatrelvir plus ritonavir (Paxlovid) probably decreases the risk of hospitalisation if taken within 5 days of onset of symptoms.

Results are based on a single phase 2/3 trial comparing nirmatrelvir plus ritonavir with placebo in 2246 unvaccinated adults with PCR-confirmed COVID-19 and mild illness (EPIC-HR) [417]. Within this trial participants were treated with oral nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days.

The benefit of nirmatrelvir plus ritonavir is likely to be greatest in those with the greatest risk of severe disease. Based on the population included within the trial, evidence demonstrates a reduction in hospitalisation when used in individuals with one or more of the following risk factors for disease progression:

- *Age ≥ 60 years*
- *Diabetes (requiring medication)*
- *BMI ≥ 25 kg/m2*
- *Cardiovascular disease*
- *Hypertension*
- *Chronic lung disease*

There were insufficient numbers of participants with the following risk factors to determine the extent to which nirmatrelvir plus ritonavir impacts hospitalisation or death, however as these conditions frequently result in poorer outcomes for adults following SARS-CoV-2 infection, they will likely benefit from treatment:

- *Chronic kidney disease (but where the eGFR ≥ 30 mL/min)**
- *Immunocompromised (e.g. bone marrow or organ transplantation, primary immune deficiencies, prolonged use of immune-weakening medications)*
- *Medical related technological dependence (e.g. CPAP not related to COVID-19)*
- *HIV positive (CD4+ count < 200 cells/mm^3)*
- *Neurodevelopmental disorders (e.g. cerebral palsy, Down syndrome)*
- *Cancer (other than localised skin cancer)*
- *Sickle cell disease*

** Individuals with an eGFR < 30 mL/min were excluded from the trial. In individuals with CKD and an eGFR of 30–60 mL/min, the dose of nirmatrelvir should be halved; i.e. nirmatrelvir/ritonavir 150/100 mg twice daily for 5 days (FDA EUA).*

Pregnant and breastfeeding women and children and adolescents were not included in the trial.

Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial.

The study was conducted before the Omicron variant was prevalent. As a result, there are no data regarding the effectiveness of nirmatrelvir plus ritonavir specific to the Omicron variant.

Available data suggests that administering nirmatrelvir plus ritonavir as an oral suspension does not alter its pharmacokinetic paramaters (Liverpool University). Although the swallowing of whole tablets remains the preferred method of administration where necessary, nirmatrelvir plus ritonavir tablets can be crushed or split and mixed with food or liquid, or alternatively administered via nasogastric tube, as indicated.

The Taskforce notes the interim results of the EPIC-SR study from Pfizer. This trial is evaluating nirmatrelvir plus ritonavir

(Paxlovid) in unvaccinated adults at low risk of hospitalisation or death, or vaccinated adults with one or more risk factors for progressing to severe illness. An analysis at 80% of enrolled patients found that 0.7% (3/428) of those who received Paxlovid were hospitalised compared with 2.4% (10/426) of patients who received placebo. No deaths were reported. These data will be reviewed when the results become available.

Ritonavir is an inhibitor, inducer and substrate of many enzymes and transporters involved in drug disposition and metabolism. It is a strong inhibitor of CYP3A, reducing the hepatic metabolism and increasing the concentration of nirmatrelvir and other CYP3A substrates. Coadministration of nirmatrelvir-ritonavir is contraindicated with drugs that are highly dependent upon CYP3A for clearance where an elevated concentration may be dangerous (e.g. anti-arrhythmics, antipsychotics, statins, anti-inflammatories, anti-cancer drugs and anticoagulants). Coadministration is also contraindicated with potent CYP3A inducers (e.g. anti-epileptics, rifampin, St John's wort), which can reduce concentrations of nirmatrelvir and/or ritonavir, reducing efficacy and increasing resistance. Induction persists many days after cessation due to time required for clearance of the inducing drug and of the induced CYP3A.

Evidence demonstrates a likely weak interaction between nirmatrelvir-ritonavir and budesonide, resulting in increased budesonide concentrations. There are no other expected interactions between nirmatrelvir-ritonavir and other therapeutics currently recommended for the treatment of COVID-19 within the Taskforce guidelines. It is crucial that consideration is given to the potential for complex, serious drug-drug interactions when prescribing and administering nirmatrelvir plus ritonavir with other medications (see Liverpool interaction checker and TGA PI).

The Taskforce has made conditional recommendations supporting the use of sotrovimab, casirivimab plus imdevimab, nirmatrelvir plus ritonavir, remdesivir and regdanvimab, and a consensus recommendation for molnupiravir, in adults who do not require oxygen. The relative effectiveness of these agents, or the effectiveness of these agents when used in combination, is unclear.

The Taskforce is aware of cases in which people with COVID-19 treated with nirmatrelvir plus ritonavir experience a re-emergence of symptoms following completion of treatment. Clinicians should be aware of the potential for symptom rebound in these patients, however in the absence of definitive high-quality evidence, the most appropriate course of action remains unclear. The Taskforce will provide additional guidance as evidence becomes available.

The Taskforce notes the publication of one additional trial comparing nirmatrelvir plus ritonavir (Paxlovid) with usual care in 264 people hospitalised with COVID-19 [583]. We are unsure of the proportion of included participants requiring oxygen—due to the reporting of limited baseline information we are unable to add these data to the existing evidence profile.

Nirmatrelvir plus ritonavir is currently listed within the Australian Pharmaceutical Benefits Scheme. Details can be found here.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Nirmatrelvir plus ritonavir probably decreases the incidence of hospitalisation and serious adverse events and has little impact on incidence of adverse events and discontinuation due to adverse events. We are unsure if nirmatrelvir plus ritonavir has an impact on death.

Certainty of the Evidence

Low

Certainty of the evidence is moderate for the composite outcomes of hospitalisation or death, hospitalisation, adverse or serious adverse events, and discontinuation due to adverse events (reliance on a single study). Certainty is low for all-cause mortality (reliance on a single study and few events).

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values. The consumer panel believes that some people would opt for this treatment while others might prefer one of the other treatment options, and some might want to wait for more evidence. The consumer panel notes that there is potential for issues

around engagement with and access to healthcare, and health literacy to impact on the equitable access to and uptake of this treatment.

The consumer panel highlights that people currently taking treatments that may interact with nirmatrelvir plus ritonavir require support to make an informed choice about the appropriateness and risks of nirmatrelvir plus ritonavir in the context of their associated conditions. They will also need advice on how to manage medications to avoid interactions with nirmatrelvir plus ritonavir.

Pregnant or breastfeeding women
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 Consumer Panel believes some women might prefer to wait while others might be more willing to opt for treatment.

Children and adolescents
We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources

Important issues, or potential issues not investigated

The limited availability of nirmatrelvir plus ritonavir, as well as the high cost of treatment, are limiting factors preventing widespread use of this treatment.

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity; however any limitations on availability and the significant cost of nirmatrelvir plus ritonavir may affect equity based on geographic area and access to nirmatrelvir plus ritonavir.

Acceptability

Important issues, or potential issues not investigated

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

Feasibility

Important issues, or potential issues not investigated

Oral nirmatrelvir plus ritonavir (Paxlovid; Pfizer Australia Pty Ltd) was granted provisional approval by the Therapeutic Goods Administration on 18 January 2022 for the treatment of COVID-19 under the Black Triangle Scheme (*ARTG number: 377572).*

Implementability could be affected by limitations to supply, however the likelihood and effect of such limitations on treating patients with COVID-19 will be dependent on the prevalence of COVID-19.

Rationale

General adult population
In adult outpatients with mild COVID-19, nirmatrelvir plus ritonavir probably reduces the risk of hospitalisation. Because of this, the Taskforce gives a conditional recommendation for nirmatrelvir plus ritonavir both within and outside a randomised trial.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Nirmatrelvir plus ritonavir
Comparator: Placebo

Summary

Evidence indicates that nirmatrelvir plus ritonavir probably reduces the incidence of hospitalisation or death in adults with mild-to-moderate COVID-19 who have one or more risk factors for disease progression.

What is the evidence informing this recommendation?
Evidence comes from a single clinical study report that compared nirmatrelvir plus ritonavir (Paxlovid) with placebo in 2246 adult outpatients with mild-to-moderate COVID-19. Participants were randomised within 5 days of onset of symptoms and had one or more risk factors for disease progression.

Study characteristics
Mean age of participants was 46 years and 49% were women. Participants received three 100 mg tablets of nirmatrelvir and one 100 mg tablet of ritonavir twice daily for five days. Pregnant and breastfeeding women and children and adolescents were ineligible.

What are the main results?
Nirmatrelvir plus ritonavir probably reduces the incidence of hospitalisation (RR 0.12, CI 95% 0.06 to 0.25; 2085 patients in 1 study) and incidence of serious adverse events (RR 0.24, CI 95% 0.15 to 0.41; 2224 patients in 1 study). Nirmatrelvir plus ritonavir probably has little impact on incidence of adverse events or discontinuation due to adverse events. We are unsure if nirmatrelvir plus ritonavir impacts all-cause mortality.

Our confidence in the results
Certainty of the evidence is moderate for the composite outcomes of hospitalisation or death, hospitalisation, adverse and serious adverse events, and discontinuation due to adverse events (reliance on a single study). Certainty is low for all-cause mortality (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The Therapeutic Goods Administration provisionally approved the use of nirmatrelvir plus ritonavir (Paxlovid) for the treatment of COVID-19 on 18 January 2022.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Paxlovid	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Hospitalisation or death Day 28, ≤5 days symptom onset 9 Critical	Relative risk 0.12 (CI 95% 0.06 — 0.25) Based on data from 2,085 participants in 1 studies. [1] (Randomized controlled)	63 per 1000 Difference:	8 per 1000 **55 fewer per 1000** (CI 95% 59 fewer — 47 fewer)	**Moderate** Due to serious imprecision [2]	Paxlovid probably decreases hospitalisation or death (74 events)
All-cause mortality Day 28, ≤5 days symptom onset	Relative risk 0.04 (CI 95% 0 — 0.68) Based on data from 2,085 participants in 1 studies. [3] (Randomized controlled)	11 per 1000 Difference:	0 per 1000 **11 fewer per 1000** (CI 95% 11	**Low** Due to very serious imprecision [4]	Paxlovid may have little impact on all-cause mortality (12 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Paxlovid	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical			fewer — 4 fewer)		
Hospitalisation Day 28, ≤ 5 days symptom onset 6 Important	Relative risk 0.12 (CI 95% 0.06 — 0.26) Based on data from 2,085 participants in 1 studies. [5] (Randomized controlled)	62 per 1000 Difference:	7 per 1000 **55 fewer per 1000** (CI 95% 58 fewer — 46 fewer)	**Moderate** Due to serious imprecision [6]	Paxlovid probably decreases hospitalisation (73 events).
Adverse events Within 28 days of commencing treatment 6 Important	Relative risk 0.95 (CI 95% 0.82 — 1.1) Based on data from 2,224 participants in 1 studies. [7] (Randomized controlled)	239 per 1000 Difference:	227 per 1000 **12 fewer per 1000** (CI 95% 43 fewer — 24 more)	**Moderate** Due to serious imprecision [8]	Paxlovid probably has little impact on adverse events (517 events).
Serious adverse events Within 28 days of commencing treatment 6 Important	Relative risk 0.24 (CI 95% 0.15 — 0.41) Based on data from 2,224 participants in 1 studies. [9] (Randomized controlled)	66 per 1000 Difference:	16 per 1000 **50 fewer per 1000** (CI 95% 56 fewer — 39 fewer)	**Moderate** Due to serious imprecision [10]	Paxlovid probably decreases serious adverse events slightly (92 events).
Discontinued due to adverse event Within 28 days of commencing treatment 6 Important	Relative risk 0.49 (CI 95% 0.3 — 0.81) Based on data from 2,228 participants in 1 studies. [11] (Randomized controlled)	42 per 1000 Difference:	21 per 1000 **21 fewer per 1000** (CI 95% 29 fewer — 8 fewer)	**Moderate** Due to serious imprecision [12]	Paxlovid probably has little impact on discontinuation due to adverse events (70 events).

Attached Images

Consensus recommendation

In addition to at-risk unvaccinated adults, also consider using nirmatrelvir plus ritonavir within 5 days of symptom onset in adults with COVID-19 who do not require oxygen and are immunocompromised; or are at particularly high risk of severe disease on the basis of advanced age and multiple risk factors.

Additional information

Decisions about the appropriateness of nirmatrelvir plus ritonavir should be based on the individual's risk of severe disease, including their age, presence of multiple risk factors, and vaccination status (including number of doses and time since last dose/ or timing of most recent infection).

Available research does not currently provide enough evidence to determine the benefits of nirmatrelvir plus ritonavir (Paxlovid) in specific subgroups of adults. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which adults are most likely to benefit from nirmatrelvir plus ritonavir.

There is no evidence evaluating the effectiveness of nirmatrelvir plus ritonavir in individuals who have received any COVID-19 vaccine. Given this, and the lower risk of deterioration in these people, it is less likely that nirmatrelvir plus ritonavir will be of benefit in individuals who have received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months, unless the patient is immunocompromised.

There is limited evidence on the effectiveness of nirmatrelvir plus ritonavir in immunocompromised patients. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that nirmatrelvir plus ritonavir will be beneficial for immunocompromised patients.

Immunocompromising conditions include:

- *Primary or acquired immunodeficiency*
  - *Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes*
  - *Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months)*
  - *Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency*
  - *Other significantly immunocompromising conditions*
- *Immunosuppressive therapy (current or recent)*
  - *Chemotherapy, whole body radiotherapy or total lymphoid irradiation*
  - *High-dose corticosteroids (≥ 20 mg of prednisone per day, or equivalent) for ≥ 14 days*
  - *All biological disease-modifying anti-rheumatic drugs (DMARDs) and most other (e.g. conventional synthetic) DMARDs [348]*

In the absence of reliable evidence, the Taskforce has developed this recommendation based on their clinical expertise and experience.

Nirmatrelvir plus ritonavir is currently listed within the Australian Pharmaceutical Benefits Scheme. Details can be found here.

7.1.5.2 Nirmatrelvir plus ritonavir (Paxlovid) for pregnant or breastfeeding women

Only in research settings

Do not use nirmatrelvir plus ritonavir for the treatment of COVID-19 in pregnant or breastfeeding women outside of randomised trials with appropriate ethical approval.

Additional information

Currently, there is no direct evidence for the use of nirmatrelvir plus ritonavir (Paxlovid) in pregnant or breastfeeding women. Trials are needed in special populations, including pregnant or breastfeeding women. Until further evidence is available, do not use nirmatrelvir plus ritonavir for the treatment of COVID-19 in pregnant or breastfeeding women unless they are eligible to be enrolled in trials.

There are no clinical data on the use of nirmatrelvir plus ritonavir in pregnant or breastfeeding women. It is unknown whether nirmatrelvir plus ritonavir is present in human or animal milk, and the effects on the breastfed newborn/infant, or the effects on milk production. A risk to the newborn/infant cannot be excluded.

There are no clinical data on the effects of nirmatrelvir plus ritonavir against the SARS-CoV-2 Omicron variant.

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives.

Animal reproductive studies indicate that nirmatrelvir plus ritonavir may have embryo-fetal development effects at high doses, which could include early resorptions, decreased fetal body weight and ossification delays and developmental variations (TGA Product Information).

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Nirmatrelvir plus ritonavir
Comparator: Placebo

Summary

Evidence indicates that nirmatrelvir plus ritonavir probably reduces the incidence of hospitalisation or death in adults with mild-to-moderate COVID-19 who have one or more risk factors for disease progression.

What is the evidence informing this recommendation?
Evidence comes from a single clinical study report that compared nirmatrelvir plus ritonavir (Paxlovid) with placebo in 2246 adult outpatients with mild-to-moderate COVID-19. Participants were randomised within 5 days of onset of symptoms and had one or more risk factors for disease progression.

Study characteristics
Mean age of participants was 46 years and 49% were women. Participants received three 100 mg tablets of nirmatrelvir and one 100 mg tablet of ritonavir twice daily for five days. Pregnant and breastfeeding women and children and adolescents were ineligible.

What are the main results?
Nirmatrelvir plus ritonavir probably reduces the incidence of hospitalisation (RR 0.12, CI 95% 0.06 to 0.25; 2085 patients in 1 study) and incidence of serious adverse events (RR 0.24, CI 95% 0.15 to 0.41; 2224 patients in 1 study). Nirmatrelvir plus ritonavir probably has little impact on incidence of adverse events or discontinuation due to adverse events. We are unsure if nirmatrelvir plus ritonavir impacts all-cause mortality.

Our confidence in the results
Certainty of the evidence is moderate for the composite outcomes of hospitalisation or death, hospitalisation, adverse and serious adverse events, and discontinuation due to adverse events (reliance on a single study). Certainty is low for all-cause mortality (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The Therapeutic Goods Administration provisionally approved the use of nirmatrelvir plus ritonavir (Paxlovid) for the treatment of COVID-19 on 18 January 2022.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Paxlovid	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Hospitalisation or death Day 28, ≤5 days symptom onset 9 Critical	Relative risk 0.12 (CI 95% 0.06 — 0.25) Based on data from 2,085 participants in 1 studies. [1] (Randomized controlled)	63 per 1000 Difference:	8 per 1000 **55 fewer per 1000** (CI 95% 59 fewer — 47 fewer)	**Moderate** Due to serious imprecision [2]	Paxlovid probably decreases hospitalisation or death (74 events)
All-cause mortality Day 28, ≤5 days symptom onset 9 Critical	Relative risk 0.04 (CI 95% 0 — 0.68) Based on data from 2,085 participants in 1 studies. [3] (Randomized controlled)	11 per 1000 Difference:	0 per 1000 **11 fewer per 1000** (CI 95% 11 fewer — 4 fewer)	**Low** Due to very serious imprecision [4]	Paxlovid may have little impact on all-cause mortality (12 events).
Hospitalisation Day 28, ≤ 5 days symptom onset 6 Important	Relative risk 0.12 (CI 95% 0.06 — 0.26) Based on data from 2,085 participants in 1 studies. [5] (Randomized controlled)	62 per 1000 Difference:	7 per 1000 **55 fewer per 1000** (CI 95% 58 fewer — 46 fewer)	**Moderate** Due to serious imprecision [6]	Paxlovid probably decreases hospitalisation (73 events).
Adverse events Within 28 days of commencing treatment 6 Important	Relative risk 0.95 (CI 95% 0.82 — 1.1) Based on data from 2,224 participants in 1 studies. [7] (Randomized controlled)	239 per 1000 Difference:	227 per 1000 **12 fewer per 1000** (CI 95% 43 fewer — 24 more)	**Moderate** Due to serious imprecision [8]	Paxlovid probably has little impact on adverse events (517 events).
Serious adverse events Within 28 days of commencing treatment	Relative risk 0.24 (CI 95% 0.15 — 0.41) Based on data from 2,224 participants in 1 studies. [9] (Randomized controlled)	66 per 1000 Difference:	16 per 1000 **50 fewer per 1000** (CI 95% 56	**Moderate** Due to serious imprecision [10]	Paxlovid probably decreases serious adverse events slightly (92 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Paxlovid	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important			fewer — 39 fewer)		
Discontinued due to adverse event Within 28 days of commencing treatment 6 Important	Relative risk 0.49 (CI 95% 0.3 — 0.81) Based on data from 2,228 participants in 1 studies. [11] (Randomized controlled)	42 per 1000 Difference:	21 per 1000 **21 fewer per 1000** (CI 95% 29 fewer — 8 fewer)	**Moderate** Due to serious imprecision [12]	Paxlovid probably has little impact on discontinuation due to adverse events (70 events).

Attached Images

7.1.5.3 Nirmatrelvir plus ritonavir (Paxlovid) for children and adolescents

Consensus recommendation

Consider using, in exceptional circumstances, nirmatrelvir plus ritonavir for the treatment of COVID-19 within 5 days of symptom onset in **children and adolescents aged 12 years and over and weighing at least 40 kg** who do not require oxygen and who are at high risk of deterioration.

Consider using nirmatrelvir plus ritonavir in eligible children and adolescents who have not received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months, or those who are immunocompromised regardless of vaccination / previous infection status. Do not routinely use nirmatrelvir plus ritonavir in children and adolescents who have received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months unless immunocompromised.

Decisions about the appropriateness of treatment with nirmatrelvir plus ritonavir should be based on the individual's risk of severe disease, including their age, presence of multiple risk factors, and whether they have received a COVID-19 vaccine dose or had a SARS-CoV-2 infection in the past 6 months.

Additional information

Decisions to provide nirmatrelvir plus ritonavir to a child or adolescent should be based on the individual's combination of risk factors for deterioration and made in consultation with a paediatrician with expertise in the management of COVID-19 in children.

Available research does not currently provide enough evidence to determine the benefits of nirmatrelvir plus ritonavir (Paxlovid) in specific subgroups of children and adolescents. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which children and adolescents are most likely to benefit from nirmatrelvir plus ritonavir. Based on international cohorts [370], potential factors to consider in patients at high risk of progression may include:

- *Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions*
- *Severe asthma*
- *Obesity*

There is no evidence evaluating the effectiveness of nirmatrelvir plus ritonavir in people who have received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months, a low likelihood of development of severe disease, and a small risk of adverse events. Given this and the lower risk of deterioration in these patients, it is unlikely that nirmatrelvir plus ritonavir will be particularly valuable in people who have received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months, unless the patient is immunocompromised.

There is no evidence on the effectiveness of nirmatrelvir plus ritonavir in immunocompromised children and adolescents. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that nirmatrelvir plus ritonavir will be beneficial for immunocompromised patients.

Ritonavir is an inhibitor, inducer and substrate of many enzymes and transporters involved in drug disposition and metabolism. It is a strong inhibitor of CYP3A, reducing the hepatic metabolism and increasing the concentration of nirmatrelvir and other CYP3A substrates. Co-administration of nirmatrelvir-ritonavir is contraindicated with drugs that are highly dependent upon CYP3A for clearance where an elevated concentration may be dangerous (e.g. anti-arrhythmics, antipsychotics, statins, anti-inflammatories, anti-cancer drugs and anticoagulants). Co-administration is also contraindicated with potent CYP3A inducers (e.g. anti-epileptics, rifampin, St John's wort), which can reduce concentrations of nirmatrelvir and/or ritonavir, reducing efficacy and increasing resistance. Induction persists many days after cessation due to time required for clearance of the inducing drug and of the induced CYP3A.

Evidence demonstrates a likely weak interaction between nirmatrelvir-ritonavir and budesonide, resulting in increased budesonide concentrations. There are no other expected interactions between nirmatrelvir-ritonavir and other therapeutics currently recommended for the treatment of COVID-19 within the Taskforce guidelines. It is crucial that consideration is given to the potential for complex, serious drug-drug interactions when prescribing and administering nirmatrelvir plus ritonavir with other medications (see Liverpool interaction checker and TGA PI).

Available data suggests that administering nirmatrelvir plus ritonavir as an oral suspension does not alter its pharmacokinetic parameters (Liverpool University). Although the swallowing of whole tablets remains the preferred method of administration where necessary, nirmatrelvir plus ritonavir tablets can be crushed or split and mixed with food or liquid, or alternatively administered via nasogastric tube, as indicated.

In the absence of clinical data in paediatric populations, it is particularly important to ensure that any adverse events are appropriately reported.

As of 9 May 2022, the Therapeutic Goods Administration has not approved nirmatrelvir plus ritonavir for this indication. In the absence of reliable evidence, the Taskforce has developed this recommendation based on their clinical expertise and experience.

Nirmatrelvir plus ritonavir is currently listed within the Australian Pharmaceutical Benefits Scheme. Details can be found here.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

In adults, nirmatrelvir plus ritonavir probably decreases the incidence of hospitalisation and serious adverse events and has little impact on incidence of adverse events and discontinuation due to adverse events. We are unsure if nirmatrelvir plus ritonavir has an impact on death.

Certainty of the Evidence

Low

In adults, certainty of the evidence is moderate for the composite outcomes of hospitalisation or death, hospitalisation, adverse or serious adverse events, and discontinuation due to adverse events (reliance on a single study). Certainty is low for all-cause mortality (reliance on a single study and few events). In children and adolescents, certainty is downgraded further for indirectness due to the absence of this population within included studies.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values. The consumer panel believes that some people would opt for this treatment while others might prefer one of the other treatment options, and some might want to wait for more evidence.

The consumer panel notes that it is highly likely that this group has significant links to the healthcare system, and that this medication is most likely to be suggested in the context of an established relationship. They also note that in this age group people's level of ability to make informed choices for themselves varies considerably, and that these decisions should be made in partnership with both parents and the patients themselves (where possible).

The consumer panel highlights that people currently taking treatments that may interact with nirmatrelvir plus ritonavir require support to make an informed choice about the appropriateness and risks of nirmatrelvir plus ritonavir in the context of their associated conditions. They will also need advice on how to manage medications to avoid interactions with nirmatrelvir plus ritonavir.

Resources

Important issues, or potential issues not investigated

The limited availability of nirmatrelvir plus ritonavir, as well as the high cost of treatment, are limiting factors preventing widespread use of this treatment.

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity; however any limitations on availability and the significant cost of nirmatrelvir plus ritonavir may affect equity based on geographic area and access to

nirmatrelvir plus ritonavir.

Acceptability

Important issues, or potential issues not investigated

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

Feasibility

Important issues, or potential issues not investigated

Oral nirmatrelvir plus ritonavir (Paxlovid; Pfizer Australia Pty Ltd) was granted provisional approval by the Therapeutic Goods Administration on 18 January 2022 for the treatment of COVID-19 for patients 18 years and over under the Black Triangle Scheme (*ARTG number: 377572*).

Implementability could be affected by limitations to supply, however the likelihood and effect of such limitations on treating patients with COVID-19 will be dependent on the prevalence of COVID-19.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Nirmatrelvir plus ritonavir
Comparator: Placebo

Summary

Evidence indicates that nirmatrelvir plus ritonavir probably reduces the incidence of hospitalisation or death in adults with mild-to-moderate COVID-19 who have one or more risk factors for disease progression.

What is the evidence informing this recommendation?
Evidence comes from a single clinical study report that compared nirmatrelvir plus ritonavir (Paxlovid) with placebo in 2246 adult outpatients with mild-to-moderate COVID-19. Participants were randomised within 5 days of onset of symptoms and had one or more risk factors for disease progression.

Study characteristics
Mean age of participants was 46 years and 49% were women. Participants received three 100 mg tablets of nirmatrelvir and one 100 mg tablet of ritonavir twice daily for five days. Pregnant and breastfeeding women and children and adolescents were ineligible.

What are the main results?
Nirmatrelvir plus ritonavir probably reduces the incidence of hospitalisation (RR 0.12, CI 95% 0.06 to 0.25; 2085 patients in 1 study) and incidence of serious adverse events (RR 0.24, CI 95% 0.15 to 0.41; 2224 patients in 1 study). Nirmatrelvir plus ritonavir probably has little impact on incidence of adverse events or discontinuation due to adverse events. We are unsure if nirmatrelvir plus ritonavir impacts all-cause mortality.

Our confidence in the results
Certainty of the evidence is moderate for the composite outcomes of hospitalisation or death, hospitalisation, adverse and serious adverse events, and discontinuation due to adverse events (reliance on a single study). Certainty is low for all-cause mortality (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The Therapeutic Goods Administration provisionally approved the use of nirmatrelvir plus ritonavir (Paxlovid) for the treatment of COVID-19 on 18 January 2022.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Paxlovid	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Hospitalisation or death Day 28, ≤5 days symptom onset 9 Critical	Relative risk 0.12 (CI 95% 0.06 — 0.25) Based on data from 2,085 participants in 1 studies. [1] (Randomized controlled)	63 per 1000 Difference:	8 per 1000 **55 fewer per 1000** (CI 95% 59 fewer — 47 fewer)	**Moderate** Due to serious imprecision [2]	Paxlovid probably decreases hospitalisation or death (74 events)
All-cause mortality Day 28, ≤5 days symptom onset 9 Critical	Relative risk 0.04 (CI 95% 0 — 0.68) Based on data from 2,085 participants in 1 studies. [3] (Randomized controlled)	11 per 1000 Difference:	0 per 1000 **11 fewer per 1000** (CI 95% 11 fewer — 4 fewer)	**Low** Due to very serious imprecision [4]	Paxlovid may have little impact on all-cause mortality (12 events).
Hospitalisation Day 28, ≤ 5 days symptom onset 6 Important	Relative risk 0.12 (CI 95% 0.06 — 0.26) Based on data from 2,085 participants in 1 studies. [5] (Randomized controlled)	62 per 1000 Difference:	7 per 1000 **55 fewer per 1000** (CI 95% 58 fewer — 46 fewer)	**Moderate** Due to serious imprecision [6]	Paxlovid probably decreases hospitalisation (73 events).
Adverse events Within 28 days of commencing treatment 6 Important	Relative risk 0.95 (CI 95% 0.82 — 1.1) Based on data from 2,224 participants in 1 studies. [7] (Randomized controlled)	239 per 1000 Difference:	227 per 1000 **12 fewer per 1000** (CI 95% 43 fewer — 24 more)	**Moderate** Due to serious imprecision [8]	Paxlovid probably has little impact on adverse events (517 events).
Serious adverse events Within 28 days of commencing treatment 6 Important	Relative risk 0.24 (CI 95% 0.15 — 0.41) Based on data from 2,224 participants in 1 studies. [9] (Randomized controlled)	66 per 1000 Difference:	16 per 1000 **50 fewer per 1000** (CI 95% 56 fewer — 39 fewer)	**Moderate** Due to serious imprecision [10]	Paxlovid probably decreases serious adverse events slightly (92 events).
Discontinued due to adverse event Within 28 days of commencing treatment	Relative risk 0.49 (CI 95% 0.3 — 0.81) Based on data from 2,228 participants in 1 studies. [11] (Randomized controlled)	42 per 1000 Difference:	21 per 1000 **21 fewer per 1000** (CI 95% 29 fewer — 8 fewer	**Moderate** Due to serious imprecision [12]	Paxlovid probably has little impact on discontinuation due to adverse events (70 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Paxlovid	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important			)		

Attached Images

Only in research settings

Do not use nirmatrelvir plus ritonavir for the treatment of COVID-19 in children under 12 years of age without risk factors for deterioration who do not require oxygen, outside of randomised trials with appropriate ethical approval.

Additional information

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

7.1.6 Other immunomodulating drugs

Info Box

The Taskforce has developed conditional recommendations supporting the use of several non-steroidal immunomodulatory agents for the treatment of COVID-19 in hospitalised patients requiring supplemental oxygen. All of these treatments demonstrate a mortality benefit when used in this patient population (moderate certainty of evidence). While the RECOVERY trial suggests a benefit when using baricitinib in conjunction with corticosteroids, tocilizumab or remdesivir *[521]*, the Taskforce notes that concomitant use of two or more of these immunomodulatory agents may increase the risk of side effects such as opportunistic infection.

All studies that contribute data to analyses underpinning these recommendations compare the treatment of interest with either standard care or placebo. In the absence of data directly comparing one agent to another, it is unclear which of these agents is clinically superior, and thus it is not possible to promote the use of one treatment over another as first line therapy based on clinical evidence alone.

The Taskforce acknowledges the importance of other factors in deciding which treatment is administered, such as availability (e.g. sarilumab has not been approved by the TGA), route of administration and cost. A table providing a comparison of clinical and non-clinical factors between the three recommended immunomodulators can be found here.

7.1.6.1 Abatacept

7.1.6.1.1 Abatacept for adults

Conditional recommendation

Consider using abatacept for the treatment of COVID-19 in adults who require supplemental oxygen but not mechanical ventilation or ECMO, particularly where there is evidence of systemic inflammation.

Additional information

In patients hospitalised with COVID-19 who require supplemental oxygen but not mechanical ventilation or ECMO, abatacept probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for abatacept use both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections).

Results are based on the ACTIV-1 IM trial, conducted from October 2020 to December 2021, comparing abatacept with placebo in 1019 patients hospitalised with mild to critical COVID-19 [566]. Subgroup analyses demonstrate no benefit when using abatacept in the ~10% of patients who required mechanical ventilation or ECMO at baseline, however further data are needed in this population. Pregnant and breastfeeding women and paediatric patients were excluded from the trial.

In accordance with the ACTIV-1 IM trial, abatacept should be administered as a single intravenous infusion over 30 minutes at a dose of 10 mg/kg body weight (maximum dose 1000 mg).

The majority of patients in the ACTIV-1 IM trial received both remdesivir and corticosteroids within 1–5 days after treatment with abatacept, and there is limited evidence regarding the use of abatacept as a standalone treatment.

There is a known risk of reactivation of latent tuberculosis following long-term treatment with immunomodulatory drugs. The risk is unknown with very short courses such as those used for COVID-19, but reactivation is considered possible following such treatment. Screening for latent tuberculosis using an interferon-gamma release assay (IGRA) should be considered in patients planned to receive immunomodulatory treatment for COVID-19, however administration of treatment should not be delayed while awaiting results.

For patients with COVID-19 requiring supplemental oxygen, the Taskforce has developed recommendations for the use of several immunomodulators, including systemic corticosteroids (e.g. dexamethasone), tocilizumab, baricitinib, infliximab and abatacept. Current evidence suggests that dexamethasone is safe to use in combination with other immunomodulators, however there are limited data available to evaluate the safety of other combinations (although evidence from the RECOVERY trial suggests a potential benefit when using dexamethasone, tocilizumab and baricitinib together).

Due to concerns that the concomitant use of two or more immunomodulatory agents may increase the risk of side effects such as opportunistic infection, the Taskforce currently recommends that patients with COVID-19 requiring supplemental oxygen receive a systemic corticosteroid (e.g. dexamethasone) and that use of one additional immunomodulator be considered; however optimal sequencing is unclear. Furthermore, the Taskforce notes a recent trial demonstrating clinical equivalence between dexamethasone and baricitinib [570]. As a result, in individuals considered to be at high risk of adverse effects from dexamethasone, baricitinib may be considered as a stand-alone therapy. All recommendations are summarised in the Drug Treatments for Adults with COVID-19 flowchart.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Abatacept
Comparator: Placebo

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Abatacept	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of treatment 9 Critical	Relative risk 0.73 (CI 95% 0.53 — 1.01) Based on data from 1,019 participants in 1 studies. [1] (Randomized controlled)	151 per 1000 Difference:	110 per 1000 **41 fewer per 1000** (CI 95% 71 fewer — 2 more)	**Moderate** Due to serious imprecision [2]	Abatacept probably decreases all-cause mortality slightly (133 events)
All-cause mortality Within 60 days of treatment 9 Critical	Relative risk 0.85 (CI 95% 0.64 — 1.13) Based on data from 1,019 participants in 1 studies. [3] (Randomized controlled)	171 per 1000 Difference:	145 per 1000 **26 fewer per 1000** (CI 95% 62 fewer — 22 more)	**Moderate** Due to serious imprecision [4]	Abatacept probably decreases all-cause mortality slightly (161 events)
Clinical recovery Within 28 days of treatment 6 Important	Relative risk 1.06 (CI 95% 0.99 — 1.13) Based on data from 1,019 participants in 1 studies. [5] (Randomized controlled)	765 per 1000 Difference:	811 per 1000 **46 more per 1000** (CI 95% 8 fewer — 99 more)	**Moderate** Due to serious imprecision [6]	Abatacept probably increases clinical recovery slightly (802 events)
Serious adverse events Within 60 days of treatment 6 Important	Relative risk 0.94 (CI 95% 0.77 — 1.16) Based on data from 1,019 participants in 1 studies. [7] (Randomized controlled)	267 per 1000 Difference:	251 per 1000 **16 fewer per 1000** (CI 95% 61 fewer — 43 more)	**Moderate** Due to serious imprecision [8]	Abatacept probably has little impact on serious adverse events (264 events)

Attached Images

7.1.6.2 Baricitinib

7.1.6.2.1 Baricitinib for adults

Conditional recommendation

Consider using baricitinib in adults hospitalised with COVID-19 who require supplemental oxygen.

Additional information

In patients hospitalised with COVID-19 who require supplemental oxygen, baricitinib probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for baricitinib use both within and outside the context of a randomised trial.

In accordance with the RECOVERY, ACTT-2 and COV-BARRIER studies, baricitinib should be administered as a 4 mg oral daily dose for up to 14 days. In patients receiving more intensive oxygen delivery where oral administration is not feasible, administer via nasogastric tube. Consider using a reduced dose of 2 mg daily in patients with an eGFR of between 30 and 60 mL/min/1.73m2.

The Taskforce previously recommended baricitinib for use in patients who required supplemental oxygen but not mechanical ventilation or ECMO due to the absence of direct evidence within this population. Data from the COV-BARRIER extension study suggests baricitinib is safe and effective in patients hospitalised with COVID-19 who require mechanical ventilation or ECMO. The Taskforce has subsequently revised the recommendation to include these patients.

There is a known risk of reactivation of latent tuberculosis following long-term treatment with immunomodulatory drugs. The risk is unknown with very short courses such as those used for COVID-19, but reactivation is considered possible following such treatment. Screening for latent tuberculosis using an interferon-gamma release assay (IGRA) should be considered in patients planned to receive immunomodulatory treatment for COVID-19, however administration of treatment should not be delayed while awaiting results.

For patients with COVID-19 requiring supplemental oxygen, the Taskforce has developed recommendations for the use of several immunomodulators, including systemic corticosteroids (e.g. dexamethasone), tocilizumab, baricitinib, infliximab and abatacept. Current evidence suggests that dexamethasone is safe to use in combination with other immunomodulators, however there are limited data available to evaluate the safety of other combinations (although evidence from the RECOVERY trial suggests a potential benefit when using dexamethasone, tocilizumab and baricitinib together).

Due to concerns that the concomitant use of two or more immunomodulatory agents may increase the risk of side effects such as opportunistic infection, the Taskforce currently recommends that patients with COVID-19 requiring supplemental oxygen receive a systemic corticosteroid (e.g. dexamethasone) and that use of one additional immunomodulator be considered; however optimal sequencing is unclear. Furthermore, the Taskforce notes a recent trial demonstrating clinical equivalence between dexamethasone and baricitinib [570]. As a result, in individuals considered to be at high risk of adverse effects from dexamethasone, baricitinib may be considered as a stand-alone therapy. All recommendations are summarised in the Drug Treatments for Adults with COVID-19 flowchart.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

In patients hospitalised with moderate or severe COVID-19 who require supplemental oxygen, baricitinib probably decreases the incidence of death and the need for invasive mechanical ventilation.

Evidence from randomised trials versus standard care demonstrates that baricitinib has an acceptable safety profile and probably reduces the incidence of serious adverse events. Consideration should be given when administering baricitinib to patients already on other immunosuppressant or immunomodulatory drugs.

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
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.

Pregnant or breastfeeding women
There is uncertainty around the benefits and harms of baricitinib for pregnant or breastfeeding women with COVID-19 as no details were reported in the trials for these populations.

Children or adolescents
As the included trials are based on adults, there remains uncertainty around the benefits and harms of baricitinib for children and adolescents with COVID-19.

Certainty of the Evidence

Moderate

Certainty of the evidence is moderate for death and low for invasive mechanical ventilation. Certainty is high for serious adverse events, moderate for adverse events and clinical recovery, and low for all other outcomes (patients requiring non-invasive ventilation or high-flow oxygen, discontinuation due to adverse events, time to recovery, and duration of hospitalisation).

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that since there are probable mortality benefits most informed patients with COVID-19 who require supplemental oxygen would agree with the recommendation and opt for treatment with baricitinib.

Pregnant or breastfeeding patients
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.

Children and adolescents
We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit-to-harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity, however this may be affected by geographic area and access to baricitinib.

Acceptability

No important issues with the recommended alternative

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

Feasibility

Important issues, or potential issues not investigated

Oral baricitinib (Olumiant; Eli Lilly Australia Pty Ltd) is listed in the Australian Register of Therapeutic Goods for the treatment of non-COVID related conditions (*ARTG numbers: 277917, 277905*; *AusPAR*). As of 3 December 2021, baricitinib is yet to be awarded provisional determination by the Therapeutic Goods Administration for the treatment of COVID-19.

Implementability could be affected by any limitations to supply, however the likelihood and effect of such limitations on treating patients with COVID-19 will be dependent on the prevalence of COVID-19.

Rationale

General adult population

In patients hospitalised with COVID-19 who require supplemental oxygen, baricitinib probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for baricitinib both within and outside a randomised trial.

Clinical Question/ PICO

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

Summary

Evidence indicates that baricitinib probably reduces the risk of death in hospitalised adults who require supplemental oxygen, and may reduce the need for invasive mechanical ventilation, non-invasive ventilation and/or high-flow oxygen.

What is the evidence informing this recommendation?

Evidence comes from three randomised trials—one that compared baricitinib plus remdesivir with remdesivir alone in 1033 adults hospitalised with suspected COVID-19 (ACTT-2) *[22]*, one that compared baricitinib with standard care in 1525 adults with mild-to-severe COVID-19 (COV-BARRIER) *[352]*, and one that compared baricitinib with standard care in 101 adults with severe-to-critical COVID-19 (COV-BARRIER) *[413]*.

Study characteristics

Mean age of participants was 57 years and 38% were women. In the ACTT-2 trial, patients received either 4 mg baricitinib plus remdesivir (200 mg on day one, 100 mg a day until day 10 or hospital discharge) or remdesivir alone (same regimen as treatment arm). In the COV-BARRIER trial, patients also received 4 mg baricitinib. Pregnant and breastfeeding women were ineligible.

What are the main results?

Baricitinib increases the risk of serious adverse events (49 fewer SAEs per 1000; RR 0.77, CI 95% 0.66 to 0.9; 2617 patients in 3 studies) and probably decreases death (45 fewer deaths per 1000; RR 0.64, CI 95% 0.51 to 0.8; 2659 patients in 3 studies) and clinical recovery (59 more per 1000; RR 1.08, CI 95% 1.01 to 1.14; 1134 patients in 2 studies).

Baricitinib may decrease the need for invasive mechanical ventilation, non-invasive ventilation and high-flow nasal oxygen therapy. Baricitinib probably has little impact on incidence of adverse events. We are uncertain whether baricitinib increases or decreases discontinuation due to adverse events, duration of hospitalisation or time to recovery.

Our confidence in the results

Certainty of the evidence is high for serious adverse events and moderate for death, adverse events and clinical recovery due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Therapeutic Goods Administration, known harms associated with baricitinib include an increased risk of serious infections, gastrointestinal disorders, thrombosis and headaches *[24]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Baricitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.84 (CI 95% 0.76 — 0.93) Based on data from 10,815 participants in 4 studies. [1] (Randomized controlled)	133 per 1000 Difference:	112 per 1000 **21 fewer per 1000** (CI 95% 32 fewer — 9 fewer)	**High**	Baricitinib decreases death slightly.
Invasive mechanical ventilation Within 28 days of commencing treatment 9 Critical	Relative risk 0.82 (CI 95% 0.71 — 0.94) Based on data from 8,827 participants in 2 studies. [2] (Randomized controlled)	90 per 1000 Difference:	74 per 1000 **16 fewer per 1000** (CI 95% 26 fewer — 5 fewer)	**Moderate** Due to serious imprecision [3]	Baricitinib may decrease requirement for invasive mechanical ventilation slightly.
Non-invasive ventilation or HFNO End of follow-up 6 Important	Relative risk 0.83 (CI 95% 0.63 — 1.1) Based on data from 706 participants in 1 studies. [4] (Randomized controlled)	236 per 1000 Difference:	196 per 1000 **40 fewer per 1000** (CI 95% 87 fewer — 24 more)	**Low** Due to very serious imprecision [5]	Baricitinib may decrease requirement for NIV / HFNO slightly (152 events).
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 1.01 — 1.05) Based on data from 8,156 participants in 1 studies. [6] (Randomized controlled)	783 per 1000 Difference:	806 per 1000 **23 more per 1000** (CI 95% 8 more — 39 more)	**Moderate** Due to serious imprecision [7]	Baricitinib probably increases discharge from hospital slightly.
Serious adverse events	Relative risk 0.77 (CI 95% 0.66 — 0.9) Based on data from	211 per 1000	162 per 1000	**High**	Baricitinib decreases serious adverse events.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Baricitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
End of follow-up 6 Important	2,617 participants in 3 studies. [8] (Randomized controlled)	Difference:	**49 fewer per 1000** (CI 95% 72 fewer — 21 fewer)		
Adverse events End of follow-up 6 Important	Relative risk 0.94 (CI 95% 0.87 — 1.01) Based on data from 2,634 participants in 3 studies. [9] (Randomized controlled)	470 per 1000 Difference:	442 per 1000 **28 fewer per 1000** (CI 95% 61 fewer — 5 more)	**Moderate** Due to serious imprecision [10]	Baricitinib probably decreases adverse events slightly.
Discontinuation due to adverse events During treatment 6 Important	Relative risk 0.8 (CI 95% 0.57 — 1.12) Based on data from 1,502 participants in 1 studies. [11] (Randomized controlled)	93 per 1000 Difference:	74 per 1000 **19 fewer per 1000** (CI 95% 40 fewer — 11 more)	**Low** Due to very serious imprecision [12]	Baricitinib may have little or no difference on discontinuation due to adverse events (126 events).
Clinical recovery End of follow-up 6 Important	Relative risk 1.08 (CI 95% 1.01 — 1.14) Based on data from 1,134 participants in 2 studies. [13] (Randomized controlled)	738 per 1000 Difference:	797 per 1000 **59 more per 1000** (CI 95% 7 more — 103 more)	**Moderate** Due to serious imprecision [14]	Baricitinib probably improves clinical recovery.
Duration of hospitalisation Mean (days) 6 Important	Lower better (Randomized controlled)	13.7 (Mean) Difference:	12.9 (Mean) **MD 0.8 lower** CI 95%	**Low** Due to very serious imprecision [15]	We are uncertain whether baricitinib increases or decreases duration of hospitalisation.
Time to recovery Median (days) 6 Important	Lower better (Randomized controlled)	11 (Median)	10 (Median) CI 95%	**Low** Due to very serious imprecision [16]	We are uncertain whether baricitinib increases or decreases time to recovery.

Attached Images

7.1.6.2.2 Baricitinib for pregnant or breastfeeding women

Only in research settings

Do not use baricitinib for the treatment of COVID-19 in pregnant or breastfeeding women outside randomised trials with appropriate ethical approval.

Additional information

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

There is uncertainty around the benefits and harms of baricitinib for pregnant or breastfeeding women with COVID-19.

In non-pregnant adult patients hospitalised with moderate or severe COVID-19 who require supplemental oxygen, baricitinib probably decreases the incidence of death and the need for invasive mechanical ventilation.

Evidence from randomised trials versus standard care demonstrates that baricitinib has an acceptable safety profile for non-pregnant adults and probably reduces the incidence of serious adverse events. Consideration should be given when administering baricitinib to patients already on other immunosuppressant or immunomodulatory drugs.

Information on use of baricitinib in pregnancy in humans is limited and insufficient (single case report) to assess the drug-associated risks for birth anomalies or pregnancy loss, though placental transfer is expected based on molecular weight *[310][311]*. However, teratogenic effects has been observed in animal studies when used in high doses *[312]*. It is also unknown whether baricitinib is excreted in human milk, though animal data have shown excretion of baricitinib in milk *[312]*.

Decisions about baricitinib administration in pregnancy need to be made with consideration of the potential maternal benefit and the theoretical fetal risks. Factors that may weigh into shared decision-making include severity of maternal status, underlying risk factors and gestational age. Placental transfer of baricitinib may be expected based on molecular weight.

Certainty of the Evidence

Low

Certainty of the evidence is moderate for death and low for patients requiring invasive mechanical ventilation. Certainty is moderate for adverse and serious adverse events and low for all other outcomes (patients requiring non-invasive ventilation or high-flow oxygen, discontinuation due to adverse events, clinical recovery and time to recovery, and duration of hospitalisation).

Values and preferences

Substantial variability is expected or uncertain

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

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity, however this may be affected by geographic area and access to baricitinib.

Acceptability

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding acceptability by pregnant or breastfeeding women.

Feasibility

Important issues, or potential issues not investigated

Implementability could be affected by any limitations to supply, however the likelihood and effect of such limitations on treating patients with COVID-19 will be dependent on the prevalence of COVID-19.

Rationale

In non-pregnant adults hospitalised with COVID-19 who require supplemental oxygen, baricitinib probably reduces the risk of death.

Information on baricitinib in pregnancy in humans is insufficient to assess the drug-associated risks for birth anomalies or pregnancy loss, though teratogenic effects have been observed in animal studies when used in high doses. It is also unknown whether baricitinib is excreted in human milk, however animal data have shown excretion of baricitinib in milk.

Clinical Question/ PICO

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

Summary

Evidence indicates that baricitinib probably reduces the risk of death in hospitalised adults who require supplemental oxygen, and may reduce the need for invasive mechanical ventilation, non-invasive ventilation and/or high-flow oxygen.

What is the evidence informing this recommendation?
Evidence comes from three randomised trials—one that compared baricitinib plus remdesivir with remdesivir alone in 1033 adults hospitalised with suspected COVID-19 (ACTT-2) *[22]*, one that compared baricitinib with standard care in 1525 adults with mild-to-severe COVID-19 (COV-BARRIER) *[352]*, and one that compared baricitinib with standard care in 101 adults with severe-to-critical COVID-19 (COV-BARRIER) *[413]*.

Study characteristics
Mean age of participants was 57 years and 38% were women. In the ACTT-2 trial, patients received either 4 mg baricitinib plus remdesivir (200 mg on day one, 100 mg a day until day 10 or hospital discharge) or remdesivir alone (same regimen as treatment arm). In the COV-BARRIER trial, patients also received 4 mg baricitinib. Pregnant and breastfeeding women were ineligible.

What are the main results?

Baricitinib increases the risk of serious adverse events (49 fewer SAEs per 1000; RR 0.77, CI 95% 0.66 to 0.9; 2617 patients in 3 studies) and probably decreases death (45 fewer deaths per 1000; RR 0.64, CI 95% 0.51 to 0.8; 2659 patients in 3 studies) and clinical recovery (59 more per 1000; RR 1.08, CI 95% 1.01 to 1.14; 1134 patients in 2 studies).

Baricitinib may decrease the need for invasive mechanical ventilation, non-invasive ventilation and high-flow nasal oxygen therapy. Baricitinib probably has little impact on incidence of adverse events. We are uncertain whether baricitinib increases or decreases discontinuation due to adverse events, duration of hospitalisation or time to recovery.

Our confidence in the results
Certainty of the evidence is high for serious adverse events and moderate for death, adverse events and clinical recovery due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Therapeutic Goods Administration, known harms associated with baricitinib include an increased risk of serious infections, gastrointestinal disorders, thrombosis and headaches *[24]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Baricitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.84 (CI 95% 0.76 — 0.93) Based on data from 10,815 participants in 4 studies. [1] (Randomized controlled)	133 per 1000 Difference:	112 per 1000 **21 fewer per 1000** (CI 95% 32 fewer — 9 fewer)	**High**	Baricitinib decreases death slightly.
Invasive mechanical ventilation Within 28 days of commencing treatment 9 Critical	Relative risk 0.82 (CI 95% 0.71 — 0.94) Based on data from 8,827 participants in 2 studies. [2] (Randomized controlled)	90 per 1000 Difference:	74 per 1000 **16 fewer per 1000** (CI 95% 26 fewer — 5 fewer)	**Moderate** Due to serious imprecision [3]	Baricitinib may decrease requirement for invasive mechanical ventilation slightly.
Non-invasive ventilation or HFNO End of follow-up 6 Important	Relative risk 0.83 (CI 95% 0.63 — 1.1) Based on data from 706 participants in 1 studies. [4] (Randomized controlled)	236 per 1000 Difference:	196 per 1000 **40 fewer per 1000** (CI 95% 87 fewer — 24 more)	**Low** Due to very serious imprecision [5]	Baricitinib may decrease requirement for NIV / HFNO slightly (152 events).
Discharge from hospital	Relative risk 1.03 (CI 95% 1.01 — 1.05)	783	806	**Moderate** Due to serious	Baricitinib probably increases discharge

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Baricitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Within 28 days of commencing treatment 6 Important	Based on data from 8,156 participants in 1 studies. [6] (Randomized controlled)	per 1000 Difference:	per 1000 **23 more per 1000** (CI 95% 8 more — 39 more)	imprecision [7]	from hospital slightly.
Serious adverse events End of follow-up 6 Important	Relative risk 0.77 (CI 95% 0.66 — 0.9) Based on data from 2,617 participants in 3 studies. [8] (Randomized controlled)	**211** per 1000 Difference:	**162** per 1000 **49 fewer per 1000** (CI 95% 72 fewer — 21 fewer)	**High**	Baricitinib decreases serious adverse events.
Adverse events End of follow-up 6 Important	Relative risk 0.94 (CI 95% 0.87 — 1.01) Based on data from 2,634 participants in 3 studies. [9] (Randomized controlled)	**470** per 1000 Difference:	**442** per 1000 **28 fewer per 1000** (CI 95% 61 fewer — 5 more)	**Moderate** Due to serious imprecision [10]	Baricitinib probably decreases adverse events slightly.
Discontinuation due to adverse events During treatment 6 Important	Relative risk 0.8 (CI 95% 0.57 — 1.12) Based on data from 1,502 participants in 1 studies. [11] (Randomized controlled)	**93** per 1000 Difference:	**74** per 1000 **19 fewer per 1000** (CI 95% 40 fewer — 11 more)	**Low** Due to very serious imprecision [12]	Baricitinib may have little or no difference on discontinuation due to adverse events (126 events).
Clinical recovery End of follow-up 6 Important	Relative risk 1.08 (CI 95% 1.01 — 1.14) Based on data from 1,134 participants in 2 studies. [13] (Randomized controlled)	**738** per 1000 Difference:	**797** per 1000 **59 more per 1000** (CI 95% 7 more — 103 more)	**Moderate** Due to serious imprecision [14]	Baricitinib probably improves clinical recovery.
Duration of hospitalisation Mean (days) 6 Important	Lower better (Randomized controlled)	**13.7** (Mean) Difference:	**12.9** (Mean) **MD 0.8 lower** CI 95%	**Low** Due to very serious imprecision [15]	We are uncertain whether baricitinib increases or decreases duration of hospitalisation.
Time to recovery	Lower better	**11** (Median)	**10** (Median)	**Low** Due to very	We are uncertain whether baricitinib

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Baricitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Median (days) 6 Important	(Randomized controlled)		CI 95%	serious imprecision [16]	increases or decreases time to recovery.

Attached Images

7.1.6.2.3 Baricitinib for children and adolescents

Consensus recommendation

Consider using baricitinib for the treatment of COVID-19 in children and adolescents who require non-invasive or invasive ventilation.

Additional information

In adult patients hospitalised with COVID-19 who require supplemental oxygen, baricitinib probably reduces the risk of death. Although there is a paucity of safety data regarding the use of baricitinib in paediatric patients, the Taskforce notes that the RECOVERY trial included 33 patients 2–18 years of age in their analyses [521]. Because of this, the Taskforce gives a consensus recommendation for baricitinib use both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections).

Baricitinib should be administered orally, either as a tablet or dissolved in 10–15 ml of water. Alternatively, if the patient is unable to swallow, baricitinib can be administered via nasogastric feeding tube, however, it may block tubes that are size 12 French or smaller. Do not crush or disperse the tablet if you are pregnant: staff who are actively trying to conceive or who are pregnant or breastfeeding should not prepare or handle a dispersed dose (NSW TAG). If cutting the tablet it should be done in a powder containment cabinet OR may be cut using a tablet cutter if wearing full PPE [457].

Following protocol information in the RECOVERY trial, the suggested dose is dependent on age:

- *Children 2–9 years: 2 mg per day*
- *Children 10–18 years: 4 mg per day*

In addition, the RECOVERY trial demonstrated a significant benefit when using corticosteroids in conjunction with baricitinib in adults. Use of combined baricitinib and corticosteroids should be considered in children and adolescents hospitalised with COVID-19 who require non-invasive or invasive ventilation, however, the optimal sequencing of baricitinib and corticosteroid use is unclear in all populations.

In the absence of reliable evidence, the Taskforce has developed this recommendation based on their clinical expertise and experience.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes some people would consider baricitinib as part of the treatment pathway while others might prefer one of the other treatment options, and some might want to wait for more evidence.

The Consumer Panel notes that it is highly likely that this group has significant links to the healthcare system, and that this medication is most likely to be suggested in the context in of an established relationship with a specialist treatment team. They also note that in this age group people's level of ability to make informed choices themselves varies considerably, and that these decisions should be made in partnership with both the patient themselves and their parents/guardians.

Clinical Question/ PICO

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

Summary

Evidence indicates that baricitinib probably reduces the risk of death in hospitalised adults who require supplemental oxygen, and may reduce the need for invasive mechanical ventilation, non-invasive ventilation and/or high-flow oxygen.

What is the evidence informing this recommendation?
Evidence comes from three randomised trials—one that compared baricitinib plus remdesivir with remdesivir alone in 1033 adults hospitalised with suspected COVID-19 (ACTT-2) *[22]*, one that compared baricitinib with standard care in 1525 adults with mild-to-severe COVID-19 (COV-BARRIER) *[352]*, and one that compared baricitinib with standard care in 101 adults with severe-to-critical COVID-19 (COV-BARRIER) *[413]*.

Study characteristics
Mean age of participants was 57 years and 38% were women. In the ACTT-2 trial, patients received either 4 mg baricitinib plus remdesivir (200 mg on day one, 100 mg a day until day 10 or hospital discharge) or remdesivir alone (same regimen as treatment arm). In the COV-BARRIER trial, patients also received 4 mg baricitinib. Pregnant and breastfeeding women were ineligible.

What are the main results?
Baricitinib increases the risk of serious adverse events (49 fewer SAEs per 1000; RR 0.77, CI 95% 0.66 to 0.9; 2617 patients in 3 studies) and probably decreases death (45 fewer deaths per 1000; RR 0.64, CI 95% 0.51 to 0.8; 2659 patients in 3 studies) and clinical recovery (59 more per 1000; RR 1.08, CI 95% 1.01 to 1.14; 1134 patients in 2 studies).

Baricitinib may decrease the need for invasive mechanical ventilation, non-invasive ventilation and high-flow nasal oxygen therapy. Baricitinib probably has little impact on incidence of adverse events. We are uncertain whether baricitinib increases or decreases discontinuation due to adverse events, duration of hospitalisation or time to recovery.

Our confidence in the results
Certainty of the evidence is high for serious adverse events and moderate for death, adverse events and clinical recovery due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Therapeutic Goods Administration, known harms associated with baricitinib include an increased risk of serious infections, gastrointestinal disorders, thrombosis and headaches *[24]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Baricitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.84 (CI 95% 0.76 — 0.93) Based on data from 10,815 participants in 4 studies. [1] (Randomized controlled)	133 per 1000 Difference:	112 per 1000 **21 fewer per 1000** (CI 95% 32 fewer — 9 fewer)	**High**	Baricitinib decreases death slightly.
Invasive mechanical ventilation	Relative risk 0.82 (CI 95% 0.71 — 0.94) Based on data from	90 per 1000	74 per 1000	**Moderate** Due to serious imprecision [3]	Baricitinib may decrease requirement for invasive

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Baricitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Within 28 days of commencing treatment 9 Critical	8,827 participants in 2 studies. [2] (Randomized controlled)	Difference:	**16 fewer per 1000** (CI 95% 26 fewer — 5 fewer)		mechanical ventilation slightly.
Non-invasive ventilation or HFNO End of follow-up 6 Important	Relative risk 0.83 (CI 95% 0.63 — 1.1) Based on data from 706 participants in 1 studies. [4] (Randomized controlled)	236 per 1000 Difference:	196 per 1000 **40 fewer per 1000** (CI 95% 87 fewer — 24 more)	**Low** Due to very serious imprecision [5]	Baricitinib may decrease requirement for NIV / HFNO slightly (152 events).
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 1.01 — 1.05) Based on data from 8,156 participants in 1 studies. [6] (Randomized controlled)	783 per 1000 Difference:	806 per 1000 **23 more per 1000** (CI 95% 8 more — 39 more)	**Moderate** Due to serious imprecision [7]	Baricitinib probably increases discharge from hospital slightly.
Serious adverse events End of follow-up 6 Important	Relative risk 0.77 (CI 95% 0.66 — 0.9) Based on data from 2,617 participants in 3 studies. [8] (Randomized controlled)	211 per 1000 Difference:	162 per 1000 **49 fewer per 1000** (CI 95% 72 fewer — 21 fewer)	**High**	Baricitinib decreases serious adverse events.
Adverse events End of follow-up 6 Important	Relative risk 0.94 (CI 95% 0.87 — 1.01) Based on data from 2,634 participants in 3 studies. [9] (Randomized controlled)	470 per 1000 Difference:	442 per 1000 **28 fewer per 1000** (CI 95% 61 fewer — 5 more)	**Moderate** Due to serious imprecision [10]	Baricitinib probably decreases adverse events slightly.
Discontinuation due to adverse events During treatment 6 Important	Relative risk 0.8 (CI 95% 0.57 — 1.12) Based on data from 1,502 participants in 1 studies. [11] (Randomized controlled)	93 per 1000 Difference:	74 per 1000 **19 fewer per 1000** (CI 95% 40 fewer — 11 more)	**Low** Due to very serious imprecision [12]	Baricitinib may have little or no difference on discontinuation due to adverse events (126 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Baricitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Clinical recovery End of follow-up 6 Important	Relative risk 1.08 (CI 95% 1.01 — 1.14) Based on data from 1,134 participants in 2 studies. [13] (Randomized controlled)	738 per 1000 Difference:	797 per 1000 **59 more per 1000** (CI 95% 7 more — 103 more)	**Moderate** Due to serious imprecision [14]	Baricitinib probably improves clinical recovery.
Duration of hospitalisation Mean (days) 6 Important	Lower better (Randomized controlled)	13.7 (Mean) Difference:	12.9 (Mean) **MD 0.8 lower** CI 95%	**Low** Due to very serious imprecision [15]	We are uncertain whether baricitinib increases or decreases duration of hospitalisation.
Time to recovery Median (days) 6 Important	Lower better (Randomized controlled)	11 (Median)	10 (Median) CI 95%	**Low** Due to very serious imprecision [16]	We are uncertain whether baricitinib increases or decreases time to recovery.

Attached Images

7.1.6.3 Infliximab

7.1.6.3.1 Infliximab for adults

Conditional recommendation

Consider using infliximab for the treatment of COVID-19 in adults who require supplemental oxygen but not mechanical ventilation or ECMO, particularly where there is evidence of systemic inflammation.

Additional information

In patients hospitalised with COVID-19 who require supplemental oxygen but not mechanical ventilation or ECMO, infliximab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for infliximab use both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections).

Results are based on the ACTIV-1 IM trial, conducted from October 2020 to December 2021, comparing infliximab with placebo in 1033 patients hospitalised with mild to critical COVID-19 [565]. Subgroup analyses demonstrate no benefit when using infliximab in the ~10% of patients who required mechanical ventilation or ECMO at baseline, however further data are needed in this population. Pregnant and breastfeeding women and paediatric patients were excluded from the trial.

In accordance with the ACTIV-1 IM trial, infliximab should be administered as a single intravenous infusion over 120 minutes at a dose of 5 mg/kg body weight.

The majority of patients in the ACTIV-1 IM trial received both remdesivir and corticosteroids within 1–5 days after treatment with infliximab, and there is limited evidence regarding the use of infliximab as a standalone treatment. The Taskforce notes that the concomitant use of two or more immunomodulatory agents may increase the risk of side effects such as opportunistic infection.

There is a known risk of reactivation of latent tuberculosis following long-term treatment with immunomodulatory drugs. The risk is unknown with very short courses such as those used for COVID-19, but reactivation is considered possible following such treatment. Screening for latent tuberculosis using an interferon-gamma release assay (IGRA) should be considered in patients planned to receive immunomodulatory treatment for COVID-19, however administration of treatment should not be delayed while awaiting results.

For patients with COVID-19 requiring supplemental oxygen, the Taskforce has developed recommendations for the use of several immunomodulators, including systemic corticosteroids (e.g. dexamethasone), tocilizumab, baricitinib, infliximab and abatacept. Current evidence suggests that dexamethasone is safe to use in combination with other immunomodulators, however there are limited data available to evaluate the safety of other combinations (although evidence from the RECOVERY trial suggests a potential benefit when using dexamethasone, tocilizumab and baricitinib together).

Due to concerns that the concomitant use of two or more immunomodulatory agents may increase the risk of side effects such as opportunistic infection, the Taskforce currently recommends that patients with COVID-19 requiring supplemental oxygen receive a systemic corticosteroid (e.g. dexamethasone) and that use of one additional immunomodulator be considered; however optimal sequencing is unclear. Furthermore, the Taskforce notes a recent trial demonstrating clinical equivalence between dexamethasone and baricitinib [570]. As a result, in individuals considered to be at high risk of adverse effects from dexamethasone, baricitinib may be considered as a stand-alone therapy. All recommendations are summarised in the Drug Treatments for Adults with COVID-19 flowchart.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Infliximab
Comparator: Placebo

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Infliximab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 60 days of treatment 9 Critical	Relative risk 0.76 (CI 95% 0.57 — 1.03) Based on data from 1,033 participants in 1 studies. [1] (Randomized controlled)	165 per 1000 Difference:	125 per 1000 **40 fewer per 1000** (CI 95% 71 fewer — 5 more)	**Moderate** Due to serious imprecision [2]	Infliximab probably decreases all-cause mortality slightly (150 events)
All cause mortality Within 28 days of treatment 9 Critical	Relative risk 0.69 (CI 95% 0.5 — 0.96) Based on data from 1,033 participants in 1 studies. [3] (Randomized controlled)	145 per 1000 Difference:	100 per 1000 **45 fewer per 1000** (CI 95% 72 fewer — 6 fewer)	**Moderate** Due to serious imprecision [4]	Infliximab probably decreases all cause mortality slightly (137 events)
Clinical Recovery Within 28 days of treatment 6 Important	Relative risk 1.04 (CI 95% 0.98 — 1.11) Based on data from 1,033 participants in 1 studies. [5] (Randomized controlled)	771 per 1000 Difference:	802 per 1000 **31 more per 1000** (CI 95% 15 fewer — 85 more)	**Moderate** Due to serious imprecision [6]	Infliximab probably increases clinical recovery slightly (814 events)
Serious Adverse Events Within 60 days of treatment 6 Important	Relative risk 0.96 (CI 95% 0.78 — 1.19) Based on data from 1,033 participants in 1 studies. [7] (Randomized controlled)	252 per 1000 Difference:	242 per 1000 **10 fewer per 1000** (CI 95% 55 fewer — 48 more)	**Moderate** Due to serious imprecision [8]	Infliximab probably has little impact on serious adverse events (255 events)

Attached Images

7.1.6.4 Sarilumab

7.1.6.4.1 Sarilumab for adults

Conditional recommendation

Consider using sarilumab for the treatment of COVID-19 in adults who require high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation.

Additional information

In patients hospitalised with COVID-19 who require high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation, sarilumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for sarilumab use both within and outside the context of a randomised trial.

Uncertainty remains whether sarilumab impacts risk of death in patients who require no ventilatory support or low-flow oxygen.

There is a known risk of reactivation of latent tuberculosis following long-term treatment with immunomodulatory drugs. The risk is unknown with very short courses such as those used for COVID-19, but reactivation is considered possible following such treatment. Screening for latent tuberculosis using an interferon-gamma release assay (IGRA) should be considered in patients planned to receive immunomodulatory treatment for COVID-19, however administration of treatment should not be delayed while awaiting results.

For patients with COVID-19 requiring supplemental oxygen, the Taskforce has developed recommendations for the use of several immunomodulators, including systemic corticosteroids (e.g. dexamethasone), tocilizumab, baricitinib, infliximab and abatacept. Current evidence suggests that dexamethasone is safe to use in combination with other immunomodulators, however there are limited data available to evaluate the safety of other combinations (although evidence from the RECOVERY trial suggests a potential benefit when using dexamethasone, tocilizumab and baricitinib together).

Due to concerns that the concomitant use of two or more immunomodulatory agents may increase the risk of side effects such as opportunistic infection, the Taskforce currently recommends that patients with COVID-19 requiring supplemental oxygen receive a systemic corticosteroid (e.g. dexamethasone) and that use of one additional immunomodulator be considered; however optimal sequencing is unclear. Furthermore, the Taskforce notes a recent trial demonstrating clinical equivalence between dexamethasone and baricitinib [570]. As a result, in individuals considered to be at high risk of adverse effects from dexamethasone, baricitinib may be considered as a stand-alone therapy. All recommendations are summarised in the Drug Treatments for Adults with COVID-19 flowchart.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

General adult population

In patients hospitalised with critical COVID-19 who require supplemental oxygen, sarilumab probably decreases the incidence of death.

Evidence from randomised trials versus standard care demonstrates that sarilumab does not increase the risk of serious adverse events, however it probably increases the risk of non-serious adverse events. According to the Therapeutic Goods Administration, common side effects and harms associated with sarilumab include upper respiratory tract infections, neutropenia and injection site reactions *[184]*.

Children and adolescents

The safety profile in children and adolescents with COVID-19 has not been established.

Certainty of the Evidence

Moderate

Certainty of the evidence is moderate for mortality, adverse and serious adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that since there are probable mortality benefits most informed patients with COVID-19 who require supplemental oxygen would agree with the recommendation and opt for sarilumab.

Pregnant or breastfeeding patients
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.

Children and adolescents
We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity; however potential limitations on availability may affect equity based on geographic area and access to sarilumab.

Acceptability

No important issues with the recommended alternative

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians, unless contraindicated (e.g. in patients with bacterial, fungal or mycobacterial infections).

Feasibility

Intervention is likely difficult to implement

Subcutaneous sarilumab (Kevzara; Sanofi-Aventis Australia Pty Ltd) is listed in the Australian Register of Therapeutic Goods for the treatment of non-COVID related conditions (ARTG numbers: 293333, 293334, 293335, 293336; AusPAR). As of 3 December 2021, sarilumab is yet to be awarded provisional determination by the Therapeutic Goods Administration for the treatment of COVID-19.

Rationale

General adult population
In patients hospitalised with COVID-19 who require supplemental oxygen, sarilumab probably reduces the risk of

death. Because of this, the Taskforce gives a conditional recommendation for sarilumab both within and outside the context of a randomised trial.

Clinical Question/ PICO

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

Summary

Evidence indicates that sarilumab probably reduces the risk of death in hospitalised adults who require high-flow oxygen, non-invasive ventilation and invasive mechanical ventilation.

What is the evidence informing this recommendation?
Evidence comes from seven randomised trials that compared sarilumab with standard care in 970 adults hospitalised with critical COVID-19 *[435][438]*, 2238 patients hospitalised with severe to critical COVID-19 *[185][423]* and 460 patients with moderate to critical COVID-19 *[156][434][437]*.

Study characteristics
Mean age of participants ranged from 58 to 63 years, and the proportion of women ranged from 19 to 36%. Pregnant and breastfeeding women were ineligible.

Consideration was given to separating data based on severity of illness (severe and critical subgroups); however it was considered inappropriate to do so due to limited data and a non-significant test for subgroup differences.

What are the main results?
Sarilumab probably decreases death slightly (28 fewer per 1000; RR 0.79, CI 95% 0.73 to 1.02; 3291 patients in 6 studies). Sarilumab probably has little impact on serious adverse events or discharge from hospital, but probably increases adverse events slightly (38 more per 1000; RR 1.07, CI 95% 0.98 to 1.18; 1946 patients in 3 studies). We are unsure whether sarilumab increases or decreases the requirement for ventilation, admission to ICU, clinical improvement or clinical recovery.

Our confidence in the results
Certainty of the evidence is moderate for death, serious adverse events and adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Australian Therapeutic Goods Administration, side effects associated with sarilumab include upper respiratory tract infections, neutropaenia, increased alanine aminotransferase (ALT) and injection site redness *[184]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Sarilumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 21-29 days of commencing treatment 9 Critical	Relative risk 0.89 (CI 95% 0.79 — 1.02) Based on data from 3,291 participants in 7 studies. [1] (Randomized controlled)	**259** per 1000 Difference:	**231** per 1000 **28 fewer per 1000** (CI 95% 54 fewer — 5 more)	**Moderate** Due to serious imprecision [2]	Sarilumab probably decreases death slightly (775 events)

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Sarilumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mechanical ventilation Within 28 days of treatment 9 Critical	Relative risk 1.15 (CI 95% 0.38 — 3.51) Based on data from 115 participants in 1 studies. [3] (Randomized controlled)	103 per 1000 Difference:	118 per 1000 **15 more per 1000** (CI 95% 64 fewer — 259 more)	**Very low** Due to extremely serious imprecision [4]	We are uncertain whether sarilumab increases or decreases need for mechanical ventilation (13 events)
Respiratory failure Within 28 days of treatment 9 Critical	Relative risk 1.03 (CI 95% 0.55 — 1.94) Based on data from 201 participants in 1 studies. [5] (Randomized controlled)	157 per 1000 Difference:	162 per 1000 **5 more per 1000** (CI 95% 71 fewer — 148 more)	**Low** Due to very serious imprecision [6]	Sarilumab may have little or no difference on respiratory failure
Requiring ventilation (HFNO, NIV, MV) End of follow-up 6 Important	Relative risk 0.93 (CI 95% 0.58 — 1.51) Based on data from 531 participants in 2 studies. [7] (Randomized controlled)	195 per 1000 Difference:	181 per 1000 **14 fewer per 1000** (CI 95% 82 fewer — 99 more)	**Low** Due to serious inconsistency and serious imprecision [8]	Sarilumab may have little impact on number of patients requiring ventilation (98 events)
Serious adverse events End of follow-up 6 Important	Relative risk 1.04 (CI 95% 0.91 — 1.18) Based on data from 2,396 participants in 4 studies. [9] (Randomized controlled)	214 per 1000 Difference:	223 per 1000 **9 more per 1000** (CI 95% 19 fewer — 39 more)	**Moderate** Due to serious imprecision [10]	Sarilumab probably has little impact on serious adverse events.
Adverse events End of follow-up 6 Important	Relative risk 1.07 (CI 95% 0.98 — 1.18) Based on data from 1,946 participants in 3 studies. [11] (Randomized controlled)	549 per 1000 Difference:	587 per 1000 **38 more per 1000** (CI 95% 11 fewer — 99 more)	**Moderate** Due to serious imprecision [12]	Sarilumab probably increases adverse events slightly.
Admission to ICU Within 28 days of treatment 6 Important	Relative risk 0.9 (CI 95% 0.5 — 1.63) Based on data from 469 participants in 2 studies. [13] (Randomized controlled)	108 per 1000 Difference:	97 per 1000 **11 fewer per 1000** (CI 95% 54 fewer — 68	**Moderate** Due to serious imprecision [14]	Sarilumab probably has little or no impact on admission to ICU (52 events)

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Sarilumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
			more)		
Clinical improvement Within 22 days of commencing treatment 6 Important	Relative risk 0.98 (CI 95% 0.87 — 1.1) Based on data from 1,097 participants in 1 studies. [15] (Randomized controlled)	608 per 1000 Difference:	596 per 1000 **12 fewer per 1000** (CI 95% 79 fewer — 61 more)	**Low** Due to very serious imprecision [16]	Sarilumab may have little impact on clinical improvement.
Clinical recovery Within 22 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.89 — 1.1) Based on data from 1,449 participants in 1 studies. [17] (Randomized controlled)	589 per 1000 Difference:	583 per 1000 **6 fewer per 1000** (CI 95% 65 fewer — 59 more)	**Low** Due to very serious imprecision [18]	Sarilumab may have little impact on clinical recovery.
Discharged from hospital End of follow-up 6 Important	Relative risk 0.99 (CI 95% 0.95 — 1.05) Based on data from 1,973 participants in 5 studies. [19] (Randomized controlled)	636 per 1000 Difference:	630 per 1000 **6 fewer per 1000** (CI 95% 32 fewer — 32 more)	**Moderate** Due to serious imprecision [20]	Sarilumab probably has little impact on discharge from hospital.

Attached Images

7.1.6.4.2 Sarilumab for pregnant or breastfeeding women

Only in research settings

Do not use sarilumab for the treatment of COVID-19 in pregnant or breastfeeding women outside randomised trials with appropriate ethical approval.

Additional information

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

There is uncertainty around the benefits and harms of sarilumab for pregnant or breastfeeding women with COVID-19.

In non-pregnant adult patients hospitalised with critical COVID-19 who require supplemental oxygen, sarilumab probably decreases the incidence of death.

Evidence from randomised trials versus standard care in non-pregnant adults demonstrates that sarilumab does not increase the risk of serious adverse events, however it probably increases the risk of non-serious adverse events. According to the Therapeutic Goods Administration, common side effects and harms associated with sarilumab include upper respiratory tract infections, neutropaenia and injection site reactions *[184]*.

Certainty of the Evidence

Low

Certainty of the evidence ismoderate for mortality, adverse and serious adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Values and preferences

Substantial variability is expected or uncertain

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

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity; however potential limitations on

availability may affect equity based on geographic area and access to sarilumab.

Acceptability

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding acceptability by pregnant or breastfeeding women.

Feasibility

Important issues, or potential issues not investigated

Implementability could be affected by any limitations to supply, however the likelihood and effect of such limitations on treating patients with COVID-19 will be dependent on the prevalence of COVID-19.

Rationale

There is no information on the use of sarilumab during pregnancy and breastfeeding in humans. Limited data are available from animal studies, where the possibility that sarilumab increases stillbirth or pregnancy loss rates cannot be ruled out. It is not known if sarilumab is present in breast milk.

In non-pregnant adult patients hospitalised with COVID-19 who require supplemental oxygen, sarilumab probably reduces the risk of death. Because of this, the Taskforce has given a conditional recommendation for sarilumab in non-pregnant adult patients both within and outside the context of a randomised trial.

Clinical Question/ PICO

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

Summary

Evidence indicates that sarilumab probably reduces the risk of death in hospitalised adults who require high-flow oxygen, non-invasive ventilation and invasive mechanical ventilation.

What is the evidence informing this recommendation?
Evidence comes from seven randomised trials that compared sarilumab with standard care in 970 adults hospitalised with critical COVID-19 *[435][438]*, 2238 patients hospitalised with severe to critical COVID-19 *[185][423]* and 460 patients with moderate to critical COVID-19 *[156][434][437]*.

Study characteristics
Mean age of participants ranged from 58 to 63 years, and the proportion of women ranged from 19 to 36%. Pregnant and breastfeeding women were ineligible.

Consideration was given to separating data based on severity of illness (severe and critical subgroups); however it was considered inappropriate to do so due to limited data and a non-significant test for subgroup differences.

What are the main results?
Sarilumab probably decreases death slightly (28 fewer per 1000; RR 0.79, CI 95% 0.73 to 1.02; 3291 patients in 6 studies). Sarilumab probably has little impact on serious adverse events or discharge from hospital, but probably increases adverse events slightly (38 more per 1000; RR 1.07, CI 95% 0.98 to 1.18; 1946 patients in 3 studies). We are unsure whether sarilumab increases or decreases the requirement for ventilation, admission to ICU, clinical improvement or clinical recovery.

Our confidence in the results
Certainty of the evidence is moderate for death, serious adverse events and adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Australian Therapeutic Goods Administration, side effects associated with sarilumab include upper respiratory tract infections, neutropaenia, increased alanine aminotransferase (ALT) and injection site redness *[184]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Sarilumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 21-29 days of commencing treatment 9 Critical	Relative risk 0.89 (CI 95% 0.79 — 1.02) Based on data from 3,291 participants in 7 studies. [1] (Randomized controlled)	259 per 1000 Difference:	231 per 1000 **28 fewer per 1000** (CI 95% 54 fewer — 5 more)	**Moderate** Due to serious imprecision [2]	Sarilumab probably decreases death slightly (775 events)
Mechanical ventilation Within 28 days of treatment 9 Critical	Relative risk 1.15 (CI 95% 0.38 — 3.51) Based on data from 115 participants in 1 studies. [3] (Randomized controlled)	103 per 1000 Difference:	118 per 1000 **15 more per 1000** (CI 95% 64 fewer — 259 more)	**Very low** Due to extremely serious imprecision [4]	We are uncertain whether sarilumab increases or decreases need for mechanical ventilation (13 events)
Respiratory failure Within 28 days of treatment 9 Critical	Relative risk 1.03 (CI 95% 0.55 — 1.94) Based on data from 201 participants in 1 studies. [5] (Randomized controlled)	157 per 1000 Difference:	162 per 1000 **5 more per 1000** (CI 95% 71 fewer — 148 more)	**Low** Due to very serious imprecision [6]	Sarilumab may have little or no difference on respiratory failure
Requiring ventilation (HFNO, NIV, MV) End of follow-up 6 Important	Relative risk 0.93 (CI 95% 0.58 — 1.51) Based on data from 531 participants in 2 studies. [7] (Randomized controlled)	195 per 1000 Difference:	181 per 1000 **14 fewer per 1000** (CI 95% 82 fewer — 99 more)	**Low** Due to serious inconsistency and serious imprecision [8]	Sarilumab may have little impact on number of patients requiring ventilation (98 events)
Serious adverse events End of follow-	Relative risk 1.04 (CI 95% 0.91 — 1.18) Based on data from 2,396 participants in 4	214 per 1000	223 per 1000	**Moderate** Due to serious imprecision [10]	Sarilumab probably has little impact on serious adverse events.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Sarilumab	Certainty of the Evidence (Quality of evidence)	Plain language summary
up 6 Important	studies. [9] (Randomized controlled)	Difference:	**9 more per 1000** (CI 95% 19 fewer — 39 more)		
Adverse events End of follow-up 6 Important	Relative risk 1.07 (CI 95% 0.98 — 1.18) Based on data from 1,946 participants in 3 studies. [11] (Randomized controlled)	549 per 1000 Difference:	587 per 1000 **38 more per 1000** (CI 95% 11 fewer — 99 more)	**Moderate** Due to serious imprecision [12]	Sarilumab probably increases adverse events slightly.
Admission to ICU Within 28 days of treatment 6 Important	Relative risk 0.9 (CI 95% 0.5 — 1.63) Based on data from 469 participants in 2 studies. [13] (Randomized controlled)	108 per 1000 Difference:	97 per 1000 **11 fewer per 1000** (CI 95% 54 fewer — 68 more)	**Moderate** Due to serious imprecision [14]	Sarilumab probably has little or no impact on admission to ICU (52 events)
Clinical improvement Within 22 days of commencing treatment 6 Important	Relative risk 0.98 (CI 95% 0.87 — 1.1) Based on data from 1,097 participants in 1 studies. [15] (Randomized controlled)	608 per 1000 Difference:	596 per 1000 **12 fewer per 1000** (CI 95% 79 fewer — 61 more)	**Low** Due to very serious imprecision [16]	Sarilumab may have little impact on clinical improvement.
Clinical recovery Within 22 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.89 — 1.1) Based on data from 1,449 participants in 1 studies. [17] (Randomized controlled)	589 per 1000 Difference:	583 per 1000 **6 fewer per 1000** (CI 95% 65 fewer — 59 more)	**Low** Due to very serious imprecision [18]	Sarilumab may have little impact on clinical recovery.
Discharged from hospital End of follow-up 6 Important	Relative risk 0.99 (CI 95% 0.95 — 1.05) Based on data from 1,973 participants in 5 studies. [19] (Randomized controlled)	636 per 1000 Difference:	630 per 1000 **6 fewer per 1000** (CI 95% 32 fewer — 32 more)	**Moderate** Due to serious imprecision [20]	Sarilumab probably has little impact on discharge from hospital.

Attached Images

7.1.6.4.3 Sarilumab for children and adolescents

Only in research settings

Do not use sarilumab for the treatment of COVID-19 in children and adolescents outside randomised trials with appropriate ethical approval.

Additional information

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

In adult patients hospitalised with critical COVID-19 who require supplemental oxygen, sarilumab probably decreases the incidence of death.

Evidence from randomised trials versus standard care in adult patients demonstrates that sarilumab does not increase the risk of serious adverse events, however it probably increases the risk of non-serious adverse events. According to the Therapeutic Goods Administration, common side effects and harms associated with sarilumab include upper respiratory tract infections, neutropaenia and injection site reactions *[184]*.

Currently there is insufficient evidence for the safety of sarilumab in children and adolescents, as it has not been approved previously for any other indication. Phase II trials are currently being conducted to assess this in children and adolescents for other indications.

Certainty of the Evidence

Low

Certainty of the evidence is moderate for mortality, adverse and serious adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit-to-harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity; however potential limitations on availability may affect equity based on geographic area and access to sarilumab.

Acceptability

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding acceptability.

Feasibility

Important issues, or potential issues not investigated

Implementability could be affected by any limitations to supply, however the likelihood and effect of such limitations on treating patients with COVID-19 will be dependent on the prevalence of COVID-19.

Rationale

Currently, sarilumab is not approved in children or adolescents for any other indication. Given this, uncertainties remain regarding the potential benefits and harms of this drug in this population.

Clinical Question/ PICO

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

Summary

Evidence indicates that sarilumab probably reduces the risk of death in hospitalised adults who require high-flow oxygen, non-invasive ventilation and invasive mechanical ventilation.

What is the evidence informing this recommendation?
Evidence comes from seven randomised trials that compared sarilumab with standard care in 970 adults hospitalised with critical COVID-19 *[435][438]*, 2238 patients hospitalised with severe to critical COVID-19 *[185][423]* and 460 patients with moderate to critical COVID-19 *[156][434][437]*.

Study characteristics
Mean age of participants ranged from 58 to 63 years, and the proportion of women ranged from 19 to 36%. Pregnant and breastfeeding women were ineligible.

Consideration was given to separating data based on severity of illness (severe and critical subgroups); however it was considered inappropriate to do so due to limited data and a non-significant test for subgroup differences.

What are the main results?
Sarilumab probably decreases death slightly (28 fewer per 1000; RR 0.79, CI 95% 0.73 to 1.02; 3291 patients in 6 studies). Sarilumab probably has little impact on serious adverse events or discharge from hospital, but probably increases adverse events slightly (38 more per 1000; RR 1.07, CI 95% 0.98 to 1.18; 1946 patients in 3 studies). We are unsure whether sarilumab increases or decreases the requirement for ventilation, admission to ICU, clinical improvement or clinical recovery.

Our confidence in the results
Certainty of the evidence is moderate for death, serious adverse events and adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Australian Therapeutic Goods Administration, side effects associated with sarilumab include upper respiratory tract infections, neutropaenia, increased alanine aminotransferase (ALT) and injection site redness *[184]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Sarilumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 21-29 days of commencing treatment 9 Critical	Relative risk 0.89 (CI 95% 0.79 — 1.02) Based on data from 3,291 participants in 7 studies. [1] (Randomized controlled)	259 per 1000 Difference:	231 per 1000 **28 fewer per 1000** (CI 95% 54 fewer — 5 more)	**Moderate** Due to serious imprecision [2]	Sarilumab probably decreases death slightly (775 events)
Mechanical ventilation Within 28 days of treatment 9 Critical	Relative risk 1.15 (CI 95% 0.38 — 3.51) Based on data from 115 participants in 1 studies. [3] (Randomized controlled)	103 per 1000 Difference:	118 per 1000 **15 more per 1000** (CI 95% 64 fewer — 259 more)	**Very low** Due to extremely serious imprecision [4]	We are uncertain whether sarilumab increases or decreases need for mechanical ventilation (13 events)
Respiratory failure Within 28 days of treatment 9 Critical	Relative risk 1.03 (CI 95% 0.55 — 1.94) Based on data from 201 participants in 1 studies. [5] (Randomized controlled)	157 per 1000 Difference:	162 per 1000 **5 more per 1000** (CI 95% 71 fewer — 148 more)	**Low** Due to very serious imprecision [6]	Sarilumab may have little or no difference on respiratory failure
Requiring ventilation (HFNO, NIV, MV) End of follow-up 6 Important	Relative risk 0.93 (CI 95% 0.58 — 1.51) Based on data from 531 participants in 2 studies. [7] (Randomized controlled)	195 per 1000 Difference:	181 per 1000 **14 fewer per 1000** (CI 95% 82 fewer — 99 more)	**Low** Due to serious inconsistency and serious imprecision [8]	Sarilumab may have little impact on number of patients requiring ventilation (98 events)
Serious adverse events End of follow-up 6 Important	Relative risk 1.04 (CI 95% 0.91 — 1.18) Based on data from 2,396 participants in 4 studies. [9] (Randomized controlled)	214 per 1000 Difference:	223 per 1000 **9 more per 1000** (CI 95% 19 fewer — 39 more)	**Moderate** Due to serious imprecision [10]	Sarilumab probably has little impact on serious adverse events.
Adverse events End of follow-up 6 Important	Relative risk 1.07 (CI 95% 0.98 — 1.18) Based on data from 1,946 participants in 3 studies. [11] (Randomized controlled)	549 per 1000 Difference:	587 per 1000 **38 more per 1000** (CI 95% 11	**Moderate** Due to serious imprecision [12]	Sarilumab probably increases adverse events slightly.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Sarilumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
			fewer — 99 more)		
Admission to ICU Within 28 days of treatment 6 Important	Relative risk 0.9 (CI 95% 0.5 — 1.63) Based on data from 469 participants in 2 studies. [13] (Randomized controlled)	108 per 1000 Difference:	97 per 1000 **11 fewer per 1000** (CI 95% 54 fewer — 68 more)	**Moderate** Due to serious imprecision [14]	Sarilumab probably has little or no impact on admission to ICU (52 events)
Clinical improvement Within 22 days of commencing treatment 6 Important	Relative risk 0.98 (CI 95% 0.87 — 1.1) Based on data from 1,097 participants in 1 studies. [15] (Randomized controlled)	608 per 1000 Difference:	596 per 1000 **12 fewer per 1000** (CI 95% 79 fewer — 61 more)	**Low** Due to very serious imprecision [16]	Sarilumab may have little impact on clinical improvement.
Clinical recovery Within 22 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.89 — 1.1) Based on data from 1,449 participants in 1 studies. [17] (Randomized controlled)	589 per 1000 Difference:	583 per 1000 **6 fewer per 1000** (CI 95% 65 fewer — 59 more)	**Low** Due to very serious imprecision [18]	Sarilumab may have little impact on clinical recovery.
Discharged from hospital End of follow-up 6 Important	Relative risk 0.99 (CI 95% 0.95 — 1.05) Based on data from 1,973 participants in 5 studies. [19] (Randomized controlled)	636 per 1000 Difference:	630 per 1000 **6 fewer per 1000** (CI 95% 32 fewer — 32 more)	**Moderate** Due to serious imprecision [20]	Sarilumab probably has little impact on discharge from hospital.

Attached Images

7.1.6.5 Tocilizumab

7.1.6.5.1 Tocilizumab for adults

Conditional recommendation

Consider using tocilizumab for the treatment of COVID-19 in adults who require supplemental oxygen, particularly where there is evidence of systemic inflammation.

Additional information

In patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for tocilizumab use both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections).

In accordance with the RECOVERY trial, tocilizumab should be administered as a single intravenous infusion over 60 minutes. The suggested dose is dependent on body weight:

- *Patients > 90 kg: 800 mg tocilizumab*
- *Patients 66–90 kg: 600 mg tocilizumab*
- *Patients 41–65 kg: 400 mg tocilizumab*
- *Patients ≤ 40 kg: 8 mg/kg tocilizumab*

In the RECOVERY trial, 29% of patients received a second dose 12–24 hours after the first dose, although results were not reported separately for this population. The decision to administer a second dose of tocilizumab should take into consideration its availability.

As tocilizumab inhibits the production of C-reactive protein (CRP), a reduction in CRP should not be used as a marker of clinical improvement.

There is a known risk of reactivation of latent tuberculosis following long-term treatment with immunomodulatory drugs. The risk is unknown with very short courses such as those used for COVID-19, but reactivation is considered possible following such treatment. Screening for latent tuberculosis using an interferon-gamma release assay (IGRA) should be considered in patients planned to receive immunomodulatory treatment for COVID-19, however administration of treatment should not be delayed while awaiting results.

For patients with COVID-19 requiring supplemental oxygen, the Taskforce has developed recommendations for the use of several immunomodulators, including systemic corticosteroids (e.g. dexamethasone), tocilizumab, baricitinib, infliximab and abatacept. Current evidence suggests that dexamethasone is safe to use in combination with other immunomodulators, however there are limited data available to evaluate the safety of other combinations (although evidence from the RECOVERY trial suggests a potential benefit when using dexamethasone, tocilizumab and baricitinib together).

Due to concerns that the concomitant use of two or more immunomodulatory agents may increase the risk of side effects such as opportunistic infection, the Taskforce currently recommends that patients with COVID-19 requiring supplemental oxygen receive a systemic corticosteroid (e.g. dexamethasone) and that use of one additional immunomodulator be considered; however optimal sequencing is unclear. Furthermore, the Taskforce notes a recent trial demonstrating clinical equivalence between dexamethasone and baricitinib [570]. As a result, in individuals considered to be at high risk of adverse effects from dexamethasone, baricitinib may be considered as a stand-alone therapy. All recommendations are summarised in the Drug Treatments for Adults with COVID-19 flowchart.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

In patients hospitalised with moderate to critical COVID-19 who require supplemental oxygen, tocilizumab decreases the need for invasive mechanical ventilation and probably reduces the incidence of death.

Evidence from randomised trials versus standard care demonstrates that tocilizumab has an acceptable safety profile and may reduce the incidence of serious adverse events. Consideration should be given when administering tocilizumab to patients already on other immunosuppressant or immunomodulatory drugs.

Healthcare providers should also be aware that concerns have been expressed over the potential for increased risk of intestinal perforations in patients receiving tocilizumab *[69]*.

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
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

Moderate

For the critical outcomes, certainty of the evidence is high for mortality and patients requiring invasive mechanical ventilation, and low for patients experiencing respiratory failure or ARDS. For the important outcomes, certainty is moderate for adverse or serious adverse events, septic shock, admission to ICU, clinical progression, discharge from hospital and duration of hospital stay, all due to serious imprecision based on wide confidence intervals. Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that since there are probable mortality benefits most informed patients with COVID-19 who require supplemental oxygen would agree with the recommendation and opt for tocilizumab.

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

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit, however there are significant costs associated with tocilizumab use (approximately AU$400 per 400 mg vial).

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity; however any limitations on availability and the significant cost of tocilizumab may affect equity based on geographic area and access to tocilizumab.

Acceptability

No important issues with the recommended alternative

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians, unless contraindicated (e.g. in patients with bacterial, fungal or mycobacterial infections).

Feasibility

Important issues, or potential issues not investigated

Intravenous tocilizumab (Actemra; Roche Products Pty Ltd) was granted provisional approval for the treatment of

COVID-19 on 1 December 2021 (*ARTG numbers: 370315, 370314, 296808, 234034, 149404, 149403, 149402; AusPAR unpublished as of 3 December 2021*)

Implementability could be affected by any limitations to supply, however the likelihood and effect of such limitations on treating patients with COVID-19 will be dependent on the prevalence of COVID-19.

Rationale

General adult population

In patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for tocilizumab both within and outside the context of a randomised trial.

Clinical Question/ PICO

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

Summary

Evidence indicates that tocilizumab probably reduces the risk of death in hospitalised adults who require supplemental oxygen, as well as reducing the need for invasive mechanical ventilation and admission to ICU.

What is the evidence informing this recommendation?

Evidence comes from 11 randomised trials that compared tocilizumab with standard care in over 7200 adults hospitalised with COVID-19 *[60][61][63][64][67][70][71][72][75][77][381]*. The majority of data are from the RECOVERY trial, which included 4116 adults hospitalised with moderate-to-critical COVID-19 *[75]*. There was variability in disease severity among patients included in the trials (Table 1).

Results from the tocilizumab arm of the REMAP-CAP trial showed a strong mortality benefit in patients with critical illness who were receiving organ support *[70]*. These data contrasted with the existing meta-analysis of randomised trials conducted by the Taskforce, in which a mortality benefit was not observed in patients using tocilizumab. However the vast majority of relevant data published before REMAP-CAP was of patients with moderate to severe illness (Table 1), with the exception of the COVACTA trial *[71]*, which included 108 patients with critical illness.

To determine whether differences in observed effect on death might be explained by differences in disease severity, the Taskforce assessed the credibility of these subgroups using the *Instrument to assess the Credibility of Effect Modification Analyses* (ICEMAN). Results from this analysis suggest that it is inappropriate to separate data based on disease severity. More specifically:

- the majority of data included in the comparison came from between trials rather than within trials
- only a single between-trial publication (REMAP-CAP) provided data for the smallest subgroup (patients with critical illness)
- the test for subgroup differences suggests that chance may be a likely explanation (P = 0.74), and that the data are largely homogenous (I^2 = 0%)
- results from the COVACTA trial conflict with those of the REMAP-CAP trial, showing no mortality benefit in critical patients treated with tocilizumab.

Following publication of the tocilizumab arm of the RECOVERY trial, the Taskforce updated the ICEMAN analysis to determine whether the inclusion of the RECOVERY data affected the appropriateness of subgroup analyses. Results from the updated analysis suggest that it is still likely to be inappropriate to separate data based on disease severity. This is because:

- There remained limited within-trial (COVACTA and RECOVERY) and between-trial publications (REMAP-CAP, COVACTA and RECOVERY) that provide data for the smallest subgroup (patients with critical illness).
- The test for subgroup differences continues to suggest that chance may be a likely explanation, with the P value increasing to 0.78 following inclusion of the RECOVERY trial. Data remains sufficiently

homogenous between data points (I^2 = 0%).

It should be noted that the ICEMAN analysis did not include the trial by Veiga et al. *[67]*, as this study pooled mortality results for patients with moderate to critical illness, and thus did not contribute data to either of the proposed subgroups. The full ICEMAN analysis can be found here.

Additional data from the REMAP-CAP investigators were published in medRxiv on 22 Jun 2021 (972 randomised to tocilizumab). These new data will be added to the existing study and an updated recommendation will be included in a future version of the guideline.

We have found two new studies comparing tocilizumab with standard care (Rutgers et al. SSRN doi: 10.2139/ssrn.3834311 and Talaschian et al. Res Sq doi: 10.21203/rs.3.rs-463921/v1). These studies are currently under review and, although not expected to change the recommendation, will be incorporated in a future version of the guideline.

Study characteristics
Mean or median age ranged from 55 to 64 years and women comprised 26 to 50% of patients across the studies. Pregnant and breastfeeding women were generally ineligible, with the exception of RECOVERY which included three pregnant patients. Studies included patients with moderate, severe and critical COVID-19 (Table 1).

Table 1: Disease severity of patients within included trials

Disease severity	Number of patients	References
Moderate–Severe	1132	*[60][61][63][64][72][77]*
Moderate–Critical	5323	*[67][71][75][381]*
Critical	755	*[70]*

All included trials reported high levels of the inflammatory marker C-reactive protein (CRP) (Table 2). Thresholds for CRP or other biomarkers of inflammation to guide use of tocilizumab within included trials were variable; however these should be considered where there is evidence of systemic inflammation.

Table 2: Baseline levels of CRP within included studies

Study	Tocilizumab	Control
RECOVERY	Median (IQR): 143 (107–203)	Median (IQR): 144 (106–205)
REMAP-CAP	Median (IQR): 150 (85–221)	Median (IQR): 130 (71–208)
Hermine 2020	Median (IQR): 120 (75–220)	Median (IQR): 127 (84–171)
Rosas 2021	Mean (SD): 168 (101)	Mean (SD): 173 (114)
Salama 2020	Mean (SD): 152 (177)	Mean (SD): 203 (405)
Salvarini 2020	Median (IQR): 105 (50–146)	Median (IQR): 65 (32–118)
Stone 2020	Median (IQR): 116 (67–191)	Median (IQR): 94 (58–142)
Veiga 2021	Mean (SD): 160 (104)	Mean (SD): 193 (283)

What are the main results?
Tocilizumab probably decreases death slightly (39 fewer per 1000; RR 0.87, CI 95% 0.8 to 0.93; 7121 patients in 10 studies) and the need for invasive mechanical ventilation (41 fewer per 1000; RR 0.79, CI 95% 0.70 to 0.9; 4248 patients in 4 studies). In addition, tocilizumab probably decreases the number of patients admitted to ICU (76 fewer per 1000; RR 0.82, CI 95% 0.54 to 1.23; 699 patients in 4 studies), and decreases duration of hospital stay.

Tocilizumab probably has little impact on adverse or serious adverse events, septic shock, number of patients discharged from hospital or clinical progression. The effect of tocilizumab on other outcomes is uncertain.

Our confidence in the results
For the critical outcomes, certainty of the evidence is high for death and patients requiring invasive mechanical ventilation, and low for patients experiencing respiratory failure or ARDS. For the important outcomes, certainty is moderate for adverse or serious adverse events, septic shock, admission to ICU, clinical progression, discharge from hospital and duration of hospital stay (RECOVERY), all due to serious imprecision based on wide confidence intervals. Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Therapeutic Goods Administration, common adverse effects related to tocilizumab are generally mild and include headache, dizziness, infections and injection site reactions *[58]*. Healthcare providers should also be aware that concerns have been expressed over the potential for increased risk of intestinal perforations in patients receiving tocilizumab.

According to the Therapeutic Goods Administration, the safety and efficacy of intravenous tocilizumab in **children under 18 years** of age with conditions other than polyarticular juvenile idiopathic arthritis (pJIA), systemic juvenile idiopathic arthritis (sJIA) or cytokine release syndrome (CRS) have not been established. The use of tocilizumab in children under two years of age has not been studied.

According to the Therapeutic Goods Administration, tocilizumab should not be used **during pregnancy** unless clearly necessary. There are no adequate data from the use of tocilizumab in pregnant women. The potential risk for humans is unknown. Women of childbearing potential should be advised to use adequate contraception during and for several months after therapy with tocilizumab. It is unknown whether tocilizumab is excreted in human breast milk, and its efficacy and safety in lactating women has not been established.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Day 21-28 after commencing treatment 9 Critical	Relative risk 0.87 (CI 95% 0.8 — 0.93) Based on data from 7,121 participants in 10 studies. [1] (Randomized controlled)	302 per 1000 Difference:	263 per 1000 **39 fewer per 1000** (CI 95% 60 fewer — 21 fewer)	**High**	Tocilizumab decreases death slightly.
Invasive mechanical ventilation End of follow-up 9 Critical	Relative risk 0.79 (CI 95% 0.7 — 0.9) Based on data from 4,248 participants in 4 studies. [2] (Randomized controlled)	193 per 1000 Difference:	152 per 1000 **41 fewer per 1000** (CI 95% 58 fewer — 19 fewer)	**High**	Tocilizumab decreases the need for invasive mechanical ventilation.
Respiratory failure or ARDS Within 14 days of commencing treatment 9 Critical	Relative risk 0.5 (CI 95% 0.25 — 1.03) Based on data from 130 participants in 1 studies. [3] (Randomized controlled)	284 per 1000 Difference:	142 per 1000 **142 fewer per 1000** (CI 95% 213 fewer — 9 more)	**Low** Due to very serious imprecision [4]	We are uncertain whether tocilizumab increases or decreases respiratory failure or ARDS (28 events).
Serious adverse events	Relative risk 0.89 (CI 95% 0.77 — 1.02) Based on data from	193 per 1000	172 per 1000	**Moderate** Due to serious imprecision [6]	Tocilizumab probably has little impact on serious adverse events

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
End of follow-up 6 Important	2,951 participants in 9 studies. [5] (Randomized controlled)	Difference:	**21 fewer per 1000** (CI 95% 44 fewer — 4 more)		
Adverse events End of follow-up 6 Important	Relative risk 1.04 (CI 95% 0.9 — 1.21) Based on data from 2,204 participants in 8 studies. [7] (Randomized controlled)	525 per 1000 Difference:	546 per 1000 **21 more per 1000** (CI 95% 53 fewer — 110 more)	**Moderate** Due to serious imprecision [8]	Tocilizumab probably has little impact on adverse events
Septic shock End of follow-up 6 Important	Relative risk 0.76 (CI 95% 0.44 — 1.33) Based on data from 1,457 participants in 3 studies. [9] (Randomized controlled)	41 per 1000 Difference:	31 per 1000 **10 fewer per 1000** (CI 95% 23 fewer — 14 more)	**Moderate** Due to serious imprecision [10]	Tocilizumab probably has little impact on septic shock (51 events).
Admission to ICU End of follow-up 6 Important	Relative risk 0.82 (CI 95% 0.54 — 1.23) Based on data from 699 participants in 4 studies. [11] (Randomized controlled)	423 per 1000 Difference:	347 per 1000 **76 fewer per 1000** (CI 95% 195 fewer — 97 more)	**Moderate** Due to serious imprecision [12]	Tocilizumab probably decreases admission to ICU.
Discharged from hospital End of follow-up 6 Important	Relative risk 1.05 (CI 95% 0.98 — 1.13) Based on data from 5,251 participants in 5 studies. [13] (Randomized controlled)	542 per 1000 Difference:	569 per 1000 **27 more per 1000** (CI 95% 11 fewer — 70 more)	**Moderate** Due to serious imprecision [14]	Tocilizumab probably decreases discharged from hospital
Clinical recovery End of follow-up 6 Important	Relative risk 1.08 (CI 95% 0.92 — 1.27) Based on data from 65 participants in 1 studies. [15] (Randomized controlled)	871 per 1000 Difference:	941 per 1000 **70 more per 1000** (CI 95% 70 fewer — 235 more)	**Low** Due to very serious imprecision [16]	We are uncertain whether tocilizumab increases or decreases clinical recovery.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Clinical improvement Within 14 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.94 — 1.12) Based on data from 242 participants in 1 studies. [17] (Randomized controlled)	889 per 1000 Difference:	916 per 1000 **27 more per 1000** (CI 95% 53 fewer — 107 more)	**Low** Due to very serious imprecision [18]	We are uncertain whether tocilizumab increases or decreases clinical improvement.
Clinical progression Within 14 days of commencing treatment 6 Important	Relative risk 1.08 (CI 95% 0.72 — 1.62) Based on data from 365 participants in 2 studies. [19] (Randomized controlled)	215 per 1000 Difference:	232 per 1000 **17 more per 1000** (CI 95% 60 fewer — 133 more)	**Moderate** Due to serious imprecision [20]	Tocilizumab probably has little impact on clinical progression.
Time to deterioration Days 6 Important	Hazard ratio 1.11 (CI 95% 0.59 — 2.1) Based on data from 45 participants in 1 studies. (Randomized controlled)			**Low** Due to very serious imprecision [21]	We are uncertain whether tocilizumab increases or decreases time to discharge.
Duration of mechanical ventilation Days 6 Important	Measured by: RECOVERY - we did not see any effect on the duration of invasive mechanical ventilation Based on data from 19 participants in 1 studies. [22] (Randomized controlled)	27.9 (Median) Difference:	15 (Median) **12.9 fewer** CI 95%	**Low** Due to very serious imprecision [23]	We are uncertain whether tocilizumab decreases duration of mechanical ventilation.
Time to improvement Days 6 Important	Based on data from 219 participants in 1 studies. [24] (Randomized controlled)	5 (Median) Difference:	6 (Median) **1 more** CI 95%	**Low** Due to very serious imprecision [25]	We are uncertain whether tocilizumab increases or decreases time to improvement.
Duration of hospital stay (mean) Days 6 Important	Based on data from 129 participants in 1 studies. [26] (Randomized controlled)	14.7 (Mean) Difference:	11.3 (Mean) **MD 3.4 lower** (CI 95% 6.2 lower — 0.6 lower)	**Low** Due to very serious imprecision [27]	We are uncertain whether tocilizumab decreases duration of hospital stay.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Duration of hospital stay (median) Days 6 Important	Lower better Based on data from 4,116 participants in 1 studies. (Randomized controlled)	28 (Median)	20 (Median)	**Moderate** Due to serious imprecision [28]	Tocilizumab probably decreases duration of hospital stay.

Attached Images

7.1.6.5.2 Tocilizumab for pregnant or breastfeeding women

Conditional recommendation

Consider using tocilizumab for the treatment of COVID-19 in pregnant or breastfeeding women who require supplemental oxygen, particularly where there is evidence of systemic inflammation.

Additional information

In patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for tocilizumab use both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections).

In accordance with the RECOVERY trial, tocilizumab should be administered as a single intravenous infusion over 60 minutes. The suggested dose is dependent on body weight:

- *Patients > 90 kg: 800 mg tocilizumab*
- *Patients 66–90 kg: 600 mg tocilizumab*
- *Patients 41–65 kg: 400 mg tocilizumab*
- *Patients ≤ 40 kg: 8 mg/kg tocilizumab*

In pregnant and breastfeeding women, dosing should be based on body weight at time of clinical need.

In the RECOVERY trial, 29% of patients received a second dose 12–24 hours after the first dose, although results were not reported separately for this population. The decision to administer a second dose of tocilizumab should take into consideration its availability.

*For the babies of women who received tocilizumab **during pregnancy** (after 20 weeks of gestation), live vaccines (rotavirus and BCG) should be avoided in the first six months of life. All non-live vaccinations are safe and should be undertaken (see factsheet).*

*In women who receive tocilizumab **while breastfeeding only**, live vaccines (rotavirus and BCG) can be given to the baby (see factsheet).*

In addition, the RECOVERY and REMAP-CAP trials have demonstrated a significant benefit when using corticosteroids in conjunction with tocilizumab. Use of combined tocilizumab and corticosteroids should be considered in patients hospitalised with COVID-19 who require oxygen, however the optimal sequencing of tocilizumab and corticosteroid use is unclear.

As tocilizumab inhibits the production of C-reactive protein (CRP), a reduction in CRP should not be used as a marker of clinical improvement.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

In patients hospitalised with moderate to critical COVID-19 who require supplemental oxygen, tocilizumab decreases the need for invasive mechanical ventilation and probably reduces the incidence of death.

Evidence from randomised trials in non-pregnant patients demonstrates that tocilizumab when compared with standard care has an acceptable safety profile and may reduce the incidence of serious adverse events. Consideration should be given when administering tocilizumab to patients already on other immunosuppressant or immunomodulatory drugs. Healthcare providers should also be aware that concerns have been expressed over the potential for increased risk of intestinal perforations in patients receiving tocilizumab *[73]*.

The safety profile of tocilizumab has not been described for pregnant and breastfeeding women. Limited observational data on the effects of tocilizumab in pregnant and breastfeeding women reported in the literature suggest that rates of congenital anomaly, pregnancy loss and other adverse outcomes are not higher than the general population *[78]*. A 2021 review of available safety data on tocilizumab in pregnant and breastfeeding people did not identify a serious safety signal, however there are currently insufficient data available, particularly on tocilizumab exposure in the second or third trimester of pregnancy *[351]*.

The RECOVERY trial protocol specified that pregnant and breastfeeding women were eligible for the tocilizumab arm. The trial specified that, for pregnant women treated with tocilizumab after 20 weeks' gestation, their infant should not be immunised with live vaccines (such as rotavirus and BCG) for the first six months of life *[81]*. The Australian Immunisation Handbook specifies that BCG can be administered up to 12 months of age *[82]*.

A small observational study of 12 pregnant women with severe COVID-19 in Spain described the use of tocilizumab, though most also received other treatments (such as lopinavir-ritonavir, azithromycin, hydroxychloroquine, corticosteroids and interferon β-1b *[79]*. All 12 pregnancies resulted in live births, though hepatotoxicity was observed in two women (which had resolved by discharge) and cytomegalovirus reactivation was detected in one woman.

In breastfeeding women, available evidence shows that very low concentrations of tocilizumab are identified in breast milk and no drug is transferred into the serum of breastfed infants *[83][84][351]*. Hence, the Pregnancy and Perinatal Care Panel considered that live vaccines (rotavirus and BCG) can still be used in babies of women who received tocilizumab during breastfeeding only.

Certainty of the Evidence

Moderate

For the critical outcomes, certainty of the evidence in non-pregnant patients is moderate for mortality, high for patients requiring invasive mechanical ventilation, and low for patients experiencing respiratory failure or ARDS. For the important outcomes, certainty is moderate for adverse or serious adverse events, septic shock, admission to ICU, clinical progression, discharge from hospital and duration of hospital stay, all due to serious imprecision based on wide confidence intervals. Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Values and preferences

Substantial variability is expected or uncertain

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

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit, however there are significant costs associated with tocilizumab use (approximately AU$400 per 400 mg vial).

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity, however any limitations on availability and the significant cost of tocilizumab may affect equity based on geographic area and access to tocilizumab.

Acceptability

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding acceptability by pregnant or breastfeeding women.

Feasibility

Important issues, or potential issues not investigated

Intravenous tocilizmab (Actemra; Roche Products Pty Ltd) was granted provisional approval for the treatment of COVID-19 on 1 December 2021 (*ARTG numbers: 370315, 370314, 296808, 234034, 149404, 149403, 149402; AusPAR unpublished as of 3 December 2021*)

Implementability could be affected by any limitations to supply, however the likelihood and effect of such limitations on treating patients with COVID-19 will be dependent on the prevalence of COVID-19.

Rationale

In non-pregnant patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Limited observational data are available on the use of tocilizumab in pregnant and breastfeeding women with severe COVID-19. While there is currently no evidence to suggest additional harms to mother or baby due to tocilizumab, further studies are needed in this population. Considering the decreased risk of death, tocilizumab's use should be considered in this population for the treatment of COVID-19 requiring supplemental oxygen. Because of this, the Taskforce gives a conditional recommendation for tocilizumab both within and outside the context of a randomised trial.

Clinical Question/ PICO

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

Summary

Evidence indicates that tocilizumab probably reduces the risk of death in hospitalised adults who require supplemental oxygen, as well as reducing the need for invasive mechanical ventilation and admission to ICU.

What is the evidence informing this recommendation?
Evidence comes from 11 randomised trials that compared tocilizumab with standard care in over 7200 adults hospitalised with COVID-19 *[60][61][63][64][67][70][71][72][75][77][381]*. The majority of data are from the RECOVERY trial, which included 4116 adults hospitalised with moderate-to-critical COVID-19 *[75]*. There was variability in disease severity among patients included in the trials (Table 1).

Results from the tocilizumab arm of the REMAP-CAP trial showed a strong mortality benefit in patients with critical illness who were receiving organ support *[70]*. These data contrasted with the existing meta-analysis of randomised trials conducted by the Taskforce, in which a mortality benefit was not observed in patients using tocilizumab. However the vast majority of relevant data published before REMAP-CAP was of patients with moderate to severe illness (Table 1), with the exception of the COVACTA trial *[71]*, which included 108 patients with critical illness.

To determine whether differences in observed effect on death might be explained by differences in disease severity, the Taskforce assessed the credibility of these subgroups using the *Instrument to assess the Credibility of Effect Modification Analyses* (ICEMAN). Results from this analysis suggest that it is inappropriate to separate data based on disease severity. More specifically:

- the majority of data included in the comparison came from between trials rather than within trials
- only a single between-trial publication (REMAP-CAP) provided data for the smallest subgroup (patients with critical illness)
- the test for subgroup differences suggests that chance may be a likely explanation (P = 0.74), and that the data are largely homogenous (I^2 = 0%)
- results from the COVACTA trial conflict with those of the REMAP-CAP trial, showing no mortality benefit in critical patients treated with tocilizumab.

Following publication of the tocilizumab arm of the RECOVERY trial, the Taskforce updated the ICEMAN analysis to determine whether the inclusion of the RECOVERY data affected the appropriateness of subgroup analyses. Results from the updated analysis suggest that it is still likely to be inappropriate to separate data based on disease severity. This is because:

- There remained limited within-trial (COVACTA and RECOVERY) and between-trial publications (REMAP-CAP, COVACTA and RECOVERY) that provide data for the smallest subgroup (patients with critical illness).
- The test for subgroup differences continues to suggest that chance may be a likely explanation, with the P value increasing to 0.78 following inclusion of the RECOVERY trial. Data remains sufficiently homogenous between data points (I^2 = 0%).

It should be noted that the ICEMAN analysis did not include the trial by Veiga et al. *[67]*, as this study pooled mortality results for patients with moderate to critical illness, and thus did not contribute data to either of the proposed subgroups. The full ICEMAN analysis can be found here.

Additional data from the REMAP-CAP investigators were published in medRxiv on 22 Jun 2021 (972 randomised to tocilizumab). These new data will be added to the existing study and an updated recommendation will be included in a future version of the guideline.

We have found two new studies comparing tocilizumab with standard care (Rutgers et al. SSRN doi: 10.2139/ssrn.3834311 and Talaschian et al. Res Sq doi: 10.21203/rs.3.rs-463921/v1). These studies are currently under review and, although not expected to change the recommendation, will be incorporated in a future version of the guideline.

Study characteristics
Mean or median age ranged from 55 to 64 years and women comprised 26 to 50% of patients across the studies. Pregnant and breastfeeding women were generally ineligible, with the exception of RECOVERY which included three pregnant patients. Studies included patients with moderate, severe and critical COVID-19 (Table 1).

Table 1: Disease severity of patients within included trials

Disease severity	Number of patients	References
Moderate–Severe	1132	*[60][61][63][64][72][77]*
Moderate–Critical	5323	*[67][71][75][381]*
Critical	755	*[70]*

All included trials reported high levels of the inflammatory marker C-reactive protein (CRP) (Table 2). Thresholds for CRP or other biomarkers of inflammation to guide use of tocilizumab within included trials were variable; however these should be considered where there is evidence of systemic inflammation.

Table 2: Baseline levels of CRP within included studies

Study	Tocilizumab	Control
RECOVERY	Median (IQR): 143 (107–203)	Median (IQR): 144 (106–205)
REMAP-CAP	Median (IQR): 150 (85–221)	Median (IQR): 130 (71–208)
Hermine 2020	Median (IQR): 120 (75–220)	Median (IQR): 127 (84–171)
Rosas 2021	Mean (SD): 168 (101)	Mean (SD): 173 (114)
Salama 2020	Mean (SD): 152 (177)	Mean (SD): 203 (405)
Salvarini 2020	Median (IQR): 105 (50–146)	Median (IQR): 65 (32–118)
Stone 2020	Median (IQR): 116 (67–191)	Median (IQR): 94 (58–142)
Veiga 2021	Mean (SD): 160 (104)	Mean (SD): 193 (283)

What are the main results?
Tocilizumab probably decreases death slightly (39 fewer per 1000; RR 0.87, CI 95% 0.8 to 0.93; 7121 patients in 10 studies) and the need for invasive mechanical ventilation (41 fewer per 1000; RR 0.79, CI 95% 0.70 to 0.9; 4248 patients in 4 studies). In addition, tocilizumab probably decreases the number of patients admitted to ICU (76 fewer per 1000; RR 0.82, CI 95% 0.54 to 1.23; 699 patients in 4 studies), and decreases duration of hospital stay.

Tocilizumab probably has little impact on adverse or serious adverse events, septic shock, number of patients discharged from hospital or clinical progression. The effect of tocilizumab on other outcomes is uncertain.

Our confidence in the results
For the critical outcomes, certainty of the evidence is high for death and patients requiring invasive mechanical ventilation, and low for patients experiencing respiratory failure or ARDS. For the important outcomes, certainty is moderate for adverse or serious adverse events, septic shock, admission to ICU, clinical progression, discharge from hospital and duration of hospital stay (RECOVERY), all due to serious imprecision based on wide confidence intervals. Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Therapeutic Goods Administration, common adverse effects related to tocilizumab are generally mild and include headache, dizziness, infections and injection site reactions *[58]*. Healthcare providers should also be aware that concerns have been expressed over the potential for increased risk of intestinal perforations in patients receiving tocilizumab.

According to the Therapeutic Goods Administration, the safety and efficacy of intravenous tocilizumab in **children under 18 years** of age with conditions other than polyarticular juvenile idiopathic arthritis (pJIA), systemic juvenile idiopathic arthritis (sJIA) or cytokine release syndrome (CRS) have not been established. The use of tocilizumab in children under two years of age has not been studied.

According to the Therapeutic Goods Administration, tocilizumab should not be used **during pregnancy** unless clearly necessary. There are no adequate data from the use of tocilizumab in pregnant women. The potential risk for humans is unknown. Women of childbearing potential should be advised to use adequate contraception during and for several months after therapy with tocilizumab. It is unknown whether tocilizumab is excreted in human breast milk, and its efficacy and safety in lactating women has not been established.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Day 21-28 after commencing treatment 9 Critical	Relative risk 0.87 (CI 95% 0.8 — 0.93) Based on data from 7,121 participants in 10 studies. [1] (Randomized controlled)	302 per 1000 Difference:	263 per 1000 **39 fewer per 1000** (CI 95% 60 fewer — 21 fewer)	**High**	Tocilizumab decreases death slightly.
Invasive mechanical ventilation End of follow-up 9 Critical	Relative risk 0.79 (CI 95% 0.7 — 0.9) Based on data from 4,248 participants in 4 studies. [2] (Randomized controlled)	193 per 1000 Difference:	152 per 1000 **41 fewer per 1000** (CI 95% 58 fewer — 19 fewer)	**High**	Tocilizumab decreases the need for invasive mechanical ventilation.
Respiratory failure or	Relative risk 0.5 (CI 95% 0.25 — 1.03) Based on data from	284 per 1000	142 per 1000	**Low** Due to very serious	We are uncertain whether tocilizumab increases or decreases

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
ARDS Within 14 days of commencing treatment 9 Critical	130 participants in 1 studies. [3] (Randomized controlled)	Difference:	**142 fewer per 1000** (CI 95% 213 fewer — 9 more)	imprecision [4]	respiratory failure or ARDS (28 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.89 (CI 95% 0.77 — 1.02) Based on data from 2,951 participants in 9 studies. [5] (Randomized controlled)	193 per 1000 Difference:	172 per 1000 **21 fewer per 1000** (CI 95% 44 fewer — 4 more)	**Moderate** Due to serious imprecision [6]	Tocilizumab probably has little impact on serious adverse events
Adverse events End of follow-up 6 Important	Relative risk 1.04 (CI 95% 0.9 — 1.21) Based on data from 2,204 participants in 8 studies. [7] (Randomized controlled)	525 per 1000 Difference:	546 per 1000 **21 more per 1000** (CI 95% 53 fewer — 110 more)	**Moderate** Due to serious imprecision [8]	Tocilizumab probably has little impact on adverse events
Septic shock End of follow-up 6 Important	Relative risk 0.76 (CI 95% 0.44 — 1.33) Based on data from 1,457 participants in 3 studies. [9] (Randomized controlled)	41 per 1000 Difference:	31 per 1000 **10 fewer per 1000** (CI 95% 23 fewer — 14 more)	**Moderate** Due to serious imprecision [10]	Tocilizumab probably has little impact on septic shock (51 events).
Admission to ICU End of follow-up 6 Important	Relative risk 0.82 (CI 95% 0.54 — 1.23) Based on data from 699 participants in 4 studies. [11] (Randomized controlled)	423 per 1000 Difference:	347 per 1000 **76 fewer per 1000** (CI 95% 195 fewer — 97 more)	**Moderate** Due to serious imprecision [12]	Tocilizumab probably decreases admission to ICU.
Discharged from hospital End of follow-up 6 Important	Relative risk 1.05 (CI 95% 0.98 — 1.13) Based on data from 5,251 participants in 5 studies. [13] (Randomized controlled)	542 per 1000 Difference:	569 per 1000 **27 more per 1000** (CI 95% 11 fewer — 70 more)	**Moderate** Due to serious imprecision [14]	Tocilizumab probably decreases discharged from hospital

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Clinical recovery End of follow-up 6 Important	Relative risk 1.08 (CI 95% 0.92 — 1.27) Based on data from 65 participants in 1 studies. [15] (Randomized controlled)	871 per 1000 Difference:	941 per 1000 **70 more per 1000** (CI 95% 70 fewer — 235 more)	**Low** Due to very serious imprecision [16]	We are uncertain whether tocilizumab increases or decreases clinical recovery.
Clinical improvement Within 14 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.94 — 1.12) Based on data from 242 participants in 1 studies. [17] (Randomized controlled)	889 per 1000 Difference:	916 per 1000 **27 more per 1000** (CI 95% 53 fewer — 107 more)	**Low** Due to very serious imprecision [18]	We are uncertain whether tocilizumab increases or decreases clinical improvement.
Clinical progression Within 14 days of commencing treatment 6 Important	Relative risk 1.08 (CI 95% 0.72 — 1.62) Based on data from 365 participants in 2 studies. [19] (Randomized controlled)	215 per 1000 Difference:	232 per 1000 **17 more per 1000** (CI 95% 60 fewer — 133 more)	**Moderate** Due to serious imprecision [20]	Tocilizumab probably has little impact on clinical progression.
Time to deterioration Days 6 Important	Hazard ratio 1.11 (CI 95% 0.59 — 2.1) Based on data from 45 participants in 1 studies. (Randomized controlled)			**Low** Due to very serious imprecision [21]	We are uncertain whether tocilizumab increases or decreases time to discharge.
Duration of mechanical ventilation Days 6 Important	Measured by: RECOVERY - we did not see any effect on the duration of invasive mechanical ventilation Based on data from 19 participants in 1 studies. [22] (Randomized controlled)	27.9 (Median) Difference:	15 (Median) **12.9 fewer** CI 95%	**Low** Due to very serious imprecision [23]	We are uncertain whether tocilizumab decreases duration of mechanical ventilation.
Time to improvement Days 6 Important	Based on data from 219 participants in 1 studies. [24] (Randomized controlled)	5 (Median) Difference:	6 (Median) **1 more** CI 95%	**Low** Due to very serious imprecision [25]	We are uncertain whether tocilizumab increases or decreases time to improvement.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Duration of hospital stay (mean) Days 6 Important	Based on data from 129 participants in 1 studies. [26] (Randomized controlled)	14.7 (Mean) Difference:	11.3 (Mean) **MD 3.4 lower** (CI 95% 6.2 lower — 0.6 lower)	**Low** Due to very serious imprecision [27]	We are uncertain whether tocilizumab decreases duration of hospital stay.
Duration of hospital stay (median) Days 6 Important	Lower better Based on data from 4,116 participants in 1 studies. (Randomized controlled)	28 (Median)	20 (Median)	**Moderate** Due to serious imprecision [28]	Tocilizumab probably decreases duration of hospital stay.

Attached Images

7.1.6.5.3 Tocilizumab for children and adolescents

Conditional recommendation

Consider using tocilizumab for the treatment of COVID-19 in children and adolescents who require supplemental oxygen, particularly where there is evidence of systemic inflammation.

Additional information

In adult patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for tocilizumab use both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections). No children were enrolled in any of the trials included.

There is no established dose for tocilizumab for the treatment of acute COVID-19 in children or adolescents. (The Taskforce notes that RECOVERY is recruiting children and adolescents with PIMS-TS for their trial of tocilizumab [74].) Tocilizumab should be administered as a single intravenous infusion over 60 minutes. Following protocol information in the RECOVERY trial, as well as previous literature on the use of tocilizumab for other indications, the suggested dose is dependent on body weight:

- *Infants < 1 year (excluded from RECOVERY trial): dosing from other uses 12 mg/kg [73]*
- *< 30 kg: 12 mg/kg*
- *≥ 30 kg: 8 mg/kg (max 800 mg)*

In the RECOVERY trial, 29% of patients received a second dose 12–24 hours after the first dose, although results were not reported separately for this population. The decision to administer a second dose of tocilizumab should take into consideration its availability.

In addition, the RECOVERY and REMAP-CAP trials have demonstrated a significant benefit when using corticosteroids in conjunction with tocilizumab in adults. Use of combined tocilizumab and corticosteroids should be considered in children and adolescents hospitalised with COVID-19 who require oxygen, however, the optimal sequencing of tocilizumab and corticosteroid use is unclear in all populations.

As tocilizumab inhibits the production of C-reactive protein (CRP), a reduction in CRP should not be used as a marker of clinical improvement.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

In adults hospitalised with moderate to critical COVID-19 who require supplemental oxygen, tocilizumab decreases the need for invasive mechanical ventilation and probably reduces the incidence of death.

Evidence from randomised trials versus standard care demonstrates that tocilizumab has an acceptable safety profile and may reduce the incidence of serious adverse events in adults. Consideration should be given when administering tocilizumab to patients already on other immunosuppressant or immunomodulatory drugs. Healthcare providers should also be aware that concerns have been expressed over the potential for increased risk of intestinal perforations in patients receiving tocilizumab *[69]*.

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
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.

Pregnant or breastfeeding women
There is uncertainty around the benefits and harms of tocilizumab for pregnant or breastfeeding women with COVID-19 as no details were reported in the trials for these populations.

Children or adolescents
As included trials are all based on adult patients, there remains uncertainty around the benefits and harms of tocilizumab use in children and adolescents with COVID-19.

Certainty of the Evidence

Low

For the critical outcomes, certainty of the evidence is moderate for mortality, high for patients requiring invasive mechanical ventilation, and low for patients experiencing respiratory failure or ARDS. For the important outcomes, certainty is moderate for adverse or serious adverse events, septic shock, admission to ICU, clinical progression, discharge from hospital and duration of hospital stay, all due to serious imprecision based on wide confidence intervals. Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values. The panel believes that since there are probable mortality benefits most patients with COVID-19 who require supplemental oxygen would opt for tocilizumab.

Pregnant or breastfeeding patients
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.

Children and adolescents
We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit-to-harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit, however there are significant costs associated with tocilizumab use (approximately AU$400 per 400 mg vial).

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity; however the any limitations on availability and the significant cost of tocilizumab may affect equity based on geographic area and access to tocilizumab.

Acceptability

No important issues with the recommended alternative

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians, unless contraindicated (e.g. in patients with bacterial, fungal or mycobacterial infections).

Feasibility

Important issues, or potential issues not investigated

Intravenous tocilizumab (Actemra; Roche Products Pty Ltd) was granted provisional approval for the treatment of COVID-19 on 1 December 2021 (*ARTG numbers: 370315, 370314, 296808, 234034, 149404, 149403, 149402; AusPAR unpublished as of 3 December 2021*)

Implementability could be affected by any limitations to supply, however the likelihood and effect of such limitations on treating patients with COVID-19 will be dependent on the prevalence of COVID-19.

Rationale

General adult population

In patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for tocilizumab both within and outside the context of a randomised trial.

Clinical Question/ PICO

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

Summary

Evidence indicates that tocilizumab probably reduces the risk of death in hospitalised adults who require supplemental oxygen, as well as reducing the need for invasive mechanical ventilation and admission to ICU.

What is the evidence informing this recommendation?

Evidence comes from 11 randomised trials that compared tocilizumab with standard care in over 7200 adults hospitalised with COVID-19 *[60][61][63][64][67][70][71][72][75][77][381]*. The majority of data are from the RECOVERY trial, which included 4116 adults hospitalised with moderate-to-critical COVID-19 *[75]*. There was variability in disease severity among patients included in the trials (Table 1).

Results from the tocilizumab arm of the REMAP-CAP trial showed a strong mortality benefit in patients with critical illness who were receiving organ support *[70]*. These data contrasted with the existing meta-analysis of randomised trials conducted by the Taskforce, in which a mortality benefit was not observed in patients using tocilizumab. However the vast majority of relevant data published before REMAP-CAP was of patients with moderate to severe illness (Table 1), with the exception of the COVACTA trial *[71]*, which included 108 patients with critical illness.

To determine whether differences in observed effect on death might be explained by differences in disease severity, the Taskforce assessed the credibility of these subgroups using the *Instrument to assess the Credibility of Effect Modification Analyses* (ICEMAN). Results from this analysis suggest that it is inappropriate to separate data based on disease severity. More specifically:

- the majority of data included in the comparison came from between trials rather than within trials
- only a single between-trial publication (REMAP-CAP) provided data for the smallest subgroup (patients with critical illness)
- the test for subgroup differences suggests that chance may be a likely explanation (P = 0.74), and that the data are largely homogenous (I^2 = 0%)
- results from the COVACTA trial conflict with those of the REMAP-CAP trial, showing no mortality benefit in critical patients treated with tocilizumab.

Following publication of the tocilizumab arm of the RECOVERY trial, the Taskforce updated the ICEMAN analysis to determine whether the inclusion of the RECOVERY data affected the appropriateness of subgroup analyses. Results from the updated analysis suggest that it is still likely to be inappropriate to separate data based on disease severity. This is because:

- There remained limited within-trial (COVACTA and RECOVERY) and between-trial publications (REMAP-CAP, COVACTA and RECOVERY) that provide data for the smallest subgroup (patients with critical illness).
- The test for subgroup differences continues to suggest that chance may be a likely explanation, with the P value increasing to 0.78 following inclusion of the RECOVERY trial. Data remains sufficiently homogenous between data points (I^2 = 0%).

It should be noted that the ICEMAN analysis did not include the trial by Veiga et al. *[67]*, as this study pooled mortality results for patients with moderate to critical illness, and thus did not contribute data to either of the proposed subgroups. The full ICEMAN analysis can be found here.

Additional data from the REMAP-CAP investigators were published in medRxiv on 22 Jun 2021 (972 randomised to tocilizumab). These new data will be added to the existing study and an updated recommendation will be included in a future version of the guideline.

We have found two new studies comparing tocilizumab with standard care (Rutgers et al. SSRN doi: 10.2139/ssrn.3834311 and Talaschian et al. Res Sq doi: 10.21203/rs.3.rs-463921/v1). These studies are currently under review and, although not expected to change the recommendation, will be incorporated in a future version of the guideline.

Study characteristics
Mean or median age ranged from 55 to 64 years and women comprised 26 to 50% of patients across the studies. Pregnant and breastfeeding women were generally ineligible, with the exception of RECOVERY which included three pregnant patients. Studies included patients with moderate, severe and critical COVID-19 (Table 1).

Table 1: Disease severity of patients within included trials

Disease severity	Number of patients	References
Moderate–Severe	1132	*[60][61][63][64][72][77]*
Moderate–Critical	5323	*[67][71][75][381]*
Critical	755	*[70]*

All included trials reported high levels of the inflammatory marker C-reactive protein (CRP) (Table 2). Thresholds for CRP or other biomarkers of inflammation to guide use of tocilizumab within included trials were variable; however these should be considered where there is evidence of systemic inflammation.

Table 2: Baseline levels of CRP within included studies

Study	Tocilizumab	Control
RECOVERY	Median (IQR): 143 (107–203)	Median (IQR): 144 (106–205)
REMAP-CAP	Median (IQR): 150 (85–221)	Median (IQR): 130 (71–208)
Hermine 2020	Median (IQR): 120 (75–220)	Median (IQR): 127 (84–171)
Rosas 2021	Mean (SD): 168 (101)	Mean (SD): 173 (114)
Salama 2020	Mean (SD): 152 (177)	Mean (SD): 203 (405)
Salvarini 2020	Median (IQR): 105 (50–146)	Median (IQR): 65 (32–118)
Stone 2020	Median (IQR): 116 (67–191)	Median (IQR): 94 (58–142)
Veiga 2021	Mean (SD): 160 (104)	Mean (SD): 193 (283)

What are the main results?
Tocilizumab probably decreases death slightly (39 fewer per 1000; RR 0.87, CI 95% 0.8 to 0.93; 7121 patients in 10 studies) and the need for invasive mechanical ventilation (41 fewer per 1000; RR 0.79, CI 95% 0.70 to 0.9; 4248 patients in 4 studies). In addition, tocilizumab probably decreases the number of patients admitted to ICU (76 fewer per 1000; RR 0.82, CI 95% 0.54 to 1.23; 699 patients in 4 studies), and decreases duration of hospital stay.

Tocilizumab probably has little impact on adverse or serious adverse events, septic shock, number of patients

discharged from hospital or clinical progression. The effect of tocilizumab on other outcomes is uncertain.

Our confidence in the results
For the critical outcomes, certainty of the evidence is high for death and patients requiring invasive mechanical ventilation, and low for patients experiencing respiratory failure or ARDS. For the important outcomes, certainty is moderate for adverse or serious adverse events, septic shock, admission to ICU, clinical progression, discharge from hospital and duration of hospital stay (RECOVERY), all due to serious imprecision based on wide confidence intervals. Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Therapeutic Goods Administration, common adverse effects related to tocilizumab are generally mild and include headache, dizziness, infections and injection site reactions *[58]*. Healthcare providers should also be aware that concerns have been expressed over the potential for increased risk of intestinal perforations in patients receiving tocilizumab.

According to the Therapeutic Goods Administration, the safety and efficacy of intravenous tocilizumab in **children under 18 years** of age with conditions other than polyarticular juvenile idiopathic arthritis (pJIA), systemic juvenile idiopathic arthritis (sJIA) or cytokine release syndrome (CRS) have not been established. The use of tocilizumab in children under two years of age has not been studied.

According to the Therapeutic Goods Administration, tocilizumab should not be used **during pregnancy** unless clearly necessary. There are no adequate data from the use of tocilizumab in pregnant women. The potential risk for humans is unknown. Women of childbearing potential should be advised to use adequate contraception during and for several months after therapy with tocilizumab. It is unknown whether tocilizumab is excreted in human breast milk, and its efficacy and safety in lactating women has not been established.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Day 21-28 after commencing treatment 9 Critical	Relative risk 0.87 (CI 95% 0.8 — 0.93) Based on data from 7,121 participants in 10 studies. [1] (Randomized controlled)	302 per 1000 Difference:	263 per 1000 **39 fewer per 1000** (CI 95% 60 fewer — 21 fewer)	**High**	Tocilizumab decreases death slightly.
Invasive mechanical ventilation End of follow-up 9 Critical	Relative risk 0.79 (CI 95% 0.7 — 0.9) Based on data from 4,248 participants in 4 studies. [2] (Randomized controlled)	193 per 1000 Difference:	152 per 1000 **41 fewer per 1000** (CI 95% 58 fewer — 19 fewer)	**High**	Tocilizumab decreases the need for invasive mechanical ventilation.
Respiratory failure or ARDS	Relative risk 0.5 (CI 95% 0.25 — 1.03) Based on data from 130 participants in 1	284 per 1000	142 per 1000	**Low** Due to very serious imprecision [4]	We are uncertain whether tocilizumab increases or decreases respiratory failure or

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Within 14 days of commencing treatment 9 Critical	studies. [3] (Randomized controlled)	Difference:	**142 fewer per 1000** (CI 95% 213 fewer — 9 more)		ARDS (28 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.89 (CI 95% 0.77 — 1.02) Based on data from 2,951 participants in 9 studies. [5] (Randomized controlled)	193 per 1000 Difference:	172 per 1000 **21 fewer per 1000** (CI 95% 44 fewer — 4 more)	**Moderate** Due to serious imprecision [6]	Tocilizumab probably has little impact on serious adverse events
Adverse events End of follow-up 6 Important	Relative risk 1.04 (CI 95% 0.9 — 1.21) Based on data from 2,204 participants in 8 studies. [7] (Randomized controlled)	525 per 1000 Difference:	546 per 1000 **21 more per 1000** (CI 95% 53 fewer — 110 more)	**Moderate** Due to serious imprecision [8]	Tocilizumab probably has little impact on adverse events
Septic shock End of follow-up 6 Important	Relative risk 0.76 (CI 95% 0.44 — 1.33) Based on data from 1,457 participants in 3 studies. [9] (Randomized controlled)	41 per 1000 Difference:	31 per 1000 **10 fewer per 1000** (CI 95% 23 fewer — 14 more)	**Moderate** Due to serious imprecision [10]	Tocilizumab probably has little impact on septic shock (51 events).
Admission to ICU End of follow-up 6 Important	Relative risk 0.82 (CI 95% 0.54 — 1.23) Based on data from 699 participants in 4 studies. [11] (Randomized controlled)	423 per 1000 Difference:	347 per 1000 **76 fewer per 1000** (CI 95% 195 fewer — 97 more)	**Moderate** Due to serious imprecision [12]	Tocilizumab probably decreases admission to ICU.
Discharged from hospital End of follow-up 6 Important	Relative risk 1.05 (CI 95% 0.98 — 1.13) Based on data from 5,251 participants in 5 studies. [13] (Randomized controlled)	542 per 1000 Difference:	569 per 1000 **27 more per 1000** (CI 95% 11 fewer — 70 more)	**Moderate** Due to serious imprecision [14]	Tocilizumab probably decreases discharged from hospital

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Clinical recovery End of follow-up 6 Important	Relative risk 1.08 (CI 95% 0.92 — 1.27) Based on data from 65 participants in 1 studies. [15] (Randomized controlled)	871 per 1000 Difference:	941 per 1000 **70 more per 1000** (CI 95% 70 fewer — 235 more)	**Low** Due to very serious imprecision [16]	We are uncertain whether tocilizumab increases or decreases clinical recovery.
Clinical improvement Within 14 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.94 — 1.12) Based on data from 242 participants in 1 studies. [17] (Randomized controlled)	889 per 1000 Difference:	916 per 1000 **27 more per 1000** (CI 95% 53 fewer — 107 more)	**Low** Due to very serious imprecision [18]	We are uncertain whether tocilizumab increases or decreases clinical improvement.
Clinical progression Within 14 days of commencing treatment 6 Important	Relative risk 1.08 (CI 95% 0.72 — 1.62) Based on data from 365 participants in 2 studies. [19] (Randomized controlled)	215 per 1000 Difference:	232 per 1000 **17 more per 1000** (CI 95% 60 fewer — 133 more)	**Moderate** Due to serious imprecision [20]	Tocilizumab probably has little impact on clinical progression.
Time to deterioration Days 6 Important	Hazard ratio 1.11 (CI 95% 0.59 — 2.1) Based on data from 45 participants in 1 studies. (Randomized controlled)			**Low** Due to very serious imprecision [21]	We are uncertain whether tocilizumab increases or decreases time to discharge.
Duration of mechanical ventilation Days 6 Important	Measured by: RECOVERY - we did not see any effect on the duration of invasive mechanical ventilation Based on data from 19 participants in 1 studies. [22] (Randomized controlled)	27.9 (Median) Difference:	15 (Median) **12.9 fewer** CI 95%	**Low** Due to very serious imprecision [23]	We are uncertain whether tocilizumab decreases duration of mechanical ventilation.
Time to improvement Days 6 Important	Based on data from 219 participants in 1 studies. [24] (Randomized controlled)	5 (Median) Difference:	6 (Median) **1 more** CI 95%	**Low** Due to very serious imprecision [25]	We are uncertain whether tocilizumab increases or decreases time to improvement.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tocilizumab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Duration of hospital stay (mean) Days 6 Important	Based on data from 129 participants in 1 studies. [26] (Randomized controlled)	14.7 (Mean) Difference:	11.3 (Mean) **MD 3.4 lower** (CI 95% 6.2 lower — 0.6 lower)	**Low** Due to very serious imprecision [27]	We are uncertain whether tocilizumab decreases duration of hospital stay.
Duration of hospital stay (median) Days 6 Important	Lower better Based on data from 4,116 participants in 1 studies. (Randomized controlled)	28 (Median)	20 (Median)	**Moderate** Due to serious imprecision [28]	Tocilizumab probably decreases duration of hospital stay.

Attached Images

7.1.7 Regdanvimab (Regkirona)

7.1.7.1 Regdanvimab (Regkirona) for adults

Consensus recommendation

Do not routinely use regdanvimab (Regkirona) for the treatment of COVID-19.

The Taskforce has previously recommended the use of regdanvimab (Regkirona) for the treatment of individuals with COVID-19 who do not require oxygen. These recommendations were based on a sequential trial (parts 1 and 2) [499][585] that included 1629 unvaccinated participants with mild COVID-19, which demonstrated a benefit with regards to hospitalisation, supplemental oxygen and clinical recovery.

All clinical trials that contributed data to the analyses were conducted prior to the emergence of Omicron as the dominant variant. Since the development of the initial recommendations, a significant body of in vitro evidence has emerged demonstrating a significant reduction in activity of regdanvimab (Regkirona) against the Omicron BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that regdanvimab (Regkirona) is effective in treating individuals with currently circulating variants of COVID-19.

Clinical Question/ PICO

Population: People with COVID-19 (not requiring oxygen)
Intervention: Regdanvimab
Comparator: Placebo

Summary

Evidence indicates that regdanvimab probably reduces the requirement of supplemental oxygen and hospitalisation, and increases clinical recovery in adults with mild COVID-19 who have one or more risk factors for disease progression.

What is the evidence informing this recommendation?
Evidence comes from one clinical trial separated into two distinct parts; part 1 consisting of 335 individuals with confirmed COVID-19 *[440]* and part 2 consisting of 1315 individuals with COVID-19. Participants were randomised within 7 days onset of symptoms and the majority had one or more risk factors for disease progression.

Study characteristics
Mean age of participants was 48 years and 49% were women. Participants received a single 40 mg/kg intravenous infusion of regdanvimab over 60 minutes or placebo. Pregnant and breastfeeding women and children and adolescents were ineligible.

What are the main results?
Regdanvimab probably reduces the requirement of supplemental oxygen (RR 0.34, CI 95% 0.21 to 0.55; 1622 patients in 2 studies), incidence of hospitalisation (RR 0.35 CI 95% 0.22 to 0.56; 1622 patients in 2 studies) and increases clinical recovery (RR 1.14, CI 95% 1.06 to 1.22; 1532 patients in 2 studies). Regdanvimab probably has little impact on incidence of adverse events. We are unsure if regdanvimab impacts all-cause mortality, mechanical ventilation, ICU admission, serious adverse events or discontinuation due to adverse events.

Our confidence in the results
Certainty of the evidence is moderate for the requirement of supplemental oxygen, hospitalisation, clinical recovery and adverse events due to wide confidence intervals or reliance on a single study. Certainty is low for all remaining outcomes due to the above in addition to few events.

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The Therapeutic Goods Administration provisionally approved the use of regdanvimab (Regkirona) for the treatment of COVID-19 on 6 December 2021. Further details of Part 2 of the study are available within the TGA's Australian Public Assessment Report (AusPAR).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Regdanvimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.5 (CI 95% 0.05 — 5.53) Based on data from 1,622 participants in 2 studies. [1] (Randomized controlled)	3 per 1000 Difference:	2 per 1000 **1 fewer per 1000** (CI 95% 3 fewer — 14 more)	**Low** Due to very serious imprecision [2]	Regdanvimab may have little impact on all-cause mortality (3 events).
Invasive mechanical ventilation Within 28 days of commencing treatment 9 Critical	Relative risk 0.43 (CI 95% 0.04 — 4.35) Based on data from 1,622 participants in 2 studies. [3] (Randomized controlled)	4 per 1000 Difference:	2 per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 13 more)	**Low** Due to very serious imprecision [4]	Regdanvimab may have little impact on invasive mechanical ventilation (4 events).
Supplemental oxygen Within 28 days of commencing treatment 6 Important	Relative risk 0.34 (CI 95% 0.21 — 0.55) Based on data from 1,622 participants in 2 studies. [5] (Randomized controlled)	76 per 1000 Difference:	26 per 1000 **50 fewer per 1000** (CI 95% 60 fewer — 34 fewer)	**Moderate** Due to serious imprecision [6]	Regdanvimab probably decreases requirement of supplemental oxygen (81 events).
Serious adverse events Within 28 days of commencing treatment 6 Important	Relative risk 3.99 (CI 95% 0.45 — 35.58) Based on data from 1,302 participants in 1 studies. [7] (Randomized controlled)	2 per 1000 Difference:	8 per 1000 **6 more per 1000** (CI 95% 1 fewer — 69 more)	**Low** Due to very serious imprecision [8]	Regdanvimab may have little impact on serious adverse events (5 events).
Adverse events Within 28 days of commencing treatment 6 Important	Relative risk 0.96 (CI 95% 0.83 — 1.11) Based on data from 1,627 participants in 2 studies. [9] (Randomized controlled)	311 per 1000 Difference:	299 per 1000 **12 fewer per 1000** (CI 95% 53 fewer — 34 more)	**Moderate** Due to serious imprecision [10]	Regdanvimab probably has little impact on adverse events (482 events).
Discontinuation due to an adverse event Within 28 days of commencing treatment	Based on data from 1,311 participants in 1 studies. [11] (Randomized controlled)			**Low** Due to very serious imprecision [12]	No patients discontinued due to an adverse event.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Regdanvimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important					
Hospitalisation Within 28 days of commencing treatment 6 Important	Relative risk 0.35 (CI 95% 0.22 — 0.56) Based on data from 1,622 participants in 2 studies. [13] (Randomized controlled)	80 per 1000 Difference:	28 per 1000 **52 fewer per 1000** (CI 95% 62 fewer — 35 fewer)	**Moderate** Due to serious imprecision [14]	Regdanvimab probably decreases hospitalisation (86 events).
ICU admission Within 28 days of commencing treatment 6 Important	Relative risk 0.09 (CI 95% 0.01 — 1.65) Based on data from 1,622 participants in 2 studies. [15] (Randomized controlled)	7 per 1000 Difference:	1 per 1000 **6 fewer per 1000** (CI 95% 7 fewer — 5 more)	**Low** Due to very serious imprecision [16]	Regdanvimab may have little impact on ICU admission (5 events).
Clinical recovery Within 28 days of commencing treatment 6 Important	Relative risk 1.14 (CI 95% 1.06 — 1.22) Based on data from 1,532 participants in 2 studies. [17] (Randomized controlled)	712 per 1000 Difference:	812 per 1000 **100 more per 1000** (CI 95% 43 more — 157 more)	**Moderate** Due to serious imprecision [18]	Regdanvimab probably increases clinical recovery.
Time to recovery Days 6 Important	Based on data from 1,302 participants in 1 studies. [19] (Randomized controlled)	13.29 (Mean) Difference:	8.39 (Mean) **MD 4.9 lower** CI 95%	**Low** Due to very serious imprecision [20]	Regdanvimab may decrease time to recovery.

Attached Images

7.1.7.2 Regdanvimab (Regkirona) for pregnant or breastfeeding women

Only in research settings

Do not use regdanvimab for the treatment of COVID-19 in pregnant or breastfeeding women outside randomised trials with appropriate ethical approval.

Additional information

Currently there is no direct evidence evaluating the effectiveness of regdanvimab (Regkirona) in pregnant and breastfeeding women. Until further evidence is available, do not use regdanvimab for the treatment of COVID-19 in pregnant and breastfeeding women unless they are eligible to be enrolled in trials.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Clinical Question/ PICO

Population: People with COVID-19 (not requiring oxygen)
Intervention: Regdanvimab
Comparator: Placebo

Summary

Evidence indicates that regdanvimab probably reduces the requirement of supplemental oxygen and hospitalisation, and increases clinical recovery in adults with mild COVID-19 who have one or more risk factors for disease progression.

What is the evidence informing this recommendation?
Evidence comes from one clinical trial separated into two distinct parts; part 1 consisting of 335 individuals with confirmed COVID-19 *[440]* and part 2 consisting of 1315 individuals with COVID-19. Participants were randomised within 7 days onset of symptoms and the majority had one or more risk factors for disease progression.

Study characteristics
Mean age of participants was 48 years and 49% were women. Participants received a single 40 mg/kg intravenous infusion of regdanvimab over 60 minutes or placebo. Pregnant and breastfeeding women and children and adolescents were ineligible.

What are the main results?
Regdanvimab probably reduces the requirement of supplemental oxygen (RR 0.34, CI 95% 0.21 to 0.55; 1622 patients in 2 studies), incidence of hospitalisation (RR 0.35 CI 95% 0.22 to 0.56; 1622 patients in 2 studies) and increases clinical recovery (RR 1.14, CI 95% 1.06 to 1.22; 1532 patients in 2 studies). Regdanvimab probably has little impact on incidence of adverse events. We are unsure if regdanvimab impacts all-cause mortality, mechanical ventilation, ICU admission, serious adverse events or discontinuation due to adverse events.

Our confidence in the results
Certainty of the evidence is moderate for the requirement of supplemental oxygen, hospitalisation, clinical recovery and adverse events due to wide confidence intervals or reliance on a single study. Certainty is low for all remaining outcomes due to the above in addition to few events.

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The Therapeutic Goods Administration provisionally approved the use of regdanvimab (Regkirona) for the treatment of COVID-19 on 6 December 2021. Further details of Part 2 of the study are available within the TGA's Australian Public Assessment Report (AusPAR).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Regdanvimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.5 (CI 95% 0.05 — 5.53) Based on data from 1,622 participants in 2 studies. [1] (Randomized controlled)	3 per 1000 Difference:	2 per 1000 **1 fewer per 1000** (CI 95% 3 fewer — 14 more)	**Low** Due to very serious imprecision [2]	Regdanvimab may have little impact on all-cause mortality (3 events).
Invasive mechanical ventilation Within 28 days of commencing treatment 9 Critical	Relative risk 0.43 (CI 95% 0.04 — 4.35) Based on data from 1,622 participants in 2 studies. [3] (Randomized controlled)	4 per 1000 Difference:	2 per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 13 more)	**Low** Due to very serious imprecision [4]	Regdanvimab may have little impact on invasive mechanical ventilation (4 events).
Supplemental oxygen Within 28 days of commencing treatment 6 Important	Relative risk 0.34 (CI 95% 0.21 — 0.55) Based on data from 1,622 participants in 2 studies. [5] (Randomized controlled)	76 per 1000 Difference:	26 per 1000 **50 fewer per 1000** (CI 95% 60 fewer — 34 fewer)	**Moderate** Due to serious imprecision [6]	Regdanvimab probably decreases requirement of supplemental oxygen (81 events).
Serious adverse events Within 28 days of commencing treatment 6 Important	Relative risk 3.99 (CI 95% 0.45 — 35.58) Based on data from 1,302 participants in 1 studies. [7] (Randomized controlled)	2 per 1000 Difference:	8 per 1000 **6 more per 1000** (CI 95% 1 fewer — 69 more)	**Low** Due to very serious imprecision [8]	Regdanvimab may have little impact on serious adverse events (5 events).
Adverse events Within 28 days of commencing treatment 6 Important	Relative risk 0.96 (CI 95% 0.83 — 1.11) Based on data from 1,627 participants in 2 studies. [9] (Randomized controlled)	311 per 1000 Difference:	299 per 1000 **12 fewer per 1000** (CI 95% 53 fewer — 34 more)	**Moderate** Due to serious imprecision [10]	Regdanvimab probably has little impact on adverse events (482 events).
Discontinuation due to an adverse event Within 28 days of commencing treatment	Based on data from 1,311 participants in 1 studies. [11] (Randomized controlled)			**Low** Due to very serious imprecision [12]	No patients discontinued due to an adverse event.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Regdanvimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important					
Hospitalisation Within 28 days of commencing treatment 6 Important	Relative risk 0.35 (CI 95% 0.22 — 0.56) Based on data from 1,622 participants in 2 studies. [13] (Randomized controlled)	80 per 1000 Difference:	28 per 1000 **52 fewer per 1000** (CI 95% 62 fewer — 35 fewer)	**Moderate** Due to serious imprecision [14]	Regdanvimab probably decreases hospitalisation (86 events).
ICU admission Within 28 days of commencing treatment 6 Important	Relative risk 0.09 (CI 95% 0.01 — 1.65) Based on data from 1,622 participants in 2 studies. [15] (Randomized controlled)	7 per 1000 Difference:	1 per 1000 **6 fewer per 1000** (CI 95% 7 fewer — 5 more)	**Low** Due to very serious imprecision [16]	Regdanvimab may have little impact on ICU admission (5 events).
Clinical recovery Within 28 days of commencing treatment 6 Important	Relative risk 1.14 (CI 95% 1.06 — 1.22) Based on data from 1,532 participants in 2 studies. [17] (Randomized controlled)	712 per 1000 Difference:	812 per 1000 **100 more per 1000** (CI 95% 43 more — 157 more)	**Moderate** Due to serious imprecision [18]	Regdanvimab probably increases clinical recovery.
Time to recovery Days 6 Important	Based on data from 1,302 participants in 1 studies. [19] (Randomized controlled)	13.29 (Mean) Difference:	8.39 (Mean) **MD 4.9 lower** CI 95%	**Low** Due to very serious imprecision [20]	Regdanvimab may decrease time to recovery.

Attached Images

7.1.7.3 Regdanvimab (Regkirona) for children and adolescents

Only in research settings

Do not use regdanvimab for the treatment of COVID-19 in children and adolescents outside of randomised trials with appropriate ethical approval.

Additional information

Currently, there is no direct evidence evaluating the effectiveness of regdanvimab (Regkirona) in children and adolescents. Until further evidence is available, do not use regdanvimab for the treatment of COVID-19 in children and adolescents unless they are eligible to be enrolled in trials.

Currently regdanvimab is not approved for use in people under 18 years of age.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Regdanvimab probably reduces the requirement of supplemental oxygen (RR 0.34, CI 95% 0.21 to 0.55; 1622 patients in 2 studies), incidence of hospitalisation (RR 0.35 CI 95% 0.22 to 0.56; 1622 patients in 2 studies) and increases clinical recovery (RR 1.14, CI 95% 1.06 to 1.22; 1532 patients in 2 studies).

Regdanvimab probably has little impact on incidence of adverse events. We are unsure if regdanvimab impacts all-cause mortality, mechanical ventilation, ICU admission, serious adverse events or discontinuation due to adverse events.

Certainty of the Evidence

Moderate

Certainty of the evidence is moderate for the requirement of supplemental oxygen, hospitalisation, clinical recovery and adverse events due to wide confidence intervals or reliance on a single study. Certainty is low for all remaining outcomes due to the above in addition to few events.

Values and preferences

Substantial variability is expected or uncertain

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

Resources

Important negative issues

The unavailability of regdanvimab within Australia is a limiting factor preventing widespread use of this treatment.

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity.

Acceptability

Important issues, or potential issues not investigated

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

Feasibility

Intervention is likely difficult to implement

Regdanvimab was approved for the treatment of people with COVID-19 who do not require oxygen on 6 December 2021; however at this time, regdanvimab is not available within Australia.

Clinical Question/ PICO

Population: People with COVID-19 (not requiring oxygen)
Intervention: Regdanvimab
Comparator: Placebo

Summary

Evidence indicates that regdanvimab probably reduces the requirement of supplemental oxygen and hospitalisation, and increases clinical recovery in adults with mild COVID-19 who have one or more risk factors for disease progression.

What is the evidence informing this recommendation?
Evidence comes from one clinical trial separated into two distinct parts; part 1 consisting of 335 individuals with confirmed COVID-19 *[440]* and part 2 consisting of 1315 individuals with COVID-19. Participants were randomised within 7 days onset of symptoms and the majority had one or more risk factors for disease progression.

Study characteristics
Mean age of participants was 48 years and 49% were women. Participants received a single 40 mg/kg intravenous infusion of regdanvimab over 60 minutes or placebo. Pregnant and breastfeeding women and children and adolescents were ineligible.

What are the main results?
Regdanvimab probably reduces the requirement of supplemental oxygen (RR 0.34, CI 95% 0.21 to 0.55; 1622 patients in 2 studies), incidence of hospitalisation (RR 0.35 CI 95% 0.22 to 0.56; 1622 patients in 2 studies) and increases clinical recovery (RR 1.14, CI 95% 1.06 to 1.22; 1532 patients in 2 studies). Regdanvimab probably has little impact on incidence of adverse events. We are unsure if regdanvimab impacts all-cause mortality, mechanical ventilation, ICU admission, serious adverse events or discontinuation due to adverse events.

Our confidence in the results
Certainty of the evidence is moderate for the requirement of supplemental oxygen, hospitalisation, clinical recovery and adverse events due to wide confidence intervals or reliance on a single study. Certainty is low for all remaining outcomes due to the above in addition to few events.

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The Therapeutic Goods Administration provisionally approved the use of regdanvimab (Regkirona) for the treatment of COVID-19 on 6 December 2021. Further details of Part 2 of the study are available within the TGA's Australian Public Assessment Report (AusPAR).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Regdanvimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment	Relative risk 0.5 (CI 95% 0.05 — 5.53) Based on data from 1,622 participants in 2 studies. [1] (Randomized controlled)	3 per 1000 Difference:	2 per 1000 **1 fewer per 1000**	**Low** Due to very serious imprecision [2]	Regdanvimab may have little impact on all-cause mortality (3 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Regdanvimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical			(CI 95% 3 fewer — 14 more)		
Invasive mechanical ventilation Within 28 days of commencing treatment 9 Critical	Relative risk 0.43 (CI 95% 0.04 — 4.35) Based on data from 1,622 participants in 2 studies. [3] (Randomized controlled)	4 per 1000 Difference:	2 per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 13 more)	**Low** Due to very serious imprecision [4]	Regdanvimab may have little impact on invasive mechanical ventilation (4 events).
Supplemental oxygen Within 28 days of commencing treatment 6 Important	Relative risk 0.34 (CI 95% 0.21 — 0.55) Based on data from 1,622 participants in 2 studies. [5] (Randomized controlled)	76 per 1000 Difference:	26 per 1000 **50 fewer per 1000** (CI 95% 60 fewer — 34 fewer)	**Moderate** Due to serious imprecision [6]	Regdanvimab probably decreases requirement of supplemental oxygen (81 events).
Serious adverse events Within 28 days of commencing treatment 6 Important	Relative risk 3.99 (CI 95% 0.45 — 35.58) Based on data from 1,302 participants in 1 studies. [7] (Randomized controlled)	2 per 1000 Difference:	8 per 1000 **6 more per 1000** (CI 95% 1 fewer — 69 more)	**Low** Due to very serious imprecision [8]	Regdanvimab may have little impact on serious adverse events (5 events).
Adverse events Within 28 days of commencing treatment 6 Important	Relative risk 0.96 (CI 95% 0.83 — 1.11) Based on data from 1,627 participants in 2 studies. [9] (Randomized controlled)	311 per 1000 Difference:	299 per 1000 **12 fewer per 1000** (CI 95% 53 fewer — 34 more)	**Moderate** Due to serious imprecision [10]	Regdanvimab probably has little impact on adverse events (482 events).
Discontinuation due to an adverse event Within 28 days of commencing treatment 6 Important	Based on data from 1,311 participants in 1 studies. [11] (Randomized controlled)			**Low** Due to very serious imprecision [12]	No patients discontinued due to an adverse event.
Hospitalisation Within 28 days of commencing	Relative risk 0.35 (CI 95% 0.22 — 0.56) Based on data from	80 per 1000	28 per 1000	**Moderate** Due to serious imprecision [14]	Regdanvimab probably decreases hospitalisation (86

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Regdanvimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
treatment 6 Important	1,622 participants in 2 studies. [13] (Randomized controlled)	Difference:	**52 fewer per 1000** (CI 95% 62 fewer — 35 fewer)		events).
ICU admission Within 28 days of commencing treatment 6 Important	Relative risk 0.09 (CI 95% 0.01 — 1.65) Based on data from 1,622 participants in 2 studies. [15] (Randomized controlled)	7 per 1000 Difference:	1 per 1000 **6 fewer per 1000** (CI 95% 7 fewer — 5 more)	**Low** Due to very serious imprecision [16]	Regdanvimab may have little impact on ICU admission (5 events).
Clinical recovery Within 28 days of commencing treatment 6 Important	Relative risk 1.14 (CI 95% 1.06 — 1.22) Based on data from 1,532 participants in 2 studies. [17] (Randomized controlled)	712 per 1000 Difference:	812 per 1000 **100 more per 1000** (CI 95% 43 more — 157 more)	**Moderate** Due to serious imprecision [18]	Regdanvimab probably increases clinical recovery.
Time to recovery Days 6 Important	Based on data from 1,302 participants in 1 studies. [19] (Randomized controlled)	13.29 (Mean) Difference:	8.39 (Mean) **MD 4.9 lower** CI 95%	**Low** Due to very serious imprecision [20]	Regdanvimab may decrease time to recovery.

Attached Images

7.1.8 Remdesivir (Veklury)

7.1.8.1 Remdesivir (Veklury) for adults

Conditional recommendation

Consider using remdesivir in adults with COVID-19 who require oxygen but do not require non-invasive or invasive ventilation.

Additional information

In patients hospitalised with COVID-19 who do not require ventilation (invasive or non-invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)) remdesivir (Veklury) probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for remdesivir use both within and outside the context of a randomised trial.

It is unclear whether older people or those requiring palliative care were included in the studies this recommendation is based on. Until further evidence in these populations is available, the Taskforce does not believe a different recommendation should apply, unless contraindicated.

We are aware of the difference between our recommendations for remdesivir and those currently issued by the World Health Organization [50]. For a full description of the rationale underpinning this decision please see here.

It is unclear which regimen of remdesivir (5-day or 10-day) provides the optimal duration of treatment. In Australia, criteria for accessing remdesivir from the National Medical Stockpile limits the treatment course to 5 days for eligible patients.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

In patients who are hospitalised with moderate COVID-19 and who do not require ventilation (non-invasive ventilation, mechanical ventilation or ECMO), remdesivir probably reduces the incidence of death.

Evidence from randomised trials versus standard care demonstrates that remdesivir has an acceptable safety profile and may reduce the incidence of serious adverse events. Based on the results of two studies that compared 10-day to 5-day courses of remdesivir, it is unclear which of these regimens provide the optimal duration of treatment—current evidence does not suggest a clear benefit for 10 days over 5 days.

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

Moderate

Certainty of the evidence is moderate for death at day 28 in patients who do not require ventilation and in patients who require ventilation. Certainty is also moderate for discharge from hospital, serious adverse events, time to recovery and time to improvement. Certainty is low for all other outcomes.

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.

Values and preferences

No substantial variability expected

We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that since there are probable mortality benefits most informed patients with COVID-19 who do not require ventilation would 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

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

Criteria for accessing remdesivir from the National Medical Stockpile, released by the Australian Government on 31 July, limits the treatment course to 5 days for eligible patients.

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity; however as remdesivir is only accessible through special arrangements with the Australian Government, this may affect equity based on geographic area and access to remdesivir.

Acceptability

No important issues with the recommended alternative

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

Important issues, or potential issues not investigated

Intravenous remdesivir (Veklury; Gilead Sciences Pty Ltd) was granted provisional approval for the treatment of COVID-19 by the Therapeutic Goods Administration on 10 July 2020 under the Black Triangle Scheme (*ARTG numbers: 338419, 338420;* AusPAR).

Treatment with remdesivir is not feasible in patients who do not meet eligibility for clinical treatment specified by the Australian Government Department of Health. 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

In patients hospitalised with COVID-19 who do not require ventilation remdesivir probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for remdesivir both within and outside the context of a randomised trial.

We are aware of the difference between our recommendations for remdesivir and those currently issued by the World Health Organization *[50]*. For a full description of the rationale underpinning this decision please see here.

It is unclear which regimen of remdesivir (5-day or 10-day) provides the optimal duration of treatment. In Australia, criteria for accessing remdesivir from the National Medical Stockpile limits the treatment course to 5 days for eligible patients.

Clinical Question/ PICO

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

Summary

Evidence indicates that remdesivir probably reduces the risk of death in hospitalised adults not requiring ventilation and increases the risk of death in hospitalised adults who require ventilation.

What is the evidence informing this recommendation?
Evidence comes from six randomised trials that compared remdesivir with standard care in over 8200 adults hospitalised with COVID-19 *[42][43][46][49][55][365]*. The majority of evidence is from the WHO Solidarity trial which randomised 5451 patients with moderate to critical COVID-19 *[49]*.

Study characteristics
For a comprehensive description, see the study characteristics table. There was variability in disease severity among patients included in the trials (see table).

Disease severity	Number of patients	References
Moderate	666	*[46][55]*
Moderate-Critical	6513	*[42][49][365]*
Severe-Critical	236	*[43]*

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (17 fewer per 1000; RR 0.81, CI 95% 0.65 to 1.01; 6904 patients in 6 studies), and probably increases death at day 28 in patients who require ventilation (35 more per 1000; RR 1.16, CI 95% 0.96 to 1.41; 1004 patients in 3 studies).

Remdesivir may decrease time to recovery by a few days (HR 1.24, 95% CI 1.08 to 1.42; 1643 patients in 2 studies) and time to improvement only slightly (HR 1.17, 95% CI 1.00 to 1.38; 810 patients in 2 studies). Clinical recovery was defined as the first day in which a patient satisfied categories 1, 2 or 3 on the 8-point WHO ordinal scale *[42]* or improvement from a baseline score of 2–5 to a score of 6 or 7 on a 7-point ordinal scale *[46]*. Clinical improvement was defined as an improvement of 2 or more points on a 7-point *[46]* or 6-point ordinal scale *[43]*.

Compared with standard care, remdesivir probably reduces serious adverse events (49 fewer per 1000; RR 0.82, CI 95% 0.65 to 1.04; 2689 patients in 4 studies). There is no important difference between remdesivir and standard care regarding the number of patients requiring ventilation, number of patients discharged from hospital at day 28, and number of patients experiencing one or more adverse events. We are uncertain whether remdesivir impacts respiratory failure or ARDS, clinical recovery at day 28, septic shock and discontinuation due to adverse events.

An additional study was identified but did not meet the inclusion criteria due to its observational design *[56]*. The study included 86 **pregnant and postpartum women** with severe COVID-19 in the USA who received compassionate-use remdesivir. Median age was 33 years (range 20–43 years) and median gestational age was 29 weeks (range 14–39 weeks). Invasive mechanical ventilation was given to 52% of women and non-invasive ventilation (NIPPV, high-flow and low-flow oxygen) to 45%—the remaining 3% were on room air at baseline. Two-thirds of pregnant women and all postpartum women were in ICU.

A more recent study by Gutierrez et al. *[453]*, a prospective cohort study published on 15 Feb 2022, assessed the use of remdesivir during pregnancy during the SARS-CoV-2 pandemic. Only 95 participants met the inclusion criteria, and were then stratified according to whether or not they received remdesivir in hospital. Ultimately the study was quite small, and the use of remdesivir within the study appeared to be safe, well tolerated within our cohort with no cases of recorded adverse reaction.

Extubation was achieved in 93% of pregnant women and 89% of postpartum women who were mechanically ventilated. Recovery at 28 days (defined as an improvement from NIV to room air) was achieved in 93% of pregnant women and 89% of postpartum women. Discharge occurred in 90% of pregnant women and 84% of postpartum women.

Adverse events were experienced by 29% of women and 16% had a serious adverse event. Examples of adverse events experienced included anaemia, DVT and dysphagia. Seven women discontinued treatment with remdesivir due to adverse events, of which five had elevated liver enzyme concentrations, one had nausea and the other had haemoptysis.

The results of this observational study are in line with the current trial evidence, demonstrating that there remains uncertainty whether remdesivir is more effective and safer than standard care in treating pregnant and postpartum women with COVID-19.

Remdesivir has been used anecdotally for the treatment of COVID-19 in **children and adolescents**. The preliminary findings from a recent cohort study of 77 hospitalised patients under 18 years of age are reassuring, but uncertainties remain about the benefits of remdesivir in this population *[314]*. Trials are currently recruiting in this population.

Our confidence in the results
Certainty of the evidence is moderate for death in both subgroups (patients who do not require ventilation, and patients who require ventilation), all due to serious imprecision (wide confidence intervals). Certainty is also moderate for patients requiring ventilation and discharge from hospital (due to reliance on a single study), serious adverse events, adverse events, time to recovery and time to improvement (due to non-blinding of patients and personnel).

Certainty of the evidence is low for respiratory failure or acute respiratory distress syndrome (due to inconsistency in direction of effect and wide confidence intervals), number of patients requiring invasive mechanical ventilation or ECMO (due to non-blinding of patients and personnel and reliance on a single study), clinical recovery, septic shock and adverse events (due to non-blinding of patients and personnel and inconsistency in direction of effect) and discontinuation due to adverse events (due to non-blinding of patients and personnel and wide confidence intervals).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
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 *[45]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality [hospital no ventilation] Within 28 days of commencing treatment 9 Critical	Relative risk 0.81 (CI 95% 0.65 — 1.01) Based on data from 6,904 participants in 8 studies. [1] (Randomized controlled)	88 per 1000 Difference:	71 per 1000 **17 fewer per 1000** (CI 95% 31 fewer — 1 more)	Moderate Due to serious imprecision [2]	Remdesivir probably decreases death slightly in hospitalised patients who do not require ventilation.
All-cause mortality [ventilation] Within 28 days of commencing treatment	Relative risk 1.16 (CI 95% 0.96 — 1.41) Based on data from 1,332 participants in 5 studies. [3] (Randomized controlled)	219 per 1000 Difference:	254 per 1000 **35 more per 1000** (CI 95% 9 fewer	Moderate Due to serious imprecision [4]	Remdesivir probably increases death in hospitalised patients requiring ventilation.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical			— 90 more)		
Respiratory failure or ARDS Within 28 days of commencing treatment 9 Critical	Relative risk 0.82 (CI 95% 0.5 — 1.33) Based on data from 2,120 participants in 3 studies. [5] (Randomized controlled)	121 per 1000 Difference:	99 per 1000 **22 fewer per 1000** (CI 95% 61 fewer — 40 more)	**Low** Due to serious imprecision and serious inconsistency [6]	We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (221 events).
Invasive mechanical ventilation or ECMO Within 28 days of commencing treatment 9 Critical	Relative risk 0.57 (CI 95% 0.42 — 0.79) Based on data from 766 participants in 1 studies. [7] (Randomized controlled)	225 per 1000 Difference:	128 per 1000 **97 fewer per 1000** (CI 95% 131 fewer — 47 fewer)	**Low** Due to serious risk of bias and serious imprecision [8]	Remdesivir may decrease the need for invasive mechanical ventilation or ECMO (134 events).
Patients requiring ventilation Within 28 days of commencing treatment 6 Important	Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 5,034 participants in 2 studies. [9] (Randomized controlled)	114 per 1000 Difference:	119 per 1000 **5 more per 1000** (CI 95% 13 fewer — 24 more)	**Moderate** Due to serious imprecision [10]	Remdesivir probably has no impact on number of patients requiring ventilation.
Clinical recovery Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.86 — 1.14) Based on data from 1,876 participants in 3 studies. [11] (Randomized controlled)	711 per 1000 Difference:	704 per 1000 **7 fewer per 1000** (CI 95% 100 fewer — 100 more)	**Low** Due to serious risk of bias and serious inconsistency [12]	We are uncertain whether remdesivir improves or worsens clinical recovery at day 28.
Septic shock Within 28 days of commencing treatment 6 Important	Relative risk 1.02 (CI 95% 0.34 — 3.01) Based on data from 1,296 participants in 2 studies. [13] (Randomized controlled)	10 per 1000 Difference:	10 per 1000 **0 fewer per 1000** (CI 95% 7 fewer — 20 more)	**Low** Due to serious risk of bias and serious inconsistency [14]	We are uncertain whether remdesivir increases or decreases septic shock (13 events).
Serious adverse events	Relative risk 0.82 (CI 95% 0.65 — 1.04)	273 per 1000	224 per 1000	**Moderate** Due to serious	Remdesivir probably decreases serious

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
End of follow-up 6 Important	Based on data from 2,689 participants in 4 studies. [15] (Randomized controlled)	Difference:	**49 fewer per 1000** (CI 95% 96 fewer — 11 more)	risk of bias [16]	adverse events slightly.
Adverse events End of follow-up 6 Important	Relative risk 1.03 (CI 95% 0.92 — 1.16) Based on data from 2,704 participants in 4 studies. [17] (Randomized controlled)	553 per 1000 Difference:	570 per 1000 **17 more per 1000** (CI 95% 44 fewer — 88 more)	**Moderate** Due to serious risk of bias [18]	Remdesivir probably has no impact on adverse events.
Discontinuation due to adverse events During treatment 6 Important	Relative risk 1.73 (CI 95% 0.57 — 5.28) Based on data from 1,880 participants in 3 studies. [19] (Randomized controlled)	93 per 1000 Difference:	161 per 1000 **68 more per 1000** (CI 95% 40 fewer — 398 more)	**Low** Due to serious risk of bias and serious imprecision [20]	We are uncertain whether remdesivir increases or decreases adverse events leading to discontinuation.
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.94 — 1.13) Based on data from 6,365 participants in 3 studies. [21] (Randomized controlled)	693 per 1000 Difference:	714 per 1000 **21 more per 1000** (CI 95% 42 fewer — 90 more)	**Moderate** Due to serious imprecision [22]	Remdesivir probably makes little or no difference to discharge from hospital.
Time to recovery Days 6 Important	Hazard ratio 1.24 (CI 95% 1.08 — 1.42) Based on data from 1,643 participants in 2 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [23]	Remdesivir may decrease time to recovery by a few days.
Time to improvement Days 6 Important	Hazard ratio 1.17 (CI 95% 1 — 1.38) Based on data from 810 participants in 2 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [24]	Remdesivir may decrease time to improvement slightly.

Attached Images

Not recommended

Do not start remdesivir in adults hospitalised with COVID-19 who require non-invasive or invasive ventilation.

Additional information

Remdesivir (Veklury) should be continued with the appropriate dose and duration, if it was started prior to requiring ventilation.

Within this population, ventilation includes invasive or non-invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO).

It is unclear whether older people or those requiring palliative care were included in the studies this recommendation is based on. Until further evidence in these populations is available, the Taskforce does not believe a different recommendation should apply, unless contraindicated.

Use of remdesivir may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include remdesivir.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

Important harms

In patients who are hospitalised with COVID-19 and who require ventilation, risk of death may be higher in patients using remdesivir compared with standard care.

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

Moderate

Certainty of the evidence is moderate for death at day 28 in hospitalised adults who require ventilation. Certainty is also moderate for patients requiring ventilation, discharge from hospital, serious adverse events, time to recovery and time to improvement. Certainty is low for all other outcomes.

Values and preferences

We expect few to want the intervention

We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is clear evidence demonstrating harms of remdesivir in patients requiring ventilation, informed patients would not choose this treatment.

Resources

No important issues with the recommended alternative

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

Equity

No important issues with the recommended alternative

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

Acceptability

No important issues with the recommended alternative

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

Feasibility

No important issues with the recommended alternative

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

Rationale

Remdesivir in adults hospitalised with COVID-19 who require ventilation probably increases the risk of death—its use should be avoided in this population.

Clinical Question/ PICO

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

Summary

Evidence indicates that remdesivir probably reduces the risk of death in hospitalised adults not requiring ventilation and increases the risk of death in hospitalised adults who require ventilation.

What is the evidence informing this recommendation?
Evidence comes from six randomised trials that compared remdesivir with standard care in over 8200 adults hospitalised with COVID-19 *[42][43][46][49][55][365]*. The majority of evidence is from the WHO Solidarity trial which randomised 5451 patients with moderate to critical COVID-19 *[49]*.

Study characteristics
For a comprehensive description, see the study characteristics table. There was variability in disease severity among patients included in the trials (see table).

Disease severity	Number of patients	References
Moderate	666	*[46][55]*
Moderate-Critical	6513	*[42][49][365]*
Severe-Critical	236	*[43]*

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (17 fewer per 1000; RR 0.81, CI 95% 0.65 to 1.01; 6904 patients in 6 studies), and probably increases death at day 28 in patients who require ventilation (35 more per 1000; RR 1.16, CI 95% 0.96 to 1.41; 1004 patients in 3 studies).

Remdesivir may decrease time to recovery by a few days (HR 1.24, 95% CI 1.08 to 1.42; 1643 patients in 2 studies) and time to improvement only slightly (HR 1.17, 95% CI 1.00 to 1.38; 810 patients in 2 studies). Clinical recovery was defined as the first day in which a patient satisfied categories 1, 2 or 3 on the 8-point WHO ordinal scale *[42]* or improvement from a baseline score of 2–5 to a score of 6 or 7 on a 7-point ordinal scale *[46]*. Clinical improvement was defined as an improvement of 2 or more points on a 7-point *[46]* or 6-point ordinal scale *[43]*.

Compared with standard care, remdesivir probably reduces serious adverse events (49 fewer per 1000; RR 0.82, CI 95% 0.65 to 1.04; 2689 patients in 4 studies). There is no important difference between remdesivir and standard care regarding the number of patients requiring ventilation, number of patients discharged from

hospital at day 28, and number of patients experiencing one or more adverse events. We are uncertain whether remdesivir impacts respiratory failure or ARDS, clinical recovery at day 28, septic shock and discontinuation due to adverse events.

An additional study was identified but did not meet the inclusion criteria due to its observational design *[56]*. The study included 86 **pregnant and postpartum women** with severe COVID-19 in the USA who received compassionate-use remdesivir. Median age was 33 years (range 20–43 years) and median gestational age was 29 weeks (range 14–39 weeks). Invasive mechanical ventilation was given to 52% of women and non-invasive ventilation (NIPPV, high-flow and low-flow oxygen) to 45%—the remaining 3% were on room air at baseline. Two-thirds of pregnant women and all postpartum women were in ICU.

A more recent study by Gutierrez et al. *[453]*, a prospective cohort study published on 15 Feb 2022, assessed the use of remdesivir during pregnancy during the SARS-CoV-2 pandemic. Only 95 participants met the inclusion criteria, and were then stratified according to whether or not they received remdesivir in hospital. Ultimately the study was quite small, and the use of remdesivir within the study appeared to be safe, well tolerated within our cohort with no cases of recorded adverse reaction.

Extubation was achieved in 93% of pregnant women and 89% of postpartum women who were mechanically ventilated. Recovery at 28 days (defined as an improvement from NIV to room air) was achieved in 93% of pregnant women and 89% of postpartum women. Discharge occurred in 90% of pregnant women and 84% of postpartum women.

Adverse events were experienced by 29% of women and 16% had a serious adverse event. Examples of adverse events experienced included anaemia, DVT and dysphagia. Seven women discontinued treatment with remdesivir due to adverse events, of which five had elevated liver enzyme concentrations, one had nausea and the other had haemoptysis.

The results of this observational study are in line with the current trial evidence, demonstrating that there remains uncertainty whether remdesivir is more effective and safer than standard care in treating pregnant and postpartum women with COVID-19.

Remdesivir has been used anecdotally for the treatment of COVID-19 in **children and adolescents**. The preliminary findings from a recent cohort study of 77 hospitalised patients under 18 years of age are reassuring, but uncertainties remain about the benefits of remdesivir in this population *[314]*. Trials are currently recruiting in this population.

Our confidence in the results
Certainty of the evidence is moderate for death in both subgroups (patients who do not require ventilation, and patients who require ventilation), all due to serious imprecision (wide confidence intervals). Certainty is also moderate for patients requiring ventilation and discharge from hospital (due to reliance on a single study), serious adverse events, adverse events, time to recovery and time to improvement (due to non-blinding of patients and personnel).

Certainty of the evidence is low for respiratory failure or acute respiratory distress syndrome (due to inconsistency in direction of effect and wide confidence intervals), number of patients requiring invasive mechanical ventilation or ECMO (due to non-blinding of patients and personnel and reliance on a single study), clinical recovery, septic shock and adverse events (due to non-blinding of patients and personnel and inconsistency in direction of effect) and discontinuation due to adverse events (due to non-blinding of patients and personnel and wide confidence intervals).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
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 *[45]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality [hospital no ventilation] Within 28 days of commencing treatment 9 Critical	Relative risk 0.81 (CI 95% 0.65 — 1.01) Based on data from 6,904 participants in 8 studies. [1] (Randomized controlled)	88 per 1000 Difference:	71 per 1000 **17 fewer per 1000** (CI 95% 31 fewer — 1 more)	Moderate Due to serious imprecision [2]	Remdesivir probably decreases death slightly in hospitalised patients who do not require ventilation.
All-cause mortality [ventilation] Within 28 days of commencing treatment 9 Critical	Relative risk 1.16 (CI 95% 0.96 — 1.41) Based on data from 1,332 participants in 5 studies. [3] (Randomized controlled)	219 per 1000 Difference:	254 per 1000 **35 more per 1000** (CI 95% 9 fewer — 90 more)	Moderate Due to serious imprecision [4]	Remdesivir probably increases death in hospitalised patients requiring ventilation.
Respiratory failure or ARDS Within 28 days of commencing treatment 9 Critical	Relative risk 0.82 (CI 95% 0.5 — 1.33) Based on data from 2,120 participants in 3 studies. [5] (Randomized controlled)	121 per 1000 Difference:	99 per 1000 **22 fewer per 1000** (CI 95% 61 fewer — 40 more)	Low Due to serious imprecision and serious inconsistency [6]	We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (221 events).
Invasive mechanical ventilation or ECMO Within 28 days of commencing treatment 9 Critical	Relative risk 0.57 (CI 95% 0.42 — 0.79) Based on data from 766 participants in 1 studies. [7] (Randomized controlled)	225 per 1000 Difference:	128 per 1000 **97 fewer per 1000** (CI 95% 131 fewer — 47 fewer)	Low Due to serious risk of bias and serious imprecision [8]	Remdesivir may decrease the need for invasive mechanical ventilation or ECMO (134 events).
Patients requiring ventilation Within 28 days of commencing treatment 6 Important	Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 5,034 participants in 2 studies. [9] (Randomized controlled)	114 per 1000 Difference:	119 per 1000 **5 more per 1000** (CI 95% 13 fewer — 24 more)	Moderate Due to serious imprecision [10]	Remdesivir probably has no impact on number of patients requiring ventilation.
Clinical recovery Within 28 days	Relative risk 0.99 (CI 95% 0.86 — 1.14) Based on data from	711 per 1000	704 per 1000	Low Due to serious risk of bias and	We are uncertain whether remdesivir improves or worsens

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
of commencing treatment 6 Important	1,876 participants in 3 studies. [11] (Randomized controlled)	Difference:	**7 fewer per 1000** (CI 95% 100 fewer — 100 more)	serious inconsistency [12]	clinical recovery at day 28.
Septic shock Within 28 days of commencing treatment 6 Important	Relative risk 1.02 (CI 95% 0.34 — 3.01) Based on data from 1,296 participants in 2 studies. [13] (Randomized controlled)	10 per 1000 Difference:	10 per 1000 **0 fewer per 1000** (CI 95% 7 fewer — 20 more)	**Low** Due to serious risk of bias and serious inconsistency [14]	We are uncertain whether remdesivir increases or decreases septic shock (13 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.82 (CI 95% 0.65 — 1.04) Based on data from 2,689 participants in 4 studies. [15] (Randomized controlled)	273 per 1000 Difference:	224 per 1000 **49 fewer per 1000** (CI 95% 96 fewer — 11 more)	**Moderate** Due to serious risk of bias [16]	Remdesivir probably decreases serious adverse events slightly.
Adverse events End of follow-up 6 Important	Relative risk 1.03 (CI 95% 0.92 — 1.16) Based on data from 2,704 participants in 4 studies. [17] (Randomized controlled)	553 per 1000 Difference:	570 per 1000 **17 more per 1000** (CI 95% 44 fewer — 88 more)	**Moderate** Due to serious risk of bias [18]	Remdesivir probably has no impact on adverse events.
Discontinuation due to adverse events During treatment 6 Important	Relative risk 1.73 (CI 95% 0.57 — 5.28) Based on data from 1,880 participants in 3 studies. [19] (Randomized controlled)	93 per 1000 Difference:	161 per 1000 **68 more per 1000** (CI 95% 40 fewer — 398 more)	**Low** Due to serious risk of bias and serious imprecision [20]	We are uncertain whether remdesivir increases or decreases adverse events leading to discontinuation.
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.94 — 1.13) Based on data from 6,365 participants in 3 studies. [21] (Randomized controlled)	693 per 1000 Difference:	714 per 1000 **21 more per 1000** (CI 95% 42 fewer — 90 more)	**Moderate** Due to serious imprecision [22]	Remdesivir probably makes little or no difference to discharge from hospital.
Time to recovery Days	Hazard ratio 1.24 (CI 95% 1.08 — 1.42) Based on data from			**Moderate** Due to serious risk of bias [23]	Remdesivir may decrease time to recovery by a few days.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important	1,643 participants in 2 studies. (Randomized controlled)				
Time to improvement Days 6 Important	Hazard ratio 1.17 (CI 95% 1 — 1.38) Based on data from 810 participants in 2 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [24]	Remdesivir may decrease time to improvement slightly.

Attached Images

Conditional recommendation

Consider using remdesivir within 7 days of symptom onset in unvaccinated* adults with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression.

Within the patient population for which remdesivir is conditionally recommended for use (see Additional information), decisions about the appropriateness of remdesivir should be based on the individual's risk of severe disease, including their age, presence of multiple risk factors, and vaccination status (including number of doses and time since last dose/ or timing of most recent infection).

** Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial. The efficacy of remdesivir is unclear in individuals who have received any COVID-19 vaccine. See consensus recommendation for guidance on use of remdesivir in vaccinated adults or in immunocompromised patients regardless of vaccination status.*

Additional information

In adults with confirmed COVID-19 who do not require oxygen, remdesivir (Veklury) probably decreases the risk of hospitalisation if taken within 7 days of onset of symptoms.

Results are based on a single trial [414], in which unvaccinated adults were administered three intravenous doses of remdesivir on consecutive days (200 mg on day 1, followed by 100 mg on days 2 and 3). Based on the inclusion criteria for this trial, risk factors for disease progression include the following:

- *Age ≥ 60 years*
- *Diabetes*
- *Obesity (BMI ≥ 30 kg/m2)*
- *Chronic kidney disease (any stage)*
- *Cardiovascular or cerebrovascular disease (coronary artery disease, congenital heart disease, heart failure, cardiomyopathy or history of stroke)*
- *Hypertension (systemic or pulmonary)*
- *Chronic liver disease*
- *Chronic lung disease (chronic obstructive pulmonary disease, moderate-severe asthma, cystic or pulmonary fibrosis)*
- *Sickle cell disease*
- *Current cancer*
- *Immunocompromised state (no definition provided)*

Pregnant and breastfeeding women were not included in the trial. Eight paediatric patients aged 12–18 years were included, none of whom progressed to hospitalisation or death.

The efficacy of remdesivir in vaccinated adults and immunocompromised patients is unknown.

The Taskforce has made conditional recommendations supporting the use of sotrovimab, casirivimab plus imdevimab, nirmatrelvir plus ritonavir, remdesivir and regdanvimab, and a consensus recommendation for molnupiravir, in adults who do not require oxygen. The relative effectiveness of these agents, or the effectiveness of these agents when used in combination, is unclear.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Remdesivir probably reduces the incidence of hospitalisation in patients who do not require oxygen and who have one or more risk factors for disease progression.

Remdesivir probably has little impact on incidence of adverse events. We are unsure if remdesivir impacts serious adverse events, discontinuation due to adverse events, or all-cause mortality.

Certainty of the Evidence

Moderate

Certainty of the evidence is moderate for hospitalisation and adverse events due to serious imprecision (reliance on a single study) and low for serious adverse events and discontinuation due to adverse events due to very serious imprecision (reliance on a single study and few events).

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values. The consumer panel believes that some people would opt for this treatment while others might prefer one of the other treatment options, and some might want to wait for more evidence. The consumer panel notes that there is potential for issues around engagement with and access to healthcare, and health literacy to impact on the equitable access to and uptake of this treatment.

Pregnant or breastfeeding patients
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.

Children and adolescents
We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. The limited availability of remdesivir, as well as the high cost of treatment, are limiting factors that may prevent widespread use of this treatment.

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity; however as remdesivir is only accessible through special arrangements with the Australian Government, this may affect equity based on geographic area and access to remdesivir.

Acceptability

No important issues with the recommended alternative

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

Feasibility

Intervention is likely difficult to implement

Intravenous remdesivir (Veklury; Gilead Sciences Pty Ltd) was granted provisional approval for the treatment of COVID-19 in hospitalised patients by the Therapeutic Goods Administration on 10 July 2020 under the Black Triangle Scheme (*ARTG numbers: 338419, 338420;* AusPAR). As of 18 February 2022, the TGA has not approved the use of remdesivir in non-hospitalised patients with mild COVID-19.

Rationale

General adult population
In adult outpatients with mild COVID-19, remdesivir probably reduces the risk of hospitalisation. Because of this, the Taskforce gives a conditional recommendation for remdesivir both within and outside a randomised trial.

Clinical Question/ PICO

Population: Outpatients with mild COVID-19
Intervention: Remdesivir
Comparator: Placebo

Summary

Evidence indicates that remdesivir probably reduces the incidence of hospitalisation in unvaccinated adults with mild COVID-19 who have one or more risk factors for disease progression.

What is the evidence informing this recommendation?
Evidence comes from a single trial that compared remdesivir with placebo in 562 unvaccinated adult outpatients with mild COVID-19 *[414]*. Participants were randomised within seven days of onset of symptoms and had one or more risk factors for disease progression.

Study characteristics
Mean age of participants was 50 years and 48% were women. Approximately one third of patients were aged 60 years or over. Participants received three intravenous doses of remdesivir on consecutive days; 200 mg on day 1, followed by 100 mg on days 2 and 3. Pregnant and breastfeeding women were ineligible for inclusion; however children aged 12 years and over were eligible for inclusion.

What are the main results?
Remdesivir probably reduces the incidence of hospitalisation (RR 0.28, CI 95% 0.11 to 0.75; 562 patients in 1 study) and probably has little impact on adverse events or serious adverse events. We are unsure if remdesivir impacts discontinuation due to adverse events, or all-cause mortality (no patients died).

Our confidence in the results
Certainty of the evidence is moderate for hospitalisation and adverse events due to serious imprecision (reliance on a single study) and low for serious adverse events and discontinuation due to adverse events due to very serious imprecision (reliance on a single study and few events).

For pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
As of 18 February 2022, the Therapeutic Goods Administration has yet to approve remdesivir for use in patients who have mild COVID-19 and who are not hospitalised.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk Based on data from 562 participants in 1 studies. [1]				No patients died.
Hospitalisation Within 28 days of commencing treatment 6 Important	Relative risk 0.28 (CI 95% 0.11 — 0.75) Based on data from 562 participants in 1 studies. [2] (Randomized controlled)	**64** per 1000 Difference:	**18** per 1000 **46 fewer per 1000** (CI 95% 57	**Moderate** Due to serious imprecision [3]	Remdesivir probably decreases hospitalisation in outpatients with mild COVID-19 (23 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
			fewer — 16 fewer)		
Adverse events End of follow-up 6 Important	Relative risk 0.91 (CI 95% 0.76 — 1.1) Based on data from 562 participants in 1 studies. [4] (Randomized controlled)	463 per 1000 Difference:	421 per 1000 **42 fewer per 1000** (CI 95% 111 fewer — 46 more)	**Moderate** Due to serious imprecision [5]	Remdesivir probably decreases adverse events slightly (249 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.27 (CI 95% 0.1 — 0.7) Based on data from 562 participants in 1 studies. [6] (Randomized controlled)	67 per 1000 Difference:	18 per 1000 **49 fewer per 1000** (CI 95% 60 fewer — 20 fewer)	**Moderate** Due to serious imprecision [7]	Remdesivir may decrease serious adverse events slightly (24 events).
Discontinuation due to an adverse event End of follow-up 6 Important	Relative risk 0.41 (CI 95% 0.08 — 2.07) Based on data from 562 participants in 1 studies. [8] (Randomized controlled)	18 per 1000 Difference:	7 per 1000 **11 fewer per 1000** (CI 95% 17 fewer — 19 more)	**Low** Due to very serious imprecision [9]	We are uncertain whether remdesivir increases or decreases discontinuation due to an adverse event (7 events).

Attached Images

Consensus recommendation

In addition to at-risk unvaccinated adults, also consider using remdesivir within 7 days of symptom onset in adults with COVID-19 who do not require oxygen and are immunocompromised; or are at particularly high risk of severe disease on the basis of advanced age and multiple risk factors.

Additional information

Decisions about the appropriateness of remdesivir should be based on the individual's risk of severe disease, including their age, presence of multiple risk factors, and vaccination status (including number of doses and time since last dose/ or timing of most recent infection).

Available research does not currently provide enough evidence to determine the benefits of remdesivir (Veklury) in specific subgroups of adults. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which adults are most likely to benefit from remdesivir.

There is no evidence evaluating the effectiveness of remdesivir in individuals who have received any COVID-19 vaccine, a low likelihood of development of severe disease, and a small risk of adverse events. Given this, and the lower risk of deterioration in these individuals, it is less likely that remdesivir will have a significant treatment benefit in individuals who have received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months, unless the individual is immunocompromised.

There is limited evidence on the effectiveness of remdesivir in immunocompromised individuals. However, given the likely higher risk of deterioration in these individuals, and the absence of reasons to believe otherwise, it is likely that remdesivir will be beneficial for immunocompromised individuals.

Immunocompromising conditions include:

- *Primary or acquired immunodeficiency*
  - *Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes*
  - *Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months)*
  - *Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency*
  - *Other significantly immunocompromising conditions*
- *Immunosuppressive therapy (current or recent)*
  - *Chemotherapy, whole body radiotherapy or total lymphoid irradiation*
  - *High-dose corticosteroids (≥ 20 mg of prednisone per day, or equivalent) for ≥ 14 days*
  - *All biological disease-modifying anti-rheumatic drugs (DMARDs) and most other (e.g. conventional synthetic) DMARDs [348]*

In the absence of reliable evidence, the Taskforce has developed this recommendation based on their clinical expertise and experience.

7.1.8.2 Remdesivir (Veklury) for pregnant or breastfeeding women

Conditional recommendation

Consider using remdesivir in pregnant or breastfeeding women hospitalised with COVID-19 who require oxygen but do not require non-invasive or invasive ventilation.

Additional information

In adults hospitalised with COVID-19 who do not require ventilation (invasive or non-invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)) remdesivir (Veklury) probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for remdesivir both within and outside the context of a randomised trial.

We are aware of the difference between our recommendations for remdesivir and those currently issued by the World Health Organization [50]. For a full description of the rationale underpinning this decision please see here.

The recommended regimen is daily intravenous infusion (200 mg initial dose, 100 mg maintenance), optimal duration of remdesivir treatment is unclear, however current evidence does not suggest a clear benefit of 10 days over 5 days.

On 31 July 2020, the Australian Government provided specific criteria that needed to be met in order to access remdesivir for clinical treatment. These included age ≥ 18 years (or 12–17 years weighing ≥ 40 kg), an oxygen saturation of SpO2 ≤ 92% on room air and requiring supplemental oxygen, and alanine aminotransferase (ALT) < 5 x upper limit of normal (ULN) and/or ALT < 3 x ULN and bilirubin < 2 ULN. Patients with evidence of multiorgan failure, renal failure or those receiving mechanical ventilation for > 48 hours at time of application or ECMO are unable to receive remdesivir.

Due to antagonism observed in vitro, concomitant use of remdesivir with chloroquine or hydroxychloroquine is not recommended [45].

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

There remains uncertainty around the benefits and harms of remdesivir for pregnant or breastfeeding women with COVID-19. Evidence from trials of non-pregnant adults comparing 10-day to 5-day courses of remdesivir is too uncertain to inform decisions regarding length of treatment at this point.

In non-pregnant patients who are hospitalised with moderate COVID-19 and who do not require ventilation (non-invasive ventilation, mechanical ventilation or ECMO), remdesivir probably reduces the risk of death.

Evidence from randomised trials versus standard care demonstrates that remdesivir has an acceptable safety profile in non-pregnant adults and may reduce the incidence of serious adverse events. Based on the results of two studies that compared 10-day to 5-day courses of remdesivir, it is unclear which of these regimens provide the optimal duration of treatment—current evidence does not suggest a clear benefit for 10 days over 5 days.

While the safety profile of remdesivir has not been described for pregnant and breastfeeding women, some observational data on the use of remdesivir in pregnant women with severe COVID-19 suggests that it is well tolerated, with a low incidence of serious adverse events *[56]*.

Certainty of the Evidence

Low

Certainty of the evidence is low for death at day 28 as the estimates are imprecise and indirect since pregnant women were excluded from the trials. Certainty is also low for patients requiring ventilation, discharge from hospital, serious adverse events, time to recovery and time to improvement. Certainty is very low for all other outcomes.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point.

The Consumer Panel believes that as there is uncertainty regarding the benefits and possible harms of this treatment to mother or unborn child, some informed pregnant or breastfeeding women may prefer to wait until the available evidence is clearer, while other informed pregnant or breastfeeding women may want this treatment.

Resources

Important issues, or potential issues not investigated

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.

Criteria for accessing remdesivir from the National Medical Stockpile, released by the Australian Government on 31 July 2020, limits the treatment course to 5 days for eligible patients.

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity; however, as remdesivir is only accessible through special arrangements with the Australian Government, this may affect equity based on geographic area and access to remdesivir.

Acceptability

No important issues with the recommended alternative

We have no systematically collected evidence regarding acceptability among pregnant or breastfeeding women.

Feasibility

Important issues, or potential issues not investigated

Intravenous remdesivir (Veklury; Gilead Sciences Pty Ltd) was granted provisional approval for the treatment of COVID-19 by the Therapeutic Goods Administration on 10 July 2020 under the Black Triangle Scheme (*ARTG numbers: 338419, 338420; AusPAR*).

Treatment with remdesivir is not feasible in patients who do not meet eligibility for clinical treatment specified by the Australian Government Department of Health. 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

Remdesivir in patients hospitalised with COVID-19 who do not require ventilation probably reduces the risk of death.

We are aware of the difference between our recommendations for remdesivir and those currently issued by the World Health Organization *[50]*. For a full description of the rationale underpinning this decision please see here.

Observational data on use of remdesivir in pregnant women with severe COVID-19 suggests it is well tolerated, though further studies are needed in this population. Considering the decreased risk of death, its use should be considered in this population. Because of this, the Taskforce gives a conditional recommendation for remdesivir both within and outside the context of a randomised trial.

It is unclear which regimen of remdesivir (5-day or 10-day) provides the optimal duration of treatment. In Australia, criteria for accessing remdesivir from the National Medical Stockpile limits the treatment course to 5 days for eligible patients.

Clinical Question/ PICO

Population: Remdesivir dosage for COVID-19
Intervention: 5 days' treatment
Comparator: Up to 10 days' treatment

Summary

There remains uncertainty whether a 5-day course of remdesivir is more effective and safer than a 10-day course.

What is the evidence informing this recommendation?
Evidence comes from two randomised trials that compared 5-day to 10-day treatment with remdesivir in 781 hospitalised patients with severe COVID-19 *[44][46]*.

Study characteristics
For a comprehensive description, see the study characteristics table.

What are the main results?
There is a lower risk of death within 14 days of treatment with a 5-day versus a 10-day course of remdesivir (16 fewer per 1000; RR 0.73, CI 95% 0.40 to 1.33; 781 patients in 2 studies). The evidence is more uncertain for death within 28 days of treatment (5 fewer per 1000; RR 0.67, CI 95% 0.11 to 3.99; 384 patients in 1 study).

There is probably little difference between a 5-day and 10-day course of remdesivir regarding adverse events, discontinuation of treatment due to adverse events and discharge from hospital.

Our confidence in the results
Certainty of the evidence is moderate for the following outcomes: death within 14 days, serious adverse events, adverse events and discharge from hospital within 14 days. Certainty is low for death within 28 days, acute respiratory failure or ARDS, clinical recovery within 14 days and discharge from hospital within 28 days. This judgement is based on serious risk of bias (problems with randomisation *[44]*, lack of blinding), serious imprecision (too few events) and very serious imprecision (reliance on a single study with few patients and/or few events).

It is important to note that Goldman et al. only presents initial results from the first 400 patients in a trial that includes nearly 5000 patients (NCT04292899) *[44]*. The trial completed recruitment in July 2020 and we await the results from the full cohort of patients.

Additional information
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 *[45]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Up to 10 days' treatment	**Intervention** 5 days' treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 14 days of commencing treatment 9 Critical	Relative risk 0.73 (CI 95% 0.4 — 1.33) Based on data from 781 participants in 2 studies. [1] (Randomized controlled)	59 per 1000 Difference:	43 per 1000 **16 fewer per 1000** (CI 95% 35 fewer — 19 more)	**Moderate** Due to serious imprecision [2]	Remdesivir 5-day treatment probably has little or no impact on death (40 deaths).
All-cause	Relative risk 0.67	16	11	**Low**	We are uncertain

Outcome Timeframe	**Study results and measurements**	**Comparator** Up to 10 days' treatment	**Intervention** 5 days' treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
mortality Within 28 days of commencing treatment 9 Critical	(CI 95% 0.11 — 3.99) Based on data from 384 participants in 1 studies. [3] (Randomized controlled)	per 1000 Difference:	per 1000 **5 fewer per 1000** (CI 95% 14 fewer — 48 more)	Due to very serious imprecision [4]	whether remdesivir 5-day treatment increases or decreases death at 28 days (5 deaths).
Acute respiratory failure or ARDS Within 30 days of commencing treatment 9 Critical	Relative risk 0.47 (CI 95% 0.24 — 0.94) Based on data from 397 participants in 1 studies. [5] (Randomized controlled)	117 per 1000 Difference:	55 per 1000 **62 fewer per 1000** (CI 95% 89 fewer — 7 fewer)	**Low** Due to very serious imprecision [6]	Remdesivir 5-day treatment may decrease acute respiratory failure or ARDS slightly (34 events).
Septic shock Within 30 days of commencing treatment 6 Important	Relative risk 0.39 (CI 95% 0.08 — 2.01) Based on data from 397 participants in 1 studies. [7] (Randomized controlled)			**Very low** Due to very serious imprecision [8]	We are uncertain whether remdesivir 5-day treatment increases or decreases septic shock (7 events).
Clinical recovery Within 14 days of commencing treatment 6 Important	Relative risk 1.2 (CI 95% 1.02 — 1.41) Based on data from 397 participants in 1 studies. [9] (Randomized controlled)	538 per 1000 Difference:	646 per 1000 **108 more per 1000** (CI 95% 11 more — 221 more)	**Low** Due to serious risk of bias and imprecision [10]	Remdesivir 5-day treatment may improve clinical recovery slightly (235 events).
Serious adverse events End of follow up 6 Important	Relative risk 0.64 (CI 95% 0.47 — 0.87) Based on data from 781 participants in 2 studies. [11] (Randomized controlled)	200 per 1000 Difference:	128 per 1000 **72 fewer per 1000** (CI 95% 106 fewer — 26 fewer)	**Moderate** Due to serious risk of bias [12]	Remdesivir 5-day treatment probably decreases serious adverse events slightly (129 events).
Adverse events End of follow up 6 Important	Relative risk 0.93 (CI 95% 0.84 — 1.03) Based on data from 781 participants in 2 studies. [13] (Randomized controlled)	662 per 1000 Difference:	616 per 1000 **46 fewer per 1000** (CI 95% 106 fewer — 20 more)	**Moderate** Due to serious risk of bias [14]	Remdesivir 5-day treatment probably makes little or no difference to adverse events (503 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Up to 10 days' treatment	**Intervention** 5 days' treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Discontinuation due to adverse events During treatment 6 Important	Relative risk 0.59 (CI 95% 0.3 — 1.15) Based on data from 781 participants in 2 studies. [15] (Randomized controlled)	56 per 1000 Difference:	33 per 1000 **23 fewer per 1000** (CI 95% 39 fewer — 8 more)	**Low** Due to serious risk of bias and imprecision [16]	Remdesivir 5-day treatment may make little or no difference to discontinuation due to adverse events (35 events).
Discharged from hospital Within 14 days of commencing treatment 6 Important	Relative risk 1.06 (CI 95% 0.93 — 1.2) Based on data from 781 participants in 2 studies. [17] (Randomized controlled)	638 per 1000 Difference:	676 per 1000 **38 more per 1000** (CI 95% 45 fewer — 128 more)	**Moderate** Due to serious risk of bias [18]	Remdesivir 5-day treatment probably makes little or no difference to number of patients discharged from hospital at day 14 (515 events)
Discharged from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.92 — 1.06) Based on data from 384 participants in 1 studies. [19] (Randomized controlled)	902 per 1000 Difference:	893 per 1000 **9 fewer per 1000** (CI 95% 72 fewer — 54 more)	**Low** Due to very serious imprecision [20]	Remdesivir 5-day treatment may make little or no difference to number of patients discharged from hospital at day 28 (344 events).

Attached Images

Clinical Question/ PICO

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

Summary

Evidence indicates that remdesivir probably reduces the risk of death in hospitalised adults not requiring ventilation and increases the risk of death in hospitalised adults who require ventilation.

What is the evidence informing this recommendation?
Evidence comes from six randomised trials that compared remdesivir with standard care in over 8200 adults hospitalised with COVID-19 *[42][43][46][49][55][365]*. The majority of evidence is from the WHO Solidarity trial which randomised 5451 patients with moderate to critical COVID-19 *[49]*.

Study characteristics
For a comprehensive description, see the study characteristics table. There was variability in disease severity among patients included in the trials (see table).

Disease severity	**Number of patients**	**References**
Moderate	666	*[46][55]*
Moderate-Critical	6513	*[42][49][365]*

Severe-Critical	236	*[43]*

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (17 fewer per 1000; RR 0.81, CI 95% 0.65 to 1.01; 6904 patients in 6 studies), and probably increases death at day 28 in patients who require ventilation (35 more per 1000; RR 1.16, CI 95% 0.96 to 1.41; 1004 patients in 3 studies).

Remdesivir may decrease time to recovery by a few days (HR 1.24, 95% CI 1.08 to 1.42; 1643 patients in 2 studies) and time to improvement only slightly (HR 1.17, 95% CI 1.00 to 1.38; 810 patients in 2 studies). Clinical recovery was defined as the first day in which a patient satisfied categories 1, 2 or 3 on the 8-point WHO ordinal scale *[42]* or improvement from a baseline score of 2–5 to a score of 6 or 7 on a 7-point ordinal scale *[46]*. Clinical improvement was defined as an improvement of 2 or more points on a 7-point *[46]* or 6-point ordinal scale *[43]*.

Compared with standard care, remdesivir probably reduces serious adverse events (49 fewer per 1000; RR 0.82, CI 95% 0.65 to 1.04; 2689 patients in 4 studies). There is no important difference between remdesivir and standard care regarding the number of patients requiring ventilation, number of patients discharged from hospital at day 28, and number of patients experiencing one or more adverse events. We are uncertain whether remdesivir impacts respiratory failure or ARDS, clinical recovery at day 28, septic shock and discontinuation due to adverse events.

An additional study was identified but did not meet the inclusion criteria due to its observational design *[56]*. The study included 86 **pregnant and postpartum women** with severe COVID-19 in the USA who received compassionate-use remdesivir. Median age was 33 years (range 20–43 years) and median gestational age was 29 weeks (range 14–39 weeks). Invasive mechanical ventilation was given to 52% of women and non-invasive ventilation (NIPPV, high-flow and low-flow oxygen) to 45%—the remaining 3% were on room air at baseline. Two-thirds of pregnant women and all postpartum women were in ICU.

A more recent study by Gutierrez et al. *[453]*, a prospective cohort study published on 15 Feb 2022, assessed the use of remdesivir during pregnancy during the SARS-CoV-2 pandemic. Only 95 participants met the inclusion criteria, and were then stratified according to whether or not they received remdesivir in hospital. Ultimately the study was quite small, and the use of remdesivir within the study appeared to be safe, well tolerated within our cohort with no cases of recorded adverse reaction.

Extubation was achieved in 93% of pregnant women and 89% of postpartum women who were mechanically ventilated. Recovery at 28 days (defined as an improvement from NIV to room air) was achieved in 93% of pregnant women and 89% of postpartum women. Discharge occurred in 90% of pregnant women and 84% of postpartum women.

Adverse events were experienced by 29% of women and 16% had a serious adverse event. Examples of adverse events experienced included anaemia, DVT and dysphagia. Seven women discontinued treatment with remdesivir due to adverse events, of which five had elevated liver enzyme concentrations, one had nausea and the other had haemoptysis.

The results of this observational study are in line with the current trial evidence, demonstrating that there remains uncertainty whether remdesivir is more effective and safer than standard care in treating pregnant and postpartum women with COVID-19.

Remdesivir has been used anecdotally for the treatment of COVID-19 in **children and adolescents**. The preliminary findings from a recent cohort study of 77 hospitalised patients under 18 years of age are reassuring, but uncertainties remain about the benefits of remdesivir in this population *[314]*. Trials are currently recruiting in this population.

Our confidence in the results
Certainty of the evidence is moderate for death in both subgroups (patients who do not require ventilation, and patients who require ventilation), all due to serious imprecision (wide confidence intervals). Certainty is also moderate for patients requiring ventilation and discharge from hospital (due to reliance on a single study), serious adverse events, adverse events, time to recovery and time to improvement (due to non-blinding of patients and personnel).

Certainty of the evidence is low for respiratory failure or acute respiratory distress syndrome (due to inconsistency in direction of effect and wide confidence intervals), number of patients requiring invasive mechanical ventilation or ECMO (due to non-blinding of patients and personnel and reliance on a single study),

clinical recovery, septic shock and adverse events (due to non-blinding of patients and personnel and inconsistency in direction of effect) and discontinuation due to adverse events (due to non-blinding of patients and personnel and wide confidence intervals).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
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 *[45]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality [hospital no ventilation] Within 28 days of commencing treatment 9 Critical	Relative risk 0.81 (CI 95% 0.65 — 1.01) Based on data from 6,904 participants in 8 studies. [1] (Randomized controlled)	88 per 1000 Difference:	71 per 1000 **17 fewer per 1000** (CI 95% 31 fewer — 1 more)	**Moderate** Due to serious imprecision [2]	Remdesivir probably decreases death slightly in hospitalised patients who do not require ventilation.
All-cause mortality [ventilation] Within 28 days of commencing treatment 9 Critical	Relative risk 1.16 (CI 95% 0.96 — 1.41) Based on data from 1,332 participants in 5 studies. [3] (Randomized controlled)	219 per 1000 Difference:	254 per 1000 **35 more per 1000** (CI 95% 9 fewer — 90 more)	**Moderate** Due to serious imprecision [4]	Remdesivir probably increases death in hospitalised patients requiring ventilation.
Respiratory failure or ARDS Within 28 days of commencing treatment 9 Critical	Relative risk 0.82 (CI 95% 0.5 — 1.33) Based on data from 2,120 participants in 3 studies. [5] (Randomized controlled)	121 per 1000 Difference:	99 per 1000 **22 fewer per 1000** (CI 95% 61 fewer — 40 more)	**Low** Due to serious imprecision and serious inconsistency [6]	We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (221 events).
Invasive mechanical ventilation or ECMO Within 28 days of commencing treatment	Relative risk 0.57 (CI 95% 0.42 — 0.79) Based on data from 766 participants in 1 studies. [7] (Randomized controlled)	225 per 1000 Difference:	128 per 1000 **97 fewer per 1000** (CI 95% 131 fewer — 47 fewer)	**Low** Due to serious risk of bias and serious imprecision [8]	Remdesivir may decrease the need for invasive mechanical ventilation or ECMO (134 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical					
Patients requiring ventilation Within 28 days of commencing treatment 6 Important	Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 5,034 participants in 2 studies. [9] (Randomized controlled)	114 per 1000 Difference:	119 per 1000 **5 more per 1000** (CI 95% 13 fewer — 24 more)	**Moderate** Due to serious imprecision [10]	Remdesivir probably has no impact on number of patients requiring ventilation.
Clinical recovery Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.86 — 1.14) Based on data from 1,876 participants in 3 studies. [11] (Randomized controlled)	711 per 1000 Difference:	704 per 1000 **7 fewer per 1000** (CI 95% 100 fewer — 100 more)	**Low** Due to serious risk of bias and serious inconsistency [12]	We are uncertain whether remdesivir improves or worsens clinical recovery at day 28.
Septic shock Within 28 days of commencing treatment 6 Important	Relative risk 1.02 (CI 95% 0.34 — 3.01) Based on data from 1,296 participants in 2 studies. [13] (Randomized controlled)	10 per 1000 Difference:	10 per 1000 **0 fewer per 1000** (CI 95% 7 fewer — 20 more)	**Low** Due to serious risk of bias and serious inconsistency [14]	We are uncertain whether remdesivir increases or decreases septic shock (13 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.82 (CI 95% 0.65 — 1.04) Based on data from 2,689 participants in 4 studies. [15] (Randomized controlled)	273 per 1000 Difference:	224 per 1000 **49 fewer per 1000** (CI 95% 96 fewer — 11 more)	**Moderate** Due to serious risk of bias [16]	Remdesivir probably decreases serious adverse events slightly.
Adverse events End of follow-up 6 Important	Relative risk 1.03 (CI 95% 0.92 — 1.16) Based on data from 2,704 participants in 4 studies. [17] (Randomized controlled)	553 per 1000 Difference:	570 per 1000 **17 more per 1000** (CI 95% 44 fewer — 88 more)	**Moderate** Due to serious risk of bias [18]	Remdesivir probably has no impact on adverse events.
Discontinuation due to adverse events During	Relative risk 1.73 (CI 95% 0.57 — 5.28) Based on data from 1,880 participants in 3	93 per 1000 Difference:	161 per 1000 **68 more per**	**Low** Due to serious risk of bias and serious	We are uncertain whether remdesivir increases or decreases adverse events leading

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
treatment 6 Important	studies. [19] (Randomized controlled)		**1000** (CI 95% 40 fewer — 398 more)	imprecision [20]	to discontinuation.
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.94 — 1.13) Based on data from 6,365 participants in 3 studies. [21] (Randomized controlled)	**693** per 1000 Difference:	**714** per 1000 **21 more per 1000** (CI 95% 42 fewer — 90 more)	**Moderate** Due to serious imprecision [22]	Remdesivir probably makes little or no difference to discharge from hospital.
Time to recovery Days 6 Important	Hazard ratio 1.24 (CI 95% 1.08 — 1.42) Based on data from 1,643 participants in 2 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [23]	Remdesivir may decrease time to recovery by a few days.
Time to improvement Days 6 Important	Hazard ratio 1.17 (CI 95% 1 — 1.38) Based on data from 810 participants in 2 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [24]	Remdesivir may decrease time to improvement slightly.

Attached Images

Not recommended

Do not start remdesivir in pregnant or breastfeeding women hospitalised with COVID-19 who require non-invasive or invasive ventilation.

Additional information

Remdesivir (Veklury) should be continued with the appropriate dose and duration, if it was started prior to requiring ventilation.

Within this population, ventilation includes invasive or non-invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO).

Use of remdesivir may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include remdesivir.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

Important harms

In pregnant or breastfeeding women who are hospitalised with COVID-19 and who require ventilation, risk of death may be higher in patients using remdesivir compared with standard care.

Certainty of the Evidence

Low

Certainty of the evidence is low for death at day 28 in hospitalised adults who require ventilation. Certainty is also low for patients requiring ventilation, discharge from hospital, serious adverse events, time to recovery and time to improvement. Certainty is very low for all other outcomes.

Values and preferences

We expect few to want the intervention

We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point.

The Consumer Panel believes that as there is clear evidence demonstrating harms of remdesivir in patients requiring ventilation, informed pregnant or breastfeeding women would not choose this treatment.

Resources

No important issues with the recommended alternative

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

Equity

No important issues with the recommended alternative

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

Acceptability

No important issues with the recommended alternative

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

Feasibility

No important issues with the recommended alternative

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

Rationale

Remdesivir in adults hospitalised with COVID-19 who require ventilation probably increases the risk of death—its use should be avoided in pregnant and breastfeeding women.

Clinical Question/ PICO

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

Summary

Evidence indicates that remdesivir probably reduces the risk of death in hospitalised adults not requiring ventilation and increases the risk of death in hospitalised adults who require ventilation.

What is the evidence informing this recommendation?
Evidence comes from six randomised trials that compared remdesivir with standard care in over 8200 adults hospitalised with COVID-19 *[42][43][46][49][55][365]*. The majority of evidence is from the WHO Solidarity trial which randomised 5451 patients with moderate to critical COVID-19 *[49]*.

Study characteristics
For a comprehensive description, see the study characteristics table. There was variability in disease severity among patients included in the trials (see table).

Disease severity	Number of patients	References
Moderate	666	*[46][55]*
Moderate-Critical	6513	*[42][49][365]*
Severe-Critical	236	*[43]*

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (17 fewer per 1000; RR 0.81, CI 95% 0.65 to 1.01; 6904 patients in 6 studies), and probably increases death at day 28 in patients who require ventilation (35 more per 1000; RR 1.16, CI 95% 0.96 to 1.41; 1004 patients in 3 studies).

Remdesivir may decrease time to recovery by a few days (HR 1.24, 95% CI 1.08 to 1.42; 1643 patients in 2 studies) and time to improvement only slightly (HR 1.17, 95% CI 1.00 to 1.38; 810 patients in 2 studies). Clinical recovery was defined as the first day in which a patient satisfied categories 1, 2 or 3 on the 8-point WHO ordinal scale *[42]* or improvement from a baseline score of 2–5 to a score of 6 or 7 on a 7-point ordinal scale *[46]*. Clinical improvement was defined as an improvement of 2 or more points on a 7-point *[46]* or 6-point ordinal scale *[43]*.

Compared with standard care, remdesivir probably reduces serious adverse events (49 fewer per 1000; RR 0.82, CI 95% 0.65 to 1.04; 2689 patients in 4 studies). There is no important difference between remdesivir and standard care regarding the number of patients requiring ventilation, number of patients discharged from hospital at day 28, and number of patients experiencing one or more adverse events. We are uncertain whether remdesivir impacts respiratory failure or ARDS, clinical recovery at day 28, septic shock and discontinuation due to adverse events.

An additional study was identified but did not meet the inclusion criteria due to its observational design *[56]*. The study included 86 **pregnant and postpartum women** with severe COVID-19 in the USA who received compassionate-use remdesivir. Median age was 33 years (range 20–43 years) and median gestational age was 29 weeks (range 14–39 weeks). Invasive mechanical ventilation was given to 52% of women and non-invasive ventilation (NIPPV, high-flow and low-flow oxygen) to 45%—the remaining 3% were on room air at baseline. Two-thirds of pregnant women and all postpartum women were in ICU.

A more recent study by Gutierrez et al. *[453]*, a prospective cohort study published on 15 Feb 2022, assessed the use of remdesivir during pregnancy during the SARS-CoV-2 pandemic. Only 95 participants met the inclusion criteria, and were then stratified according to whether or not they received remdesivir in hospital. Ultimately the study was quite small, and the use of remdesivir within the study appeared to be safe, well tolerated within our cohort with no cases of recorded adverse reaction.

Extubation was achieved in 93% of pregnant women and 89% of postpartum women who were mechanically ventilated. Recovery at 28 days (defined as an improvement from NIV to room air) was achieved in 93% of pregnant women and 89% of postpartum women. Discharge occurred in 90% of pregnant women and 84% of postpartum women.

Adverse events were experienced by 29% of women and 16% had a serious adverse event. Examples of adverse events experienced included anaemia, DVT and dysphagia. Seven women discontinued treatment with remdesivir due to adverse events, of which five had elevated liver enzyme concentrations, one had nausea and the other had haemoptysis.

The results of this observational study are in line with the current trial evidence, demonstrating that there remains uncertainty whether remdesivir is more effective and safer than standard care in treating pregnant and

postpartum women with COVID-19.

Remdesivir has been used anecdotally for the treatment of COVID-19 in **children and adolescents**. The preliminary findings from a recent cohort study of 77 hospitalised patients under 18 years of age are reassuring, but uncertainties remain about the benefits of remdesivir in this population *[314]*. Trials are currently recruiting in this population.

Our confidence in the results
Certainty of the evidence is moderate for death in both subgroups (patients who do not require ventilation, and patients who require ventilation), all due to serious imprecision (wide confidence intervals). Certainty is also moderate for patients requiring ventilation and discharge from hospital (due to reliance on a single study), serious adverse events, adverse events, time to recovery and time to improvement (due to non-blinding of patients and personnel).

Certainty of the evidence is low for respiratory failure or acute respiratory distress syndrome (due to inconsistency in direction of effect and wide confidence intervals), number of patients requiring invasive mechanical ventilation or ECMO (due to non-blinding of patients and personnel and reliance on a single study), clinical recovery, septic shock and adverse events (due to non-blinding of patients and personnel and inconsistency in direction of effect) and discontinuation due to adverse events (due to non-blinding of patients and personnel and wide confidence intervals).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
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 *[45]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality [hospital no ventilation] Within 28 days of commencing treatment 9 Critical	Relative risk 0.81 (CI 95% 0.65 — 1.01) Based on data from 6,904 participants in 8 studies. [1] (Randomized controlled)	88 per 1000 Difference:	71 per 1000 **17 fewer per 1000** (CI 95% 31 fewer — 1 more)	Moderate Due to serious imprecision [2]	Remdesivir probably decreases death slightly in hospitalised patients who do not require ventilation.
All-cause mortality [ventilation] Within 28 days of commencing treatment 9 Critical	Relative risk 1.16 (CI 95% 0.96 — 1.41) Based on data from 1,332 participants in 5 studies. [3] (Randomized controlled)	219 per 1000 Difference:	254 per 1000 **35 more per 1000** (CI 95% 9 fewer — 90 more)	Moderate Due to serious imprecision [4]	Remdesivir probably increases death in hospitalised patients requiring ventilation.
Respiratory failure or ARDS	Relative risk 0.82 (CI 95% 0.5 — 1.33) Based on data from	121 per 1000	99 per 1000	Low Due to serious imprecision and	We are uncertain whether remdesivir increases or decreases

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Within 28 days of commencing treatment 9 Critical	2,120 participants in 3 studies. [5] (Randomized controlled)	Difference:	**22 fewer per 1000** (CI 95% 61 fewer — 40 more)	serious inconsistency [6]	respiratory failure or ARDS (221 events).
Invasive mechanical ventilation or ECMO Within 28 days of commencing treatment 9 Critical	Relative risk 0.57 (CI 95% 0.42 — 0.79) Based on data from 766 participants in 1 studies. [7] (Randomized controlled)	225 per 1000 Difference:	128 per 1000 **97 fewer per 1000** (CI 95% 131 fewer — 47 fewer)	**Low** Due to serious risk of bias and serious imprecision [8]	Remdesivir may decrease the need for invasive mechanical ventilation or ECMO (134 events).
Patients requiring ventilation Within 28 days of commencing treatment 6 Important	Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 5,034 participants in 2 studies. [9] (Randomized controlled)	114 per 1000 Difference:	119 per 1000 **5 more per 1000** (CI 95% 13 fewer — 24 more)	**Moderate** Due to serious imprecision [10]	Remdesivir probably has no impact on number of patients requiring ventilation.
Clinical recovery Within 28 days of commencing treatment 6 Important	Relative risk 0.99 (CI 95% 0.86 — 1.14) Based on data from 1,876 participants in 3 studies. [11] (Randomized controlled)	711 per 1000 Difference:	704 per 1000 **7 fewer per 1000** (CI 95% 100 fewer — 100 more)	**Low** Due to serious risk of bias and serious inconsistency [12]	We are uncertain whether remdesivir improves or worsens clinical recovery at day 28.
Septic shock Within 28 days of commencing treatment 6 Important	Relative risk 1.02 (CI 95% 0.34 — 3.01) Based on data from 1,296 participants in 2 studies. [13] (Randomized controlled)	10 per 1000 Difference:	10 per 1000 **0 fewer per 1000** (CI 95% 7 fewer — 20 more)	**Low** Due to serious risk of bias and serious inconsistency [14]	We are uncertain whether remdesivir increases or decreases septic shock (13 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.82 (CI 95% 0.65 — 1.04) Based on data from 2,689 participants in 4 studies. [15] (Randomized controlled)	273 per 1000 Difference:	224 per 1000 **49 fewer per 1000** (CI 95% 96 fewer — 11 more)	**Moderate** Due to serious risk of bias [16]	Remdesivir probably decreases serious adverse events slightly.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Adverse events End of follow-up 6 Important	Relative risk 1.03 (CI 95% 0.92 — 1.16) Based on data from 2,704 participants in 4 studies. [17] (Randomized controlled)	553 per 1000 Difference:	570 per 1000 **17 more per 1000** (CI 95% 44 fewer — 88 more)	**Moderate** Due to serious risk of bias [18]	Remdesivir probably has no impact on adverse events.
Discontinuation due to adverse events During treatment 6 Important	Relative risk 1.73 (CI 95% 0.57 — 5.28) Based on data from 1,880 participants in 3 studies. [19] (Randomized controlled)	93 per 1000 Difference:	161 per 1000 **68 more per 1000** (CI 95% 40 fewer — 398 more)	**Low** Due to serious risk of bias and serious imprecision [20]	We are uncertain whether remdesivir increases or decreases adverse events leading to discontinuation.
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.94 — 1.13) Based on data from 6,365 participants in 3 studies. [21] (Randomized controlled)	693 per 1000 Difference:	714 per 1000 **21 more per 1000** (CI 95% 42 fewer — 90 more)	**Moderate** Due to serious imprecision [22]	Remdesivir probably makes little or no difference to discharge from hospital.
Time to recovery Days 6 Important	Hazard ratio 1.24 (CI 95% 1.08 — 1.42) Based on data from 1,643 participants in 2 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [23]	Remdesivir may decrease time to recovery by a few days.
Time to improvement Days 6 Important	Hazard ratio 1.17 (CI 95% 1 — 1.38) Based on data from 810 participants in 2 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [24]	Remdesivir may decrease time to improvement slightly.

Attached Images

Conditional recommendation

Consider using remdesivir within 7 days of symptom onset in pregnant women with COVID-19 who do not require oxygen and who have one or more additional risk factors for disease progression.

Additional information

In adults with confirmed COVID-19 who do not require oxygen, remdesivir (Veklury) probably decreases the risk of hospitalisation if taken within 7 days of onset of symptoms.

Results are based on a single trial [414], in which unvaccinated adults were administered three intravenous doses of remdesivir on consecutive days (200 mg on day 1, followed by 100 mg on days 2 and 3). Based on the inclusion criteria for this trial, risk factors for disease progression include the following:

- *Age ≥ 60 years*
- *Diabetes*
- *Obesity (BMI ≥ 30 kg/m2)*
- *Chronic kidney disease (any stage)*
- *Cardiovascular or cerebrovascular disease (coronary artery disease, congenital heart disease, heart failure, cardiomyopathy or history of stroke)*
- *Hypertension (systemic or pulmonary)*
- *Chronic liver disease*
- *Chronic lung disease (chronic obstructive pulmonary disease, moderate-severe asthma, cystic or pulmonary fibrosis)*
- *Sickle cell disease*
- *Current cancer*
- *Immunocompromised state (no definition provided)*

Pregnant and breastfeeding women were not included in the trial. Eight paediatric patients aged 12–18 years were included, none of whom progressed to hospitalisation or death.

The efficacy of remdesivir in vaccinated and immunocompromised patients is unknown.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

7.1.8.3 Remdesivir (Veklury) for children and adolescents

Info Box

Children and adolescents who are suspected to be at high risk of deterioration should be managed by and discussed with a multidisciplinary team. Decisions about exceptional use of treatments outside the recommendations made by the Taskforce should be taken in consultation with experts, in the light of the potential for rapid deterioration, with appropriate involvement of hospital drug and therapeutics committee and awareness of the CATAG guidance for off-label use of medications *(see CATAG guiding principles for the quality use of off label medicines)*.

Consensus recommendation

Consider using, in exceptional circumstances, remdesivir for the treatment of COVID-19 within 7 days of symptom onset in **children and adolescents aged 28 days and over and weighing at least 3 kg** who do not require oxygen and are at high risk of deterioration, where other treatments are not available / appropriate.

Consider using remdesivir in eligible children and adolescents who have not received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months, those who are immunocompromised regardless of vaccination / previous infection status, or those who are not eligible for vaccination based on age but who are at high risk of disease progression. Do not routinely use remdesivir in children and adolescents who have received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months unless immunocompromised.

Decisions about the appropriateness of treatment with remdesivir should be based on the individual's risk of severe disease, including their age, presence of multiple risk factors, and whether they have received a COVID-19 vaccine dose or had a SARS-CoV-2 infection in the past 6 months.

Additional information

Please note:

1. Remdesivir (Veklury) is not TGA approved for mild disease in children < 40 kg

2. There are potential concerns with the use of cyclodextrin in infants, so the benefits and risks should be carefully assessed

Decisions to provide remdesivir to a child or adolescent should be based on the individual's combination of risk factors for deterioration and made in consultation with a paediatrician with expertise in the management of COVID-19 in children.

Available research does not currently provide enough evidence to determine the potential benefits and risks of remdesivir in specific subgroups of children and adolescents. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which children and adolescents are most likely to benefit from remdesivir. Based on international cohorts [370] potential factors to consider in patients at high risk of progression may include:

- *Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions*
- *Severe asthma*
- *Obesity*

There is no evidence evaluating the effectiveness of remdesivir in fully vaccinated patients, a low likelihood of development of severe disease, and a small risk of adverse events. Given this and the lower risk of deterioration in these patients, it is unlikely that remdesivir will be particularly valuable in patients who have received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months, unless the patient is immunocompromised.

There is no evidence on the effectiveness of remdesivir in immunocompromised children and adolescents. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that remdesivir will be beneficial for immunocompromised patients.

In the absence of reliable evidence, the Taskforce has developed this recommendation based on their clinical expertise and experience.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that some people would opt for this treatment while others might prefer one of the other treatment options, and some might want to wait for more evidence.

The Consumer Panel notes that it is highly likely that this group has significant links to the healthcare system, and

that this medication is most likely to be suggested in the context of an established relationship. They also note that in this age group people's level of ability to make informed choices themselves varies considerably, and that these decisions should be made in partnership with both parents and the patients themselves.

Clinical Question/ PICO

Population: Outpatients with mild COVID-19
Intervention: Remdesivir
Comparator: Placebo

Summary

Evidence indicates that remdesivir probably reduces the incidence of hospitalisation in unvaccinated adults with mild COVID-19 who have one or more risk factors for disease progression.

What is the evidence informing this recommendation?
Evidence comes from a single trial that compared remdesivir with placebo in 562 unvaccinated adult outpatients with mild COVID-19 *[414]*. Participants were randomised within seven days of onset of symptoms and had one or more risk factors for disease progression.

Study characteristics
Mean age of participants was 50 years and 48% were women. Approximately one third of patients were aged 60 years or over. Participants received three intravenous doses of remdesivir on consecutive days; 200 mg on day 1, followed by 100 mg on days 2 and 3. Pregnant and breastfeeding women were ineligible for inclusion; however children aged 12 years and over were eligible for inclusion.

What are the main results?
Remdesivir probably reduces the incidence of hospitalisation (RR 0.28, CI 95% 0.11 to 0.75; 562 patients in 1 study) and probably has little impact on adverse events or serious adverse events. We are unsure if remdesivir impacts discontinuation due to adverse events, or all-cause mortality (no patients died).

Our confidence in the results
Certainty of the evidence is moderate for hospitalisation and adverse events due to serious imprecision (reliance on a single study) and low for serious adverse events and discontinuation due to adverse events due to very serious imprecision (reliance on a single study and few events).

For pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
As of 18 February 2022, the Therapeutic Goods Administration has yet to approve remdesivir for use in patients who have mild COVID-19 and who are not hospitalised.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk Based on data from 562 participants in 1 studies. [1]				No patients died.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Hospitalisation Within 28 days of commencing treatment 6 Important	Relative risk 0.28 (CI 95% 0.11 — 0.75) Based on data from 562 participants in 1 studies. [2] (Randomized controlled)	64 per 1000 Difference:	18 per 1000 **46 fewer per 1000** (CI 95% 57 fewer — 16 fewer)	**Moderate** Due to serious imprecision [3]	Remdesivir probably decreases hospitalisation in outpatients with mild COVID-19 (23 events).
Adverse events End of follow-up 6 Important	Relative risk 0.91 (CI 95% 0.76 — 1.1) Based on data from 562 participants in 1 studies. [4] (Randomized controlled)	463 per 1000 Difference:	421 per 1000 **42 fewer per 1000** (CI 95% 111 fewer — 46 more)	**Moderate** Due to serious imprecision [5]	Remdesivir probably decreases adverse events slightly (249 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.27 (CI 95% 0.1 — 0.7) Based on data from 562 participants in 1 studies. [6] (Randomized controlled)	67 per 1000 Difference:	18 per 1000 **49 fewer per 1000** (CI 95% 60 fewer — 20 fewer)	**Moderate** Due to serious imprecision [7]	Remdesivir may decrease serious adverse events slightly (24 events).
Discontinuation due to an adverse event End of follow-up 6 Important	Relative risk 0.41 (CI 95% 0.08 — 2.07) Based on data from 562 participants in 1 studies. [8] (Randomized controlled)	18 per 1000 Difference:	7 per 1000 **11 fewer per 1000** (CI 95% 17 fewer — 19 more)	**Low** Due to very serious imprecision [9]	We are uncertain whether remdesivir increases or decreases discontinuation due to an adverse event (7 events).

Attached Images

Consensus recommendation

Consider using, in exceptional circumstances, remdesivir for the treatment of COVID-19 in **children and adolescents aged 28 days or older and weighing at least 3 kg** who are hospitalised with severe COVID-19 (considered likely to progress to ventilation), who require systemic corticosteroids and oxygen but do not require non-invasive or invasive ventilation, where other treatments are not available / appropriate.

Additional information

Please note:

1. Remdesivir (Veklury) is not TGA approved for mild disease in children < 40 kg

2. There are potential concerns with the use of cyclodextrin in infants, so the benefits and risks should be carefully assessed

Decisions to provide remdesivir to a child or adolescent should be based on the individual's combination of risk factors for deterioration and be made in consultation with a paediatrician with expertise in the management of COVID-19 in children.

Available research does not currently provide enough evidence to determine the potential benefits and risks of remdesivir in specific subgroups of children and adolescents. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which children and adolescents are most likely to benefit from remdesivir. Based on international cohorts [370] potential factors to consider in patients at high risk of progression may include:

- *Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions*
- *Severe asthma*
- *Obesity*

In the absence of reliable evidence, the Taskforce has developed this recommendation based on their clinical expertise and experience.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that some people would opt for this treatment while others might prefer one of the other treatment options, and some might want to wait for more evidence.

The Consumer Panel notes that it is highly likely that this group has significant links to the healthcare system, and that this medication is most likely to be suggested in the context of an established relationship. They also note that in this age group people's level of ability to make informed choices themselves varies considerably, and that these decisions should be made in partnership with both parents and the patients themselves.

Not recommended

Do not start Remdesivir in children and adolescents hospitalised with COVID-19 who require non-invasive or invasive ventilation.

Additional information

Remdesivir (Veklury) should be continued with the appropriate dose and duration, if it was started prior to the patient requiring ventilation.

Within this population, ventilation includes invasive or non-invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO).

Use of remdesivir may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include remdesivir.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

Important harms

In patients who are hospitalised with COVID-19 and who require ventilation, risk of death may be higher in patients using remdesivir compared with standard care.

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

Moderate

Certainty of the evidence is moderate for death at day 28 in hospitalised adults who require ventilation. Certainty is also moderate for patients requiring ventilation, discharge from hospital, serious adverse events, time to recovery and time to improvement. Certainty is low for all other outcomes.

Values and preferences

We expect few to want the intervention

We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is clear evidence demonstrating harms of remdesivir in patients requiring ventilation, informed patients would not choose this treatment.

Resources

No important issues with the recommended alternative

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

Equity

No important issues with the recommended alternative

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

Acceptability

No important issues with the recommended alternative

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

Feasibility

No important issues with the recommended alternative

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

Rationale

Remdesivir in adults hospitalised with COVID-19 who require ventilation probably increases the risk of death—its use should be avoided in this population.

Clinical Question/ PICO

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

Summary

Evidence indicates that remdesivir probably reduces the risk of death in hospitalised adults not requiring ventilation and increases the risk of death in hospitalised adults who require ventilation.

What is the evidence informing this recommendation?
Evidence comes from six randomised trials that compared remdesivir with standard care in over 8200 adults hospitalised with COVID-19 *[42][43][46][49][55][365]*. The majority of evidence is from the WHO Solidarity trial which randomised 5451 patients with moderate to critical COVID-19 *[49]*.

Study characteristics
For a comprehensive description, see the study characteristics table. There was variability in disease severity among patients included in the trials (see table).

Disease severity	Number of patients	References
Moderate	666	*[46][55]*
Moderate-Critical	6513	*[42][49][365]*
Severe-Critical	236	*[43]*

What are the main results?
Compared with standard care, remdesivir probably reduces death at day 28 in hospitalised patients who do not require ventilation (17 fewer per 1000; RR 0.81, CI 95% 0.65 to 1.01; 6904 patients in 6 studies), and probably increases death at day 28 in patients who require ventilation (35 more per 1000; RR 1.16, CI 95% 0.96 to 1.41; 1004 patients in 3 studies).

Remdesivir may decrease time to recovery by a few days (HR 1.24, 95% CI 1.08 to 1.42; 1643 patients in 2 studies) and time to improvement only slightly (HR 1.17, 95% CI 1.00 to 1.38; 810 patients in 2 studies). Clinical recovery was defined as the first day in which a patient satisfied categories 1, 2 or 3 on the 8-point WHO ordinal scale *[42]* or improvement from a baseline score of 2–5 to a score of 6 or 7 on a 7-point ordinal scale *[46]*. Clinical improvement was defined as an improvement of 2 or more points on a 7-point *[46]* or 6-point ordinal scale *[43]*.

Compared with standard care, remdesivir probably reduces serious adverse events (49 fewer per 1000; RR 0.82, CI 95% 0.65 to 1.04; 2689 patients in 4 studies). There is no important difference between remdesivir and standard care regarding the number of patients requiring ventilation, number of patients discharged from

hospital at day 28, and number of patients experiencing one or more adverse events. We are uncertain whether remdesivir impacts respiratory failure or ARDS, clinical recovery at day 28, septic shock and discontinuation due to adverse events.

An additional study was identified but did not meet the inclusion criteria due to its observational design *[56]*. The study included 86 **pregnant and postpartum women** with severe COVID-19 in the USA who received compassionate-use remdesivir. Median age was 33 years (range 20–43 years) and median gestational age was 29 weeks (range 14–39 weeks). Invasive mechanical ventilation was given to 52% of women and non-invasive ventilation (NIPPV, high-flow and low-flow oxygen) to 45%—the remaining 3% were on room air at baseline. Two-thirds of pregnant women and all postpartum women were in ICU.

A more recent study by Gutierrez et al. *[453]*, a prospective cohort study published on 15 Feb 2022, assessed the use of remdesivir during pregnancy during the SARS-CoV-2 pandemic. Only 95 participants met the inclusion criteria, and were then stratified according to whether or not they received remdesivir in hospital. Ultimately the study was quite small, and the use of remdesivir within the study appeared to be safe, well tolerated within our cohort with no cases of recorded adverse reaction.

Extubation was achieved in 93% of pregnant women and 89% of postpartum women who were mechanically ventilated. Recovery at 28 days (defined as an improvement from NIV to room air) was achieved in 93% of pregnant women and 89% of postpartum women. Discharge occurred in 90% of pregnant women and 84% of postpartum women.

Adverse events were experienced by 29% of women and 16% had a serious adverse event. Examples of adverse events experienced included anaemia, DVT and dysphagia. Seven women discontinued treatment with remdesivir due to adverse events, of which five had elevated liver enzyme concentrations, one had nausea and the other had haemoptysis.

The results of this observational study are in line with the current trial evidence, demonstrating that there remains uncertainty whether remdesivir is more effective and safer than standard care in treating pregnant and postpartum women with COVID-19.

Remdesivir has been used anecdotally for the treatment of COVID-19 in **children and adolescents**. The preliminary findings from a recent cohort study of 77 hospitalised patients under 18 years of age are reassuring, but uncertainties remain about the benefits of remdesivir in this population *[314]*. Trials are currently recruiting in this population.

Our confidence in the results
Certainty of the evidence is moderate for death in both subgroups (patients who do not require ventilation, and patients who require ventilation), all due to serious imprecision (wide confidence intervals). Certainty is also moderate for patients requiring ventilation and discharge from hospital (due to reliance on a single study), serious adverse events, adverse events, time to recovery and time to improvement (due to non-blinding of patients and personnel).

Certainty of the evidence is low for respiratory failure or acute respiratory distress syndrome (due to inconsistency in direction of effect and wide confidence intervals), number of patients requiring invasive mechanical ventilation or ECMO (due to non-blinding of patients and personnel and reliance on a single study), clinical recovery, septic shock and adverse events (due to non-blinding of patients and personnel and inconsistency in direction of effect) and discontinuation due to adverse events (due to non-blinding of patients and personnel and wide confidence intervals).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
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 *[45]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality [hospital no ventilation] Within 28 days of commencing treatment 9 Critical	Relative risk 0.81 (CI 95% 0.65 — 1.01) Based on data from 6,904 participants in 8 studies. [1] (Randomized controlled)	88 per 1000 Difference:	71 per 1000 **17 fewer per 1000** (CI 95% 31 fewer — 1 more)	Moderate Due to serious imprecision [2]	Remdesivir probably decreases death slightly in hospitalised patients who do not require ventilation.
All-cause mortality [ventilation] Within 28 days of commencing treatment 9 Critical	Relative risk 1.16 (CI 95% 0.96 — 1.41) Based on data from 1,332 participants in 5 studies. [3] (Randomized controlled)	219 per 1000 Difference:	254 per 1000 **35 more per 1000** (CI 95% 9 fewer — 90 more)	Moderate Due to serious imprecision [4]	Remdesivir probably increases death in hospitalised patients requiring ventilation.
Respiratory failure or ARDS Within 28 days of commencing treatment 9 Critical	Relative risk 0.82 (CI 95% 0.5 — 1.33) Based on data from 2,120 participants in 3 studies. [5] (Randomized controlled)	121 per 1000 Difference:	99 per 1000 **22 fewer per 1000** (CI 95% 61 fewer — 40 more)	Low Due to serious imprecision and serious inconsistency [6]	We are uncertain whether remdesivir increases or decreases respiratory failure or ARDS (221 events).
Invasive mechanical ventilation or ECMO Within 28 days of commencing treatment 9 Critical	Relative risk 0.57 (CI 95% 0.42 — 0.79) Based on data from 766 participants in 1 studies. [7] (Randomized controlled)	225 per 1000 Difference:	128 per 1000 **97 fewer per 1000** (CI 95% 131 fewer — 47 fewer)	Low Due to serious risk of bias and serious imprecision [8]	Remdesivir may decrease the need for invasive mechanical ventilation or ECMO (134 events).
Patients requiring ventilation Within 28 days of commencing treatment 6 Important	Relative risk 1.04 (CI 95% 0.89 — 1.21) Based on data from 5,034 participants in 2 studies. [9] (Randomized controlled)	114 per 1000 Difference:	119 per 1000 **5 more per 1000** (CI 95% 13 fewer — 24 more)	Moderate Due to serious imprecision [10]	Remdesivir probably has no impact on number of patients requiring ventilation.
Clinical recovery Within 28 days	Relative risk 0.99 (CI 95% 0.86 — 1.14) Based on data from	711 per 1000	704 per 1000	Low Due to serious risk of bias and	We are uncertain whether remdesivir improves or worsens

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
of commencing treatment 6 Important	1,876 participants in 3 studies. [11] (Randomized controlled)	Difference:	**7 fewer per 1000** (CI 95% 100 fewer — 100 more)	serious inconsistency [12]	clinical recovery at day 28.
Septic shock Within 28 days of commencing treatment 6 Important	Relative risk 1.02 (CI 95% 0.34 — 3.01) Based on data from 1,296 participants in 2 studies. [13] (Randomized controlled)	10 per 1000 Difference:	10 per 1000 **0 fewer per 1000** (CI 95% 7 fewer — 20 more)	**Low** Due to serious risk of bias and serious inconsistency [14]	We are uncertain whether remdesivir increases or decreases septic shock (13 events).
Serious adverse events End of follow-up 6 Important	Relative risk 0.82 (CI 95% 0.65 — 1.04) Based on data from 2,689 participants in 4 studies. [15] (Randomized controlled)	273 per 1000 Difference:	224 per 1000 **49 fewer per 1000** (CI 95% 96 fewer — 11 more)	**Moderate** Due to serious risk of bias [16]	Remdesivir probably decreases serious adverse events slightly.
Adverse events End of follow-up 6 Important	Relative risk 1.03 (CI 95% 0.92 — 1.16) Based on data from 2,704 participants in 4 studies. [17] (Randomized controlled)	553 per 1000 Difference:	570 per 1000 **17 more per 1000** (CI 95% 44 fewer — 88 more)	**Moderate** Due to serious risk of bias [18]	Remdesivir probably has no impact on adverse events.
Discontinuation due to adverse events During treatment 6 Important	Relative risk 1.73 (CI 95% 0.57 — 5.28) Based on data from 1,880 participants in 3 studies. [19] (Randomized controlled)	93 per 1000 Difference:	161 per 1000 **68 more per 1000** (CI 95% 40 fewer — 398 more)	**Low** Due to serious risk of bias and serious imprecision [20]	We are uncertain whether remdesivir increases or decreases adverse events leading to discontinuation.
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.94 — 1.13) Based on data from 6,365 participants in 3 studies. [21] (Randomized controlled)	693 per 1000 Difference:	714 per 1000 **21 more per 1000** (CI 95% 42 fewer — 90 more)	**Moderate** Due to serious imprecision [22]	Remdesivir probably makes little or no difference to discharge from hospital.
Time to recovery Days	Hazard ratio 1.24 (CI 95% 1.08 — 1.42) Based on data from			**Moderate** Due to serious risk of bias [23]	Remdesivir may decrease time to recovery by a few days.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important	1,643 participants in 2 studies. (Randomized controlled)				
Time to improvement Days 6 Important	Hazard ratio 1.17 (CI 95% 1 — 1.38) Based on data from 810 participants in 2 studies. (Randomized controlled)			**Moderate** Due to serious risk of bias [24]	Remdesivir may decrease time to improvement slightly.

Attached Images

7.1.9 Sotrovimab (Xevudy)

7.1.9.1 Sotrovimab (Xevudy) for adults

Consensus recommendation

Do not routinely use sotrovimab (Xevudy) for the treatment of COVID-19.

The Taskforce has previously recommended the use of sotrovimab (Xevudy) for the treatment of unvaccinated individuals with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression. These recommendations were based on the COMET-ICE trial [439] that included 1057 participants with mild-to-moderate COVID-19, which demonstrated a benefit with regards to hospitalisation.

All clinical trials that contributed data to the analyses were conducted before the emergence of Omicron as the dominant variant. Since the development of the initial recommendations, a significant body of in vitro evidence has emerged demonstrating a significant reduction in activity of sotrovimab (Xevudy) against the Omicron BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that sotrovimab (Xevudy) is effective in treating individuals with currently circulating variants of COVID-19.

Clinical Question/ PICO

Population: Patients with mild or moderate COVID-19
Intervention: Sotrovimab
Comparator: Placebo

Summary

Evidence indicates that sotrovimab probably reduces incidence of hospitalisation in patients with mild COVID-19 illness who have one or more risk factors for disease progression, if received within 5 days of symptom onset.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial (COMET-ICE) that compared sotrovimab with placebo in 1057 adult outpatients with mild-to-moderate COVID-19 *[439]*.

Study characteristics
Median age of participants was 52 years and 54% were women. All eligible patients required one or more risk factors for disease progression, including diabetes (requiring medication), obesity, chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, moderate to severe asthma or adults over 55 years of age. Pregnant women were ineligible, and only six patients were aged under 19 years.

What are the main results?
Sotrovimab probably decreases the incidence of hospitalisation (42 fewer per 1000; RR 0.24, CI 95% 0.11 to 0.55; 1057 patients in 1 study), the composite outcome of hospitalisation (for longer than 24 hours) or death (46 fewer per 1000; RR 0.20, CI 95% 0.08 to 0.48; 1057 patients in 1 study) and serious adverse events (40 fewer per 1000; RR 0.35, CI 95% 0.18 to 0.68; 1049 patients from 1 study). We are unsure if sotrovimab impacts death or the requirement for invasive mechanical ventilation.

Sotrovimab probably has little impact on intensive care unit (ICU) admission, the requirement of non-invasive ventilation or high-flown nasal oxygen (HFNO), or adverse events.

Our confidence in the results
Certainty of the evidence for the composite outcome of hospitalisation (for longer than 24 hours) or death, hospitalisation, ICU admission, requirement for non-invasive ventilation or HFNO, and serious adverse events is moderate due to serious imprecision (reliance on a single study). Certainty for all-cause mortality and the requirement for invasive mechanical ventilation is low due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty has been downgraded further due to serious indirectness (absence or limited of inclusion of these populations in the included study).

Additional information
There is currently limited supply of sotrovimab available for use within Australia and this may affect the feasibility of widespread treatment in this population.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Sotrovimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Hospitalisation (≥ 24 hours) or death [composite] Within 29 days of treatment 9 Critical	Relative risk 0.2 (CI 95% 0.08 — 0.48) Based on data from 1,057 participants in 1 studies. [1] (Randomized controlled)	57 per 1000 Difference:	11 per 1000 **46 fewer per 1000** (CI 95% 52 fewer — 30 fewer)	**Moderate** Due to serious imprecision [2]	Sotrovimab probably decreases hospitalisation (≥ 24 hours) or death (36 events).
All-cause mortality Within 29 days of treatment 9 Critical	Relative risk 0.2 (CI 95% 0.01 — 4.16) Based on data from 1,057 participants in 1 studies. [3] (Randomized controlled)	4 per 1000 Difference:	1 per 1000 **3 fewer per 1000** (CI 95% 4 fewer — 13 more)	**Low** Due to very serious imprecision [4]	We are uncertain whether sotrovimab impacts death (2 events).
Hospitalisation [any cause any duration] Within 29 days of treatment 6 Important	Relative risk 0.21 (CI 95% 0.09 — 0.5) Based on data from 1,057 participants in 1 studies. [5] (Randomized controlled)	55 per 1000 Difference:	12 per 1000 **43 fewer per 1000** (CI 95% 50 fewer — 28 fewer)	**Moderate** Due to serious imprecision [6]	Sotrovimab probably decreases hospitalisation [any cause or duration] (35 events).
ICU admission Within 29 days of treatment 6 Important	Relative risk 0.05 (CI 95% 0 — 0.81) Based on data from 1,057 participants in 1 studies. [7] (Randomized controlled)	19 per 1000 Difference:	1 per 1000 **18 fewer per 1000** (CI 95% 19 fewer — 4 fewer)	**Moderate** Due to serious imprecision [8]	Sotrovimab probably has little impact on ICU admission (10 events).
Invasive mechanical ventilation Within 29 days of treatment 9 Critical	Relative risk 0.11 (CI 95% 0.01 — 2.06) Based on data from 1,057 participants in 1 studies. [9] (Randomized controlled)	8 per 1000 Difference:	1 per 1000 **7 fewer per 1000** (CI 95% 8 fewer — 8 more)	**Low** Due to very serious imprecision [10]	We are uncertain whether sotrovimab impacts invasive mechanical ventilation (4 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Sotrovimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Non-invasive ventilation / HFNO Within 29 days of treatment 6 Important	Relative risk 0.05 (CI 95% 0 — 0.81) Based on data from 1,057 participants in 1 studies. [11] (Randomized controlled)	19 per 1000 Difference:	1 per 1000 **18 fewer per 1000** (CI 95% 19 fewer — 4 fewer)	**Moderate** Due to serious imprecision [12]	Sotrovimab probably has little impact on non-invasive ventilation / HFNO (10 events).
Adverse events Within 29 days of treatment 6 Important	Relative risk 0.93 (CI 95% 0.74 — 1.17) Based on data from 1,049 participants in 1 studies. [13] (Randomized controlled)	234 per 1000 Difference:	218 per 1000 **16 fewer per 1000** (CI 95% 61 fewer — 40 more)	**Moderate** Due to serious imprecision [14]	Sotrovimab probably has little impact on adverse events (237 events).
Serious adverse events Within 29 days of treatment 6 Important	Relative risk 0.35 (CI 95% 0.18 — 0.68) Based on data from 1,049 participants in 1 studies. [15] (Randomized controlled)	61 per 1000 Difference:	21 per 1000 **40 fewer per 1000** (CI 95% 50 fewer — 20 fewer)	**Moderate** Due to serious imprecision [16]	Sotrovimab probably decreases serious adverse events (43 events).

Attached Images

7.1.9.2 Sotrovimab (Xevudy) for pregnant women

Consensus recommendation

Do not routinely use sotrovimab (Xevudy) for the treatment of COVID-19 in pregnant or breastfeeding women.

The Taskforce has previously recommended the use of sotrovimab (Xevudy) for the treatment of pregnant women with COVID-19 in the second or third trimester who do not require oxygen and who have one or more additional risk factors for disease progression. These recommendations were based on the COMET-ICE trial [439] that included 1057 participants with mild-to-moderate COVID-19, which demonstrated a benefit with regards to hospitalisation.

All clinical trials that contributed data to the analyses were conducted before the emergence of Omicron as the dominant variant. Since the development of the initial recommendations, a significant body of in vitro evidence has emerged demonstrating a significant reduction in activity of sotrovimab (Xevudy) against the Omicron BA.2, BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that sotrovimab (Xevudy) is effective in treating individuals with currently circulating variants of COVID-19.

Clinical Question/ PICO

Population: Patients with mild or moderate COVID-19
Intervention: Sotrovimab
Comparator: Placebo

Summary

Evidence indicates that sotrovimab probably reduces incidence of hospitalisation in patients with mild COVID-19 illness who have one or more risk factors for disease progression, if received within 5 days of symptom onset.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial (COMET-ICE) that compared sotrovimab with placebo in 1057 adult outpatients with mild-to-moderate COVID-19 *[439]*.

Study characteristics
Median age of participants was 52 years and 54% were women. All eligible patients required one or more risk factors for disease progression, including diabetes (requiring medication), obesity, chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, moderate to severe asthma or adults over 55 years of age. Pregnant women were ineligible, and only six patients were aged under 19 years.

What are the main results?
Sotrovimab probably decreases the incidence of hospitalisation (42 fewer per 1000; RR 0.24, CI 95% 0.11 to 0.55; 1057 patients in 1 study), the composite outcome of hospitalisation (for longer than 24 hours) or death (46 fewer per 1000; RR 0.20, CI 95% 0.08 to 0.48; 1057 patients in 1 study) and serious adverse events (40 fewer per 1000; RR 0.35, CI 95% 0.18 to 0.68; 1049 patients from 1 study). We are unsure if sotrovimab impacts death or the requirement for invasive mechanical ventilation.

Sotrovimab probably has little impact on intensive care unit (ICU) admission, the requirement of non-invasive ventilation or high-flown nasal oxygen (HFNO), or adverse events.

Our confidence in the results
Certainty of the evidence for the composite outcome of hospitalisation (for longer than 24 hours) or death, hospitalisation, ICU admission, requirement for non-invasive ventilation or HFNO, and serious adverse events is moderate due to serious imprecision (reliance on a single study). Certainty for all-cause mortality and the requirement for invasive mechanical ventilation is low due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty has been downgraded further due to serious indirectness (absence or limited of inclusion of these populations in the included study).

Additional information
There is currently limited supply of sotrovimab available for use within Australia and this may affect the feasibility of widespread treatment in this population.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Sotrovimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Hospitalisation (≥ 24 hours) or death [composite] Within 29 days of treatment 9 Critical	Relative risk 0.2 (CI 95% 0.08 — 0.48) Based on data from 1,057 participants in 1 studies. [1] (Randomized controlled)	57 per 1000 Difference:	11 per 1000 **46 fewer per 1000** (CI 95% 52 fewer — 30 fewer)	**Moderate** Due to serious imprecision [2]	Sotrovimab probably decreases hospitalisation (≥ 24 hours) or death (36 events).
All-cause mortality Within 29 days of treatment 9 Critical	Relative risk 0.2 (CI 95% 0.01 — 4.16) Based on data from 1,057 participants in 1 studies. [3] (Randomized controlled)	4 per 1000 Difference:	1 per 1000 **3 fewer per 1000** (CI 95% 4 fewer — 13 more)	**Low** Due to very serious imprecision [4]	We are uncertain whether sotrovimab impacts death (2 events).
Hospitalisation [any cause any duration] Within 29 days of treatment 6 Important	Relative risk 0.21 (CI 95% 0.09 — 0.5) Based on data from 1,057 participants in 1 studies. [5] (Randomized controlled)	55 per 1000 Difference:	12 per 1000 **43 fewer per 1000** (CI 95% 50 fewer — 28 fewer)	**Moderate** Due to serious imprecision [6]	Sotrovimab probably decreases hospitalisation [any cause or duration] (35 events).
ICU admission Within 29 days of treatment 6 Important	Relative risk 0.05 (CI 95% 0 — 0.81) Based on data from 1,057 participants in 1 studies. [7] (Randomized controlled)	19 per 1000 Difference:	1 per 1000 **18 fewer per 1000** (CI 95% 19 fewer — 4 fewer)	**Moderate** Due to serious imprecision [8]	Sotrovimab probably has little impact on ICU admission (10 events).
Invasive mechanical ventilation Within 29 days of treatment 9 Critical	Relative risk 0.11 (CI 95% 0.01 — 2.06) Based on data from 1,057 participants in 1 studies. [9] (Randomized controlled)	8 per 1000 Difference:	1 per 1000 **7 fewer per 1000** (CI 95% 8 fewer — 8 more)	**Low** Due to very serious imprecision [10]	We are uncertain whether sotrovimab impacts invasive mechanical ventilation (4 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Sotrovimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Non-invasive ventilation / HFNO Within 29 days of treatment 6 Important	Relative risk 0.05 (CI 95% 0 — 0.81) Based on data from 1,057 participants in 1 studies. [11] (Randomized controlled)	19 per 1000 Difference:	1 per 1000 **18 fewer per 1000** (CI 95% 19 fewer — 4 fewer)	**Moderate** Due to serious imprecision [12]	Sotrovimab probably has little impact on non-invasive ventilation / HFNO (10 events).
Adverse events Within 29 days of treatment 6 Important	Relative risk 0.93 (CI 95% 0.74 — 1.17) Based on data from 1,049 participants in 1 studies. [13] (Randomized controlled)	234 per 1000 Difference:	218 per 1000 **16 fewer per 1000** (CI 95% 61 fewer — 40 more)	**Moderate** Due to serious imprecision [14]	Sotrovimab probably has little impact on adverse events (237 events).
Serious adverse events Within 29 days of treatment 6 Important	Relative risk 0.35 (CI 95% 0.18 — 0.68) Based on data from 1,049 participants in 1 studies. [15] (Randomized controlled)	61 per 1000 Difference:	21 per 1000 **40 fewer per 1000** (CI 95% 50 fewer — 20 fewer)	**Moderate** Due to serious imprecision [16]	Sotrovimab probably decreases serious adverse events (43 events).

Attached Images

7.1.9.3 Sotrovimab (Xevudy) for children and adolescents

Info Box

Children and adolescents who are suspected to be at high risk of deterioration should be managed by and discussed with a multidisciplinary team. Decisions about exceptional use of treatments outside the recommendations made by the Taskforce should be taken in consultation with experts, in the light of the potential for rapid deterioration, with appropriate involvement of hospital drug and therapeutics committee and awareness of the CATAG guidance for off-label use of medications *(see CATAG guiding principles for the quality use of off label medicines)*.

Consensus recommendation

Do not routinely use sotrovimab (Xevudy) for the treatment of COVID-19 in children.

The Taskforce has previously only recommended the use of sotrovimab for the treatment of children aged over 12 years and over 40 kg in exceptional circumstances who do not require oxygen and who are at high risk of deterioration. These recommendations were based on indirect evidence from the COMET-ICE trial [439] that included 1057 participants with mild-to-moderate COVID-19, which demonstrated a benefit with regards to hospitalisation.

All clinical trials that contributed data to the analyses were conducted before the emergence of Omicron as the dominant variant. Since the development of the initial recommendations, a significant body of in vitro evidence has emerged demonstrating a significant reduction in activity of sotrovimab (Xevudy) against the Omicron BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that sotrovimab (Xevudy) is effective in treating individuals with currently circulating variants of COVID-19.

Clinical Question/ PICO

Population: Patients with mild or moderate COVID-19
Intervention: Sotrovimab
Comparator: Placebo

Summary

Evidence indicates that sotrovimab probably reduces incidence of hospitalisation in patients with mild COVID-19 illness who have one or more risk factors for disease progression, if received within 5 days of symptom onset.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial (COMET-ICE) that compared sotrovimab with placebo in 1057 adult outpatients with mild-to-moderate COVID-19 *[439]*.

Study characteristics
Median age of participants was 52 years and 54% were women. All eligible patients required one or more risk factors for disease progression, including diabetes (requiring medication), obesity, chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, moderate to severe asthma or adults over 55 years of age. Pregnant women were ineligible, and only six patients were aged under 19 years.

What are the main results?
Sotrovimab probably decreases the incidence of hospitalisation (42 fewer per 1000; RR 0.24, CI 95% 0.11 to 0.55; 1057 patients in 1 study), the composite outcome of hospitalisation (for longer than 24 hours) or death (46 fewer per 1000; RR 0.20, CI 95% 0.08 to 0.48; 1057 patients in 1 study) and serious adverse events (40 fewer per 1000; RR 0.35, CI 95% 0.18 to 0.68; 1049 patients from 1 study). We are unsure if sotrovimab impacts death or the requirement for invasive mechanical ventilation.

Sotrovimab probably has little impact on intensive care unit (ICU) admission, the requirement of non-invasive

ventilation or high-flown nasal oxygen (HFNO), or adverse events.

Our confidence in the results
Certainty of the evidence for the composite outcome of hospitalisation (for longer than 24 hours) or death, hospitalisation, ICU admission, requirement for non-invasive ventilation or HFNO, and serious adverse events is moderate due to serious imprecision (reliance on a single study). Certainty for all-cause mortality and the requirement for invasive mechanical ventilation is low due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty has been downgraded further due to serious indirectness (absence or limited of inclusion of these populations in the included study).

Additional information
There is currently limited supply of sotrovimab available for use within Australia and this may affect the feasibility of widespread treatment in this population.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Sotrovimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Hospitalisation (≥ 24 hours) or death [composite] Within 29 days of treatment 9 Critical	Relative risk 0.2 (CI 95% 0.08 — 0.48) Based on data from 1,057 participants in 1 studies. [1] (Randomized controlled)	**57** per 1000 Difference:	**11** per 1000 **46 fewer per 1000** (CI 95% 52 fewer — 30 fewer)	**Moderate** Due to serious imprecision [2]	Sotrovimab probably decreases hospitalisation (≥ 24 hours) or death (36 events).
All-cause mortality Within 29 days of treatment 9 Critical	Relative risk 0.2 (CI 95% 0.01 — 4.16) Based on data from 1,057 participants in 1 studies. [3] (Randomized controlled)	**4** per 1000 Difference:	**1** per 1000 **3 fewer per 1000** (CI 95% 4 fewer — 13 more)	**Low** Due to very serious imprecision [4]	We are uncertain whether sotrovimab impacts death (2 events).
Hospitalisation [any cause any duration] Within 29 days of treatment 6 Important	Relative risk 0.21 (CI 95% 0.09 — 0.5) Based on data from 1,057 participants in 1 studies. [5] (Randomized controlled)	**55** per 1000 Difference:	**12** per 1000 **43 fewer per 1000** (CI 95% 50 fewer — 28 fewer)	**Moderate** Due to serious imprecision [6]	Sotrovimab probably decreases hospitalisation [any cause or duration] (35 events).
ICU admission Within 29 days of treatment 6 Important	Relative risk 0.05 (CI 95% 0 — 0.81) Based on data from 1,057 participants in 1 studies. [7] (Randomized controlled)	**19** per 1000 Difference:	**1** per 1000 **18 fewer per 1000** (CI 95% 19 fewer — 4 fewer)	**Moderate** Due to serious imprecision [8]	Sotrovimab probably has little impact on ICU admission (10 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Sotrovimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Invasive mechanical ventilation Within 29 days of treatment 9 Critical	Relative risk 0.11 (CI 95% 0.01 — 2.06) Based on data from 1,057 participants in 1 studies. [9] (Randomized controlled)	8 per 1000 Difference:	1 per 1000 **7 fewer per 1000** (CI 95% 8 fewer — 8 more)	**Low** Due to very serious imprecision [10]	We are uncertain whether sotrovimab impacts invasive mechanical ventilation (4 events).
Non-invasive ventilation / HFNO Within 29 days of treatment 6 Important	Relative risk 0.05 (CI 95% 0 — 0.81) Based on data from 1,057 participants in 1 studies. [11] (Randomized controlled)	19 per 1000 Difference:	1 per 1000 **18 fewer per 1000** (CI 95% 19 fewer — 4 fewer)	**Moderate** Due to serious imprecision [12]	Sotrovimab probably has little impact on non-invasive ventilation / HFNO (10 events).
Adverse events Within 29 days of treatment 6 Important	Relative risk 0.93 (CI 95% 0.74 — 1.17) Based on data from 1,049 participants in 1 studies. [13] (Randomized controlled)	234 per 1000 Difference:	218 per 1000 **16 fewer per 1000** (CI 95% 61 fewer — 40 more)	**Moderate** Due to serious imprecision [14]	Sotrovimab probably has little impact on adverse events (237 events).
Serious adverse events Within 29 days of treatment 6 Important	Relative risk 0.35 (CI 95% 0.18 — 0.68) Based on data from 1,049 participants in 1 studies. [15] (Randomized controlled)	61 per 1000 Difference:	21 per 1000 **40 fewer per 1000** (CI 95% 50 fewer — 20 fewer)	**Moderate** Due to serious imprecision [16]	Sotrovimab probably decreases serious adverse events (43 events).

Attached Images

Only in research settings

Do not routinely use sotrovimab outside of randomised trials with appropriate ethical approval for the treatment of COVID-19 in children and adolescents under 12 years of age and without high risk factors for deterioration.

Where infection with Omicron BA.2, BA.4 or BA.5 is confirmed or considered likely, use of sotrovimab should only be considered where other treatments are not suitable or available.

Additional information

Where infection with Omicron BA.2, BA.4 or BA.5 is confirmed or considered likely, use of sotrovimab in children and adolescents should only be considered where other treatments are not suitable or available. There are limited evidence-based alternatives for children and adolescents currently (e.g. inhaled corticosteroids)

While the clinical evidence supports use of sotrovimab to treat mild COVID-19 (in adults at high risk of severe disease), there is no clinical evidence to evaluate its effectiveness against the Omicron variant or BA.1, BA.2, BA.4 or BA.5 sub-variants. The Taskforce is aware of in vitro data that suggest potentially reduced efficacy against these variants and while the clinical implications of this are not certain, given the availability of other treatments, where infection with Omicron BA.2, BA.4 or BA.5 is confirmed or considered likely, use of sotrovimab should not be considered unless other treatments are unsuitable or unavailable.

Children and adolescents were not included in the COMET-ICE trial. However trials are underway in which children over 12 years of age are eligible for inclusion (OPTIMISE-C19, NCT04913675).

The efficacy of sotrovimab (Xevudy) in vaccinated or immunocompromised patients is unknown.

Specific sub-populations may be considered for treatment with sotrovimab, such as children over 12 years with a high risk of deterioration (see recommendation below).

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

In non-hospitalised adults with mild COVID-19 who receive treatment within 5 days of symptom onset, sotrovimab probably decreases hospitalisation and serious adverse events. Based on the results of the COMET-ICE trial, sotrovimab has an acceptable safety profile.

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.

People requiring palliative care
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 for symptom management are uncertain.

Pregnant and breastfeeding women
There is uncertainty around the benefits and harms of sotrovimab for pregnant or breastfeeding women as they were excluded from the trial.

Children and adolescents
There is uncertainty around the benefits and harms of sotrovimab for children or adolescents as they were excluded from the trial. There are presently two randomised trials underway in which children aged 12 years and over are eligible for inclusion (OPTIMISE-C19, NCT04913675).

Certainty of the Evidence

Low

Certainty of the evidence for the composite outcome of hospitalisation (for longer than 24 hours) or death,

hospitalisation, ICU admission, the requirement of non-invasive ventilation or HFNO and serious adverse events is moderate due to serious imprecision (reliance on a single study). Certainty for all-cause mortality and the requirement of invasive mechanical ventilation is low due to very serious imprecision (reliance on a single study and low number of events).

For children and adolescents, certainty has been downgraded further due to serious indirectness (absence of inclusion of these populations in the study).

Values and preferences

Substantial variability is expected or uncertain

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

Children and adolescents
We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

Resources

Important issues, or potential issues not investigated

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

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity.

Acceptability

Important issues, or potential issues not investigated

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

Feasibility

Important issues, or potential issues not investigated

The Therapeutic Goods Administration is currently considering an application by the Sponsor regarding conditional approval of sotrovimab within Australia to treat patients with mild COVID-19 who have one or more risk factors. There is currently limited supply of sotrovimab available for use within Australia and this may affect the feasibility of widespread treatment in this population.

Clinical Question/ PICO

Population: Patients with mild or moderate COVID-19
Intervention: Sotrovimab
Comparator: Placebo

Summary

Evidence indicates that sotrovimab probably reduces incidence of hospitalisation in patients with mild COVID-19 illness who have one or more risk factors for disease progression, if received within 5 days of

symptom onset.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial (COMET-ICE) that compared sotrovimab with placebo in 1057 adult outpatients with mild-to-moderate COVID-19 *[439]*.

Study characteristics
Median age of participants was 52 years and 54% were women. All eligible patients required one or more risk factors for disease progression, including diabetes (requiring medication), obesity, chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, moderate to severe asthma or adults over 55 years of age. Pregnant women were ineligible, and only six patients were aged under 19 years.

What are the main results?
Sotrovimab probably decreases the incidence of hospitalisation (42 fewer per 1000; RR 0.24, CI 95% 0.11 to 0.55; 1057 patients in 1 study), the composite outcome of hospitalisation (for longer than 24 hours) or death (46 fewer per 1000; RR 0.20, CI 95% 0.08 to 0.48; 1057 patients in 1 study) and serious adverse events (40 fewer per 1000; RR 0.35, CI 95% 0.18 to 0.68; 1049 patients from 1 study). We are unsure if sotrovimab impacts death or the requirement for invasive mechanical ventilation.

Sotrovimab probably has little impact on intensive care unit (ICU) admission, the requirement of non-invasive ventilation or high-flown nasal oxygen (HFNO), or adverse events.

Our confidence in the results
Certainty of the evidence for the composite outcome of hospitalisation (for longer than 24 hours) or death, hospitalisation, ICU admission, requirement for non-invasive ventilation or HFNO, and serious adverse events is moderate due to serious imprecision (reliance on a single study). Certainty for all-cause mortality and the requirement for invasive mechanical ventilation is low due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty has been downgraded further due to serious indirectness (absence or limited of inclusion of these populations in the included study).

Additional information
There is currently limited supply of sotrovimab available for use within Australia and this may affect the feasibility of widespread treatment in this population.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Sotrovimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Hospitalisation (≥ 24 hours) or death [composite] Within 29 days of treatment 9 Critical	Relative risk 0.2 (CI 95% 0.08 — 0.48) Based on data from 1,057 participants in 1 studies. [1] (Randomized controlled)	57 per 1000 Difference:	11 per 1000 **46 fewer per 1000** (CI 95% 52 fewer — 30 fewer)	**Moderate** Due to serious imprecision [2]	Sotrovimab probably decreases hospitalisation (≥ 24 hours) or death (36 events).
All-cause mortality Within 29 days of treatment 9 Critical	Relative risk 0.2 (CI 95% 0.01 — 4.16) Based on data from 1,057 participants in 1 studies. [3] (Randomized controlled)	4 per 1000 Difference:	1 per 1000 **3 fewer per 1000** (CI 95% 4 fewer — 13 more)	**Low** Due to very serious imprecision [4]	We are uncertain whether sotrovimab impacts death (2 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Sotrovimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Hospitalisation [any cause any duration] Within 29 days of treatment 6 Important	Relative risk 0.21 (CI 95% 0.09 — 0.5) Based on data from 1,057 participants in 1 studies. [5] (Randomized controlled)	55 per 1000 Difference:	12 per 1000 **43 fewer per 1000** (CI 95% 50 fewer — 28 fewer)	**Moderate** Due to serious imprecision [6]	Sotrovimab probably decreases hospitalisation [any cause or duration] (35 events).
ICU admission Within 29 days of treatment 6 Important	Relative risk 0.05 (CI 95% 0 — 0.81) Based on data from 1,057 participants in 1 studies. [7] (Randomized controlled)	19 per 1000 Difference:	1 per 1000 **18 fewer per 1000** (CI 95% 19 fewer — 4 fewer)	**Moderate** Due to serious imprecision [8]	Sotrovimab probably has little impact on ICU admission (10 events).
Invasive mechanical ventilation Within 29 days of treatment 9 Critical	Relative risk 0.11 (CI 95% 0.01 — 2.06) Based on data from 1,057 participants in 1 studies. [9] (Randomized controlled)	8 per 1000 Difference:	1 per 1000 **7 fewer per 1000** (CI 95% 8 fewer — 8 more)	**Low** Due to very serious imprecision [10]	We are uncertain whether sotrovimab impacts invasive mechanical ventilation (4 events).
Non-invasive ventilation / HFNO Within 29 days of treatment 6 Important	Relative risk 0.05 (CI 95% 0 — 0.81) Based on data from 1,057 participants in 1 studies. [11] (Randomized controlled)	19 per 1000 Difference:	1 per 1000 **18 fewer per 1000** (CI 95% 19 fewer — 4 fewer)	**Moderate** Due to serious imprecision [12]	Sotrovimab probably has little impact on non-invasive ventilation / HFNO (10 events).
Adverse events Within 29 days of treatment 6 Important	Relative risk 0.93 (CI 95% 0.74 — 1.17) Based on data from 1,049 participants in 1 studies. [13] (Randomized controlled)	234 per 1000 Difference:	218 per 1000 **16 fewer per 1000** (CI 95% 61 fewer — 40 more)	**Moderate** Due to serious imprecision [14]	Sotrovimab probably has little impact on adverse events (237 events).
Serious adverse events Within 29 days of treatment 6 Important	Relative risk 0.35 (CI 95% 0.18 — 0.68) Based on data from 1,049 participants in 1 studies. [15] (Randomized controlled)	61 per 1000 Difference:	21 per 1000 **40 fewer per 1000** (CI 95% 50 fewer — 20 fewer)	**Moderate** Due to serious imprecision [16]	Sotrovimab probably decreases serious adverse events (43 events).

Attached Images

7.1.10 Tixagevimab plus cilgavimab (Evusheld)

7.1.10.1 Tixagevimab plus cilgavimab (Evusheld) for adults

Consensus recommendation

Do not routinely use tixagevimab plus cilgavimab (Evusheld) for the treatment of COVID-19.

The Taskforce has previously recommended the use of tixagevimab plus cilgavimab (Evusheld) for the treatment of individuals with COVID-19 who do not require mechanical ventilation. Recommendations for those not requiring oxygen were based on the TACKLE trial [519] that included 903 unvaccinated adults with mild COVID-19, which demonstrated a benefit with regards to progression to severe COVID-19, adverse events and hospitalisation. Recommendations for those requiring oxygen were based on the ACTIV-3-TICO trial [502] that included 1088 predominately unvaccinated individuals, which demonstrated a benefit with regards to all-cause mortality at 28 and 90 days.

All clinical trials that contributed data to the analyses were conducted before the emergence of Omicron as the dominant variant. Since the development of the initial recommendations, a significant body of in vitro evidence has emerged demonstrating a significant reduction in activity of tixagevimab plus cilgavimab (Evusheld) against the Omicron BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that tixagevimab plus cilgavimab (Evusheld) is effective in treating individuals with currently circulating variants of COVID-19. Use maybe considered for known Omicron BA2 as in vitro evidence suggests that some efficacy remains for this variant.

Clinical Question/ PICO

Population: Patients with COVID-19 (not requiring oxygen)
Intervention: Evusheld
Comparator: Placebo

Summary

Evidence indicates that tixagevimab plus cilgavimab probably reduces the incidence of clinical deterioration in adults with mild COVID-19 who have one or more risk factors for disease progression, if used within 5 days onset of symptoms.

What is the evidence informing this recommendation?
Evidence comes from a single randomised trial that compared tixagevimab plus cilgavimab (Evusheld) with placebo in 903 adult outpatients with mild COVID-19 *[519]*. Participants were randomised within 7 days of onset of symptoms and had one or more risk factors for disease progression.

Study characteristics
Mean age of participants was 46 years and 50% were women. The majority of participants were under 65 years of age (87%). Participants received a single dose of Evusheld, consisting of two simultaneous intramuscular injections (150 mg tixagevimab and 150 mg cilgavimab). Pregnant and breastfeeding women and children and adolescents were ineligible.

What are the main results?
Tixagevimab plus cilgavimab probably reduces progression to severe disease or death (RR 0.50, CI 95% 0.29 to 0.86; 822 patients in 1 study), with the greatest benefit observed in those participants treated within 5 days of onset of symptoms (RR 0.33, CI 905% 0.15 to 0.72; 447 patients in 1 study). Tixagevimab plus cilgavimab probably decreases incidence of adverse events (RR 0.81, CI 95% 0.67 to 0.98; 903 patients in 1 study) and serious adverse events (RR 0.61, CI 95% 0.40 to 0.92; 903 patients in 1 study). Tixagevimab plus cilgavimab probably has little impact on respiratory failure or hospitalisation, and we are unsure if it impacts all-cause mortality and discontinuation due to adverse events.

Our confidence in the results
Certainty of the evidence is moderate for the composite outcomes of progression to severe disease or death (total cohort and patients treated within 5 days onset of symptoms), progression to severe disease, hospitalisation, adverse events and serious adverse events, due to serious imprecision (reliance on a single study). Certainty was low for all-cause mortality, progression to severe disease or death (patients treated more than 5 days after onset of symptoms), respiratory failure and discontinuation due to adverse events due to very serious imprecision (reliance on a single study and limited events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The Therapeutic Goods Administration has granted provisional determination for Evusheld. As of 24 February 2022, Evusheld is not approved for use for the treatment of COVID-19.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Evusheld	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 29 days of treatment 9 Critical	Relative risk 1.26 (CI 95% 0.12 — 13.6) Based on data from 1,151 participants in 2 studies. [1] (Randomized controlled)	4 per 1000 Difference:	5 per 1000 **1 more per 1000** (CI 95% 4 fewer — 50 more)	**Low** Due to very serious imprecision [2]	Tixagevimab plus cilgavimab may have little impact on all-cause mortality (5 events).
Severe COVID or death [3] Within 29 days of treatment 9 Critical	Relative risk 0.5 (CI 95% 0.29 — 0.86) Based on data from 822 participants in 1 studies. [4] (Randomized controlled)	89 per 1000 Difference:	45 per 1000 **45 fewer per 1000** (CI 95% 63 fewer — 12 fewer)	**Moderate** Due to serious imprecision [5]	Evusheld probably decreases progression to severe COVID (55 events)
Severe COVID Within 29 days of treatment 6 Important	Relative risk 0.44 (CI 95% 0.25 — 0.78) Based on data from 822 participants in 1 studies. [6] (Randomized controlled)	89 per 1000 Difference:	39 per 1000 **50 fewer per 1000** (CI 95% 67 fewer — 20 fewer)	**Moderate** Due to serious imprecision [7]	Evusheld probably decreases progression to severe COVID (53 events)
Severe COVID or death (> 5 days symptom onset, high risk) Within 29 days of treatment 9 Critical	Relative risk 1.06 (CI 95% 0.43 — 2.59) Based on data from 288 participants in 1 studies. [8] (Randomized controlled)	61 per 1000 Difference:	65 per 1000 **4 more per 1000** (CI 95% 35 fewer — 97 more)	**Low** Due to very serious imprecision [9]	Evusheld may have little or no difference on severe COVID or death (> 5 days symptom onset in high risk patients; 18 events)
Respiratory failure Within 29 days of treatment	Relative risk 0.28 (CI 95% 0.08 — 0.99) Based on data from 817 participants in 1 studies. [10] (Randomized	27 per 1000 Difference:	8 per 1000 **19 fewer per 1000** (CI 95% 25	**Low** Due to very serious imprecision [11]	Evusheld may have little impact on respiratory failure (14 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Evusheld	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important	controlled)		fewer — 0 fewer)		
Severe COVID or death (≤ 5 days symptom onset, high risk) Within 29 days of treatment 9 Critical	Relative risk 0.33 (CI 95% 0.15 — 0.72) Based on data from 447 participants in 1 studies. [12] (Randomized controlled)	108 per 1000 Difference:	36 per 1000 **72 fewer per 1000** (CI 95% 92 fewer — 30 fewer)	**Moderate** Due to serious imprecision [13]	Evusheld probably decreases progression to severe COVID or death (≤ 5 days symptom onset in high risk patients; 32 events)
Hospitalisation Within 29 days of treatment 6 Important	Relative risk 0.83 (CI 95% 0.6 — 1.16) Based on data from 903 participants in 1 studies. [14] (Randomized controlled)	149 per 1000 Difference:	124 per 1000 **25 fewer per 1000** (CI 95% 60 fewer — 24 more)	**Moderate** Due to serious imprecision [15]	Evusheld probably has little or no impact on hospitalisation (123 events)
Adverse events Within 29 days of treatment 6 Important	Relative risk 0.81 (CI 95% 0.67 — 0.98) Based on data from 903 participants in 1 studies. [16] (Randomized controlled)	361 per 1000 Difference:	292 per 1000 **69 fewer per 1000** (CI 95% 119 fewer — 7 fewer)	**Moderate** Due to serious imprecision [17]	Evusheld probably decreases adverse events (295 events)
Serious adverse events End of follow-up	Relative risk 0.73 (CI 95% 0.5 — 1.06) Based on data from 2,320 participants in 2 studies. [18] (Randomized controlled)	79 per 1000 Difference:	58 per 1000 **21 fewer per 1000** (CI 95% 40 fewer — 5 more)	**High** [19]	Tixagevimab plus cilgavimab has little impact on serious adverse events (159 events).
Discontinuation due to AEs	Relative risk 0.2 (CI 95% 0.01 — 4.14) Based on data from 910 participants in 1 studies. [20] (Randomized controlled)	4 per 1000 Difference:	1 per 1000 **3 fewer per 1000** (CI 95% 4 fewer — 13 more)	**Low** Due to very serious imprecision [21]	We are uncertain whether evusheld increases or decreases discontinuation due to AEs (2 events)

Attached Images

Only in research settings

Do not use tixagevimab plus cilgavimab for the treatment of COVID-19 in adults who require mechanical ventilation outside of randomised trials with appropriate ethical approval.

Additional information

Currently, there is no evidence evaluating the effectiveness of tixagevimab plus cilgavimab in individuals who are hospitalised and require mechanical ventilation.

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 tixagevimab plus cilgavimab to treat COVID-19 in patients who require mechanical ventilation unless they are eligible to be enrolled in trials.

This is a high priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

7.1.10.2 Tixagevimab plus cilgavimab (Evusheld) for pregnant or breastfeeding women

Only in research settings

Do not use tixagevimab plus cilgavimab for the treatment of COVID-19 in pregnant or breastfeeding women outside of randomised trials with appropriate ethical approval.

Additional information

Currently, there is no direct evidence for the use of tixagevimab plus cilgavimab (Evusheld) in pregnant or breastfeeding women. Trials are needed in special populations, including pregnant or breastfeeding women. Until further evidence is available, do not routinely use tixagevimab plus cilgavimab for the treatment of COVID-19 in pregnant or breastfeeding women unless they are eligible to be enrolled in trials.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

7.1.10.3 Tixagevimab plus cilgavimab (Evusheld) for children and adolescents

Info Box

Children and adolescents who are suspected to be at high risk of deterioration should be managed by and discussed with a multidisciplinary team. Decisions about exceptional use of treatments outside the recommendations made by the Taskforce should be taken in consultation with experts, in the light of the potential for rapid deterioration, with appropriate involvement of hospital drug and therapeutics committee and awareness of the CATAG guidance for off-label use of medications *(see CATAG guiding principles for the quality use of off label medicines)*.

Consensus recommendation

Do not routinely use tixagevimab plus cilgavimab (Evusheld) for the treatment of COVID-19 in children and adolescents.

The Taskforce has previously only recommended the use of tixagevimab plus cilgavimab (Evusheld) in exceptional circumstances for the treatment of COVID-19 in children and adolescents aged 12 years and over and weighing at least 40 kg who were at high risk of deterioration but did not require mechanical ventilation. This was due to no direct evidence being available to inform it use.

Since the development of the initial recommendations, a significant body of in vitro evidence has emerged demonstrating a significant reduction in activity of tixagevimab plus cilgavimab (Evusheld) against the Omicron BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that tixagevimab plus cilgavimab (Evusheld) is effective in treating individuals with currently circulating variants of COVID-19. Use may be considered for known Omicron BA2 as in vitro evidence suggests that some efficacy remains for this variant.

Clinical Question/ PICO

Population: Patients with COVID-19 (not requiring oxygen)
Intervention: Evusheld
Comparator: Placebo

Summary

Evidence indicates that tixagevimab plus cilgavimab probably reduces the incidence of clinical deterioration in adults with mild COVID-19 who have one or more risk factors for disease progression, if used within 5 days onset of symptoms.

What is the evidence informing this recommendation?
Evidence comes from a single randomised trial that compared tixagevimab plus cilgavimab (Evusheld) with placebo in 903 adult outpatients with mild COVID-19 *[519]*. Participants were randomised within 7 days of onset of symptoms and had one or more risk factors for disease progression.

Study characteristics
Mean age of participants was 46 years and 50% were women. The majority of participants were under 65 years of age (87%). Participants received a single dose of Evusheld, consisting of two simultaneous intramuscular injections (150 mg tixagevimab and 150 mg cilgavimab). Pregnant and breastfeeding women and children and adolescents were ineligible.

What are the main results?
Tixagevimab plus cilgavimab probably reduces progression to severe disease or death (RR 0.50, CI 95% 0.29 to 0.86; 822 patients in 1 study), with the greatest benefit observed in those participants treated within 5 days of onset of symptoms (RR 0.33, CI 905% 0.15 to 0.72; 447 patients in 1 study). Tixagevimab plus cilgavimab probably decreases incidence of adverse events (RR 0.81, CI 95% 0.67 to 0.98; 903 patients in 1 study) and serious adverse events (RR 0.61, CI 95% 0.40 to 0.92; 903 patients in 1 study). Tixagevimab plus cilgavimab probably has little impact on respiratory failure or hospitalisation, and we are unsure if it impacts all-cause

mortality and discontinuation due to adverse events.

Our confidence in the results
Certainty of the evidence is moderate for the composite outcomes of progression to severe disease or death (total cohort and patients treated within 5 days onset of symptoms), progression to severe disease, hospitalisation, adverse events and serious adverse events, due to serious imprecision (reliance on a single study). Certainty was low for all-cause mortality, progression to severe disease or death (patients treated more than 5 days after onset of symptoms), respiratory failure and discontinuation due to adverse events due to very serious imprecision (reliance on a single study and limited events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The Therapeutic Goods Administration has granted provisional determination for Evusheld. As of 24 February 2022, Evusheld is not approved for use for the treatment of COVID-19.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Evusheld	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 29 days of treatment 9 Critical	Relative risk 1.26 (CI 95% 0.12 — 13.6) Based on data from 1,151 participants in 2 studies. [1] (Randomized controlled)	4 per 1000 Difference:	5 per 1000 **1 more per 1000** (CI 95% 4 fewer — 50 more)	**Low** Due to very serious imprecision [2]	Tixagevimab plus cilgavimab may have little impact on all-cause mortality (5 events).
Severe COVID or death [3] Within 29 days of treatment 9 Critical	Relative risk 0.5 (CI 95% 0.29 — 0.86) Based on data from 822 participants in 1 studies. [4] (Randomized controlled)	89 per 1000 Difference:	45 per 1000 **45 fewer per 1000** (CI 95% 63 fewer — 12 fewer)	**Moderate** Due to serious imprecision [5]	Evusheld probably decreases progression to severe COVID (55 events)
Severe COVID Within 29 days of treatment 6 Important	Relative risk 0.44 (CI 95% 0.25 — 0.78) Based on data from 822 participants in 1 studies. [6] (Randomized controlled)	89 per 1000 Difference:	39 per 1000 **50 fewer per 1000** (CI 95% 67 fewer — 20 fewer)	**Moderate** Due to serious imprecision [7]	Evusheld probably decreases progression to severe COVID (53 events)
Severe COVID or death (> 5 days symptom onset, high risk) Within 29 days of treatment	Relative risk 1.06 (CI 95% 0.43 — 2.59) Based on data from 288 participants in 1 studies. [8] (Randomized controlled)	61 per 1000 Difference:	65 per 1000 **4 more per 1000** (CI 95% 35 fewer — 97 more)	**Low** Due to very serious imprecision [9]	Evusheld may have little or no difference on severe COVID or death (> 5 days symptom onset in high risk patients; 18 events)

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Evusheld	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical					
Respiratory failure Within 29 days of treatment 6 Important	Relative risk 0.28 (CI 95% 0.08 — 0.99) Based on data from 817 participants in 1 studies. [10] (Randomized controlled)	27 per 1000 Difference:	8 per 1000 **19 fewer per 1000** (CI 95% 25 fewer — 0 fewer)	**Low** Due to very serious imprecision [11]	Evusheld may have little impact on respiratory failure (14 events).
Severe COVID or death (≤ 5 days symptom onset, high risk) Within 29 days of treatment 9 Critical	Relative risk 0.33 (CI 95% 0.15 — 0.72) Based on data from 447 participants in 1 studies. [12] (Randomized controlled)	108 per 1000 Difference:	36 per 1000 **72 fewer per 1000** (CI 95% 92 fewer — 30 fewer)	**Moderate** Due to serious imprecision [13]	Evusheld probably decreases progression to severe COVID or death (≤ 5 days symptom onset in high risk patients; 32 events)
Hospitalisation Within 29 days of treatment 6 Important	Relative risk 0.83 (CI 95% 0.6 — 1.16) Based on data from 903 participants in 1 studies. [14] (Randomized controlled)	149 per 1000 Difference:	124 per 1000 **25 fewer per 1000** (CI 95% 60 fewer — 24 more)	**Moderate** Due to serious imprecision [15]	Evusheld probably has little or no impact on hospitalisation (123 events)
Adverse events Within 29 days of treatment 6 Important	Relative risk 0.81 (CI 95% 0.67 — 0.98) Based on data from 903 participants in 1 studies. [16] (Randomized controlled)	361 per 1000 Difference:	292 per 1000 **69 fewer per 1000** (CI 95% 119 fewer — 7 fewer)	**Moderate** Due to serious imprecision [17]	Evusheld probably decreases adverse events (295 events)
Serious adverse events End of follow-up	Relative risk 0.73 (CI 95% 0.5 — 1.06) Based on data from 2,320 participants in 2 studies. [18] (Randomized controlled)	79 per 1000 Difference:	58 per 1000 **21 fewer per 1000** (CI 95% 40 fewer — 5 more)	**High** [19]	Tixagevimab plus cilgavimab has little impact on serious adverse events (159 events).
Discontinuation due to AEs	Relative risk 0.2 (CI 95% 0.01 — 4.14) Based on data from	4 per 1000	1 per 1000	**Low** Due to very serious	We are uncertain whether evusheld increases or decreases

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Evusheld	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	910 participants in 1 studies. [20] (Randomized controlled)	Difference:	**3 fewer per 1000** (CI 95% 4 fewer — 13 more)	imprecision [21]	discontinuation due to AEs (2 events)

Attached Images

Only in research settings

Do not use tixagevimab plus cilgavimab for the treatment of COVID-19 in children under 12 years of age without risk factors for deterioration who do not require oxygen outside of randomised trials with appropriate ethical approval.

Additional information

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

7.2 Drug treatments that are not recommended

7.2.1 Aspirin

Not recommended

Do not use aspirin for the treatment of COVID-19.

Additional information

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of aspirin for treatment of COVID-19 may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include aspirin.

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

This is a moderate priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

General adult population
Evidence indicates no difference between aspirin and standard care in incidence of death, requirement of mechanical ventilation or duration of hospital stay. Uncertainty remains regarding the incidence of adverse or serious adverse events.

Certainty of the Evidence

Moderate

Certainty of the evidence is moderate for all outcomes due to serious imprecision (reliance on a single study).

Values and preferences

Substantial variability is expected or uncertain

General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this 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.

Resources

No important issues with the recommended alternative

As aspirin is not recommended there are no resource considerations.

Equity

No important issues with the recommended alternative

As aspirin is not recommended there are no equity considerations.

Acceptability

No important issues with the recommended alternative

As aspirin is not recommended there are no acceptability considerations.

Feasibility

No important issues with the recommended alternative

As aspirin is not recommended there are no feasibility considerations.

Rationale

Based on the available evidence, aspirin is no more effective than standard care in treating patients with COVID-19. We therefore recommend that aspirin should not be used.

Clinical Question/ PICO

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

Summary

Evidence indicates that aspirin is no more effective than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from a single randomised trial (RECOVERY) that compared aspirin with standard care in 14,892 adults hospitalised with moderate-to-critical COVID-19 *[396]*.

Study characteristics
Median age of participants was 59 years and the proportion of women was 38%. Two-thirds of patients required either no oxygen or simple (low-flow) oxygen, 28% required non-invasive ventilation and 5% required invasive mechanical ventilation. Most patients (94%) received concomitant corticosteroids.

Equity, diversity and inclusion

The characteristics of trial participants related to equity, diversity and inclusion (see technical report) were reported in minimal detail in the included studies. Ethnicity was reported in one study. As a result, the specific population(s) to whom this data directly applies is unclear.

None of these trials were conducted in Australia. This participant data comes from India, Indonesia, Nepal and the United Kingdom.

The Taskforce will continue to extract and identify characteristics relevant to equity, diversity and inclusion where available.

What are the main results?
Aspirin probably has no impact on risk of death (5 fewer per 1000; RR 0.97, CI 95% 0.90 to 1.04; 14,892 patients in 1 study) or invasive mechanical ventilation (6 fewer per 1000; RR 0.95, CI 95% 0.87 to 1.05; 14,162 patients in 1 study). There is probably little difference between aspirin and standard care for the composite outcome of death or invasive mechanical ventilation, or discharge from hospital at 28 days.

Our confidence in the results
Certainty of the evidence is moderate for all outcomes due to serious imprecision (reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Outcome Timeframe	**Study results and measurements**	**Comparator** standard care	**Intervention** Aspirin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.97 (CI 95% 0.9 — 1.04) Based on data from 14,892 participants in 1 studies. [1] (Randomized controlled)	172 per 1000 Difference:	167 per 1000 **5 fewer per 1000** (CI 95% 17 fewer — 7 more)	Moderate Due to serious imprecision [2]	Aspirin probably has little or no impact on death.
Invasive mechanical ventilation or death End of follow-up 9 Critical	Relative risk 0.96 (CI 95% 0.9 — 1.03) Based on data from 14,162 participants in 1 studies. [3] (Randomized controlled)	219 per 1000 Difference:	210 per 1000 **9 fewer per 1000** (CI 95% 22 fewer — 7 more)	Moderate Due to serious imprecision [4]	Aspirin probably has little impact on invasive mechanical ventilation or death.
Invasive mechanical ventilation End of follow-up 9 Critical	Relative risk 0.95 (CI 95% 0.87 — 1.05) Based on data from 14,162 participants in 1 studies. [5] (Randomized controlled)	116 per 1000 Difference:	110 per 1000 **6 fewer per 1000** (CI 95% 15 fewer — 6 more)	Moderate Due to serious imprecision [6]	Aspirin probably has little impact on invasive mechanical ventilation.
Discharge from hospital End of follow-up 6 Important	Relative risk 1.02 (CI 95% 1 — 1.04) Based on data from 14,892 participants in 1 studies. [7] (Randomized controlled)	736 per 1000 Difference:	751 per 1000 **15 more per 1000** (CI 95% 0 fewer — 29 more)	Moderate Due to serious imprecision [8]	Aspirin probably has little impact on discharge from hospital.

Attached Images

7.2.2 Azithromycin

Not recommended

Do not use azithromycin for the treatment of COVID-19.

Additional information

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of azithromycin may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include azithromycin.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

General adult population
Evidence indicates no difference between azithromycin and standard care in incidence of death, requirement of mechanical ventilation or ECMO, or duration of hospital stay. Uncertainty remains regarding the incidence of adverse or serious adverse events.

According to the Therapeutic Goods Administration, reported adverse events are generally mild or moderate and include rash, heart palpitations, urinary tract infection, headache, fatigue and gastrointestinal symptoms such as dyspepsia and vomiting *[88]*.

Pregnant and breastfeeding women
As azithromycin has only been taken by a limited number of pregnant women and women of childbearing age, its safety profile is therefore uncertain.

Children and adolescents
The safety and effectiveness of azithromycin in children has not been established.

Certainty of the Evidence

High

General adult population
Certainty of the evidence is high for the critical outcome of mortality and patients requiring mechanical ventilation or ECMO. Certainty is moderate for adverse events, serious adverse events, discharge from hospital, and time to discharge from hospital—all based on serious imprecision due to wide confidence intervals or reliance on a single study (duration of hospital stay). Certainty is low for adverse events, clinical progression and discharge from hospital based on very serious imprecision due to wide confidence intervals 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 downgraded further because of indirectness due to limited inclusion (or absence) of these populations in the trials.

Values and preferences

Substantial variability is expected or uncertain

General adult population

We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this 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.

Resources

No important issues with the recommended alternative

As azithromycin is not recommended there are no resource considerations.

Equity

No important issues with the recommended alternative

As azithromycin is not recommended there are no equity considerations.

Acceptability

No important issues with the recommended alternative

As azithromycin is not recommended there are no acceptability considerations.

Feasibility

No important issues with the recommended alternative

As azithromycin is not recommended there are no feasibility considerations.

Rationale

Based on the available evidence, azithromycin is no more effective than standard care in treating patients with COVID-19. We therefore recommend that azithromycin should not be used.

Clinical Question/ PICO

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

Summary

Evidence indicates that azithromycin is no more effective than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from eight randomised trials, six that compared azithromycin with standard care in over 10,000 adults hospitalised with COVID-19 *[86][87][91][93][122][476]* and two that compared azithromycin with standard care in 555 adult outpatients with mild or moderate COVID-19 *[474][475]*.

The vast majority of data are from the RECOVERY trial, which included 7763 adults hospitalised with moderate-to-critical COVID-19 *[91]*. One trial compared azithromycin with standard care in 1388 adult outpatients with mild COVID-19 *[93]*, two trials compared azithromycin plus hydroxychloroquine with hydroxychloroquine alone in 397 adults hospitalised with severe or critical COVID-19 *[86]* and 331 with moderate COVID-19 *[122]*, and one trial compared azithromycin plus hydroxychloroquine and lopinavir-ritonavir with hydroxychloroquine and lopinavir-ritonavir alone in 111 adults hospitalised with severe COVID-19 *[87]*.

Study characteristics
For a comprehensive description, see the study characteristics table.

Equity, diversity and inclusion

The characteristics of trial participants related to equity, diversity and inclusion (see technical report) were reported in minimal detail in the included studies. Ethnicity was reported in five studies and the reporting of ethnicity varied between trials. As a result, the specific population(s) to whom this data directly applies is unclear.

None of these trials were conducted in Australia. This participant data comes from Belgium, Brazil, Iran, United Kingdom and the United States.

The Taskforce will continue to extract and identify characteristics relevant to equity, diversity and inclusion where available.

What are the main results?
Azithromycin has no impact on risk of death compared with standard care (2 more per 1000 with azithromycin; RR 1.01, CI 95% 0.92 to 1.10; 9887 patients in 5 studies) and has little impact on the number of patients requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO) (4 fewer per 1000; RR 0.94, CI 95% 0.79 to 1.14; 8433 patients in 2 studies).

Azithromycin probably increases the incidence of adverse events (RR 1.44, CI 95% 0.95 to 2.17; 838 patients in 3 studies) and serious adverse events (RR 1.14, CI 95% 0.91 to 1.42; 1060 patients in 3 studies), probably decreases the number of patients discharged from hospital at 28 days (RR 0.92, CI 95% 0.71 to 1.19; 8161 patients in 2 studies), and probably has no impact on median duration of hospital stay.

We are uncertain if azithromycin increases or decreases clinical progression (as measured by admission to ICU).

Our confidence in the results
Certainty of the evidence is high for the critical outcomes of death and number of patients requiring mechanical ventilation or ECMO. Certainty is moderate for adverse events, serious adverse events, discharge from hospital, and time to discharge from hospital (duration of hospital stay)—all based on serious imprecision due to wide confidence intervals or reliance on a single study. Certainty is low for clinical progression (defined as admission to intensive care unit) based on very serious imprecision due to wide confidence intervals.

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Therapeutic Goods Administration, reported adverse events are generally mild or moderate and include rash, heart palpitations, urinary tract infection, dizziness, headache, fatigue and gastrointestinal symptoms such as dyspepsia and vomiting *[88]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Azithromycin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 1.01 (CI 95% 0.92 — 1.1) Based on data from 9,887 participants in 5 studies. [1] (Randomized controlled)	168 per 1000 Difference:	170 per 1000 **2 more per 1000** (CI 95% 13 fewer — 17 more)	High	Azithromycin has no impact on death.
Mechanical ventilation or ECMO	Relative risk 0.94 (CI 95% 0.79 — 1.14) Based on data from	60 per 1000	56 per 1000	High	Azithromycin has little or no impact on mechanical ventilation

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Azithromycin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Within 28 days of commencing treatment 9 Critical	8,433 participants in 2 studies. [2] (Randomized controlled)	Difference:	**4 fewer per 1000** (CI 95% 13 fewer — 8 more)		or ECMO.
Supplemental oxygen [3] Within 28 days of commencing treatment 6 Important	Relative risk 0.84 (CI 95% 0.38 — 1.85) Based on data from 1,122 participants in 1 studies. [4] (Randomized controlled)	24 per 1000 Difference:	20 per 1000 **4 fewer per 1000** (CI 95% 15 fewer — 20 more)	**Low** Due to very serious imprecision [5]	Azithromycin may have little or no difference on need for supplemental oxygen (25 events).
Serious adverse events End of treatment 6 Important	Relative risk 1.14 (CI 95% 0.91 — 1.42) Based on data from 1,060 participants in 3 studies. [6] (Randomized controlled)	182 per 1000 Difference:	207 per 1000 **25 more per 1000** (CI 95% 16 fewer — 76 more)	**Moderate** Due to serious imprecision [7]	Azithromycin probably increases number of patients experiencing serious adverse events.
Adverse events End of treatment 6 Important	Relative risk 1.44 (CI 95% 0.95 — 2.17) Based on data from 838 participants in 3 studies. [8] (Randomized controlled)	296 per 1000 Difference:	426 per 1000 **130 more per 1000** (CI 95% 15 fewer — 346 more)	**Moderate** Due to serious imprecision [9]	Azithromycin probably increases adverse events
Hospitalisation Within 28 days of commencing treatment 6 Important	Relative risk 1.46 (CI 95% 0.26 — 8.09) Based on data from 489 participants in 2 studies. [10] (Randomized controlled)	78 per 1000 Difference:	114 per 1000 **36 more per 1000** (CI 95% 58 fewer — 553 more)	**Low** Due to very serious imprecision [11]	Azithromycin may increase hospitalisation slightly (37 events).
ICU admission End of follow-up 6 Important	Relative risk 0.48 (CI 95% 0.17 — 1.35) Based on data from 1,231 participants in 2 studies. [12] (Randomized controlled)	18 per 1000 Difference:	9 per 1000 **9 fewer per 1000** (CI 95% 15 fewer — 6 more)	**Low** Due to very serious imprecision [13]	We are uncertain whether azithromycin increases or decreases ICU admission (17 events).
Clinical recovery Within 21–28 days of	Relative risk 0.96 (CI 95% 0.89 — 1.04) Based on data from 1,326 participants in 2	652 per 1000	626 per 1000	**Moderate** Due to serious imprecision [15]	Azithromycin probably decreases clinical recovery slightly.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Azithromycin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
commencing treatment 6 Important	studies. [14] (Randomized controlled)	Difference:	**26 fewer per 1000** (CI 95% 72 fewer — 26 more)		
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.92 (CI 95% 0.71 — 1.19) Based on data from 8,161 participants in 2 studies. [16] (Randomized controlled)	586 per 1000 Difference:	539 per 1000 **47 fewer per 1000** (CI 95% 170 fewer — 111 more)	**Moderate** Due to serious imprecision [17]	Azithromycin probably decreases discharge from hospital slightly (4765 events).
Duration of hospital stay Mean 6 Important	Based on data from 442 participants in 2 studies. [18] (Randomized controlled)	Difference:	**MD 0.41 lower** (CI 95% 2.42 lower — 1.59 higher)	**Low** Due to serious inconsistency and imprecision [19]	Azithromycin may have little impact on duration of hospital stay.
Duration of hospital stay [20] Median 6 Important	Lower better Based on data from 7,764 participants in 1 studies. (Randomized controlled)	13 (Median)	12 (Median) CI 95%	**Moderate** Due to serious imprecision [21]	Azithromycin probably makes little difference to duration of hospital stay.

Attached Images

7.2.3 Colchicine

Not recommended

Do not use colchicine for the treatment of COVID-19.

Additional information

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of colchicine may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include colchicine.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

General adult population
Evidence indicates no difference between colchicine and standard care in incidence of death, requirement of mechanical ventilation or extracorporeal membrane oxygenation, or duration of hospital stay. Uncertainty remains regarding the incidence of adverse or serious adverse events.

Certainty of the Evidence

High

Certainty of the evidence is high for mortality, mechanical ventilation and discharge from hospital, and moderate for adverse and serious adverse events due to serious imprecision (wide confidence intervals).

Certainty is low for discontinuation due to adverse events, clinical progression, admission to intensive care unit and discharge from hospital due to very serious imprecision (either reliance on a single study and wide confidence intervals, or few events).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Values and preferences

Substantial variability is expected or uncertain

General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this 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.

Resources

No important issues with the recommended alternative

As colchicine is not recommended there are no resource considerations.

Equity

No important issues with the recommended alternative

As colchicine is not recommended there are no equity considerations.

Acceptability

No important issues with the recommended alternative

As colchicine is not recommended there are no acceptability considerations.

Feasibility

No important issues with the recommended alternative

As colchicine is not recommended there are no feasibility considerations.

Rationale

Based on the available evidence, colchicine is no more effective than standard care in treating patients with COVID-19. We therefore recommend that colchicine should not be used.

Clinical Question/ PICO

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

Summary

Evidence indicates that colchicine is no more effective than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from eight randomised trials that compared colchicine with standard care or placebo in over 17,700 patients. The majority of evidence comes from the RECOVERY trial, which included 11,340 patients hospitalised with moderate-to-critical COVID-19 *[388]*. Five additional trials compared colchicine with standard care or placebo in 1585 adults hospitalised with COVID-19 *[160][470][472][473][481]* and two trials compared colchicine with placebo or standard care in 4764 non-hospitalised adults with confirmed COVID-19 *[308][471]*.

See 'Removal of studies' section below for information on studies previously included in this recommendation.

Study characteristics
In RECOVERY the mean age of participants was ~63 years and 30% were women. In COLCORONA mean age was ~55 years and 54% were women.

Equity, diversity and inclusion

The characteristics of trial participants related to equity, diversity and inclusion (see technical report) were reported in minimal detail in the included studies. Ethnicity was reported in three studies. As a result, the specific population(s) to whom this data directly applies is unclear.

None of these trials were conducted in Australia. This participant data comes from Argentina, Brazil, Greece, Indonesia, Mexico, Nepal, South Africa, Spain, United Kingdom and the United States.

The Taskforce will continue to extract and identify characteristics relevant to equity, diversity and inclusion where available.

What are the main results?
Colchicine has no impact on risk of death (2 fewer per 1000; RR 0.99, CI 95% 0.93 to 1.06; 17,779 patients in 8 studies), mechanical ventilation (1 more per 1000; RR 1.01, CI 95% 0.91 to 1.12; 15,782 patients in 5 studies) or discharge from hospital. We are uncertain whether colchicine increases or decreases the likelihood of experiencing a serious adverse event. However, colchicine probably increases adverse events (119 more per 1000; RR 1.60, CI 95% 1.22 to 2.08; 6013 patients in 3 studies).

For the outcomes of discontinuation due to adverse events, clinical progression (defined as an increase of two grades on a seven-grade scale) and ICU admission, there were too few events to determine whether colchicine makes a

difference.

Our confidence in the results
Certainty of the evidence is high for risk of death, mechanical ventilation and discharge from hospital, and moderate for adverse and serious adverse events due to serious imprecision (wide confidence intervals). Certainty is low for discontinuation due to adverse events, clinical progression, admission to intensive care unit and discharge from hospital due to very serious imprecision (either reliance on a single study and wide confidence intervals, or few events).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
According to the Therapeutic Goods Administration, known acute harms for colchicine include diarrhoea and stomach cramps. Colchicine overdose can cause severe diarrhoea and dehydration, bone marrow suppression, metabolic acidosis and shock *[159]*. There are several known and potential interactions with other drugs *[159]*.

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.

Colchicine should be avoided in **pregnancy and during breastfeeding**, and in children under 2 years of age.

Caution should be taken when prescribing colchicine to **older people living with frailty or cognitive impairment** who may be more susceptible to cumulative toxicity.

Removal of studies
The following study, previously included as part of the evidence informing this recommendation, was removed from version 44 due to inconsistencies that were identified in the reported data (Salehdazeh et al. preprint posted to Research Square on 21 Sep 2020) *[163]*. Removal of this study did not change the strength or direction of the recommendation that was current at the time of its removal.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Colchicine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 21-28 days of commencing treatment 9 Critical	Relative risk 0.99 (CI 95% 0.93 — 1.06) Based on data from 17,779 participants in 8 studies. [1] (Randomized controlled)	152 per 1000 Difference:	150 per 1000 **2 fewer per 1000** (CI 95% 11 fewer — 9 more)	High	Colchicine does not impact death.
Mechanical ventilation Within 21–28 days of commencing treatment 9 Critical	Relative risk 1.01 (CI 95% 0.91 — 1.12) Based on data from 15,782 participants in 5 studies. [2] (Randomized controlled)	78 per 1000 Difference:	79 per 1000 **1 more per 1000** (CI 95% 7 fewer — 9 more)	High	Colchicine has little or no impact on mechanical ventilation.
Non-invasive ventilation NIV / High-flow	Relative risk 0.98 (CI 95% 0.14 — 6.7) Based on data from 379 participants in 2 studies.	12 per 1000	12 per 1000		

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Colchicine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
HFNO Within 28 days of commencing treatment 6 Important	[3]	Difference:	**0 fewer per 1000** (CI 95% 10 fewer — 68 more)		
Adverse events End of follow-up 6 Important	Relative risk 1.6 (CI 95% 1.22 — 2.08) Based on data from 6,013 participants in 5 studies. [4] (Randomized controlled)	199 per 1000 Difference:	318 per 1000 **119 more per 1000** (CI 95% 44 more — 215 more)	**Moderate** Due to serious imprecision [5]	Colchicine probably increases adverse events.
Serious adverse events End of follow-up 6 Important	Relative risk 0.78 (CI 95% 0.61 — 1) Based on data from 4,517 participants in 2 studies. [6] (Randomized controlled)	61 per 1000 Difference:	48 per 1000 **13 fewer per 1000** (CI 95% 24 fewer — 0 fewer)	**Moderate** Due to serious imprecision [7]	Colchicine probably has little impact on serious adverse events (247 events).
ICU admission Within 21 days of commencing treatment 6 Important	Relative risk 0.5 (CI 95% 0.15 — 1.58) Based on data from 452 participants in 3 studies. [8] (Randomized controlled)	38 per 1000 Difference:	19 per 1000 **19 fewer per 1000** (CI 95% 32 fewer — 22 more)	**Low** Due to very serious imprecision [9]	Colchicine may have little impact on ICU admission (12 events).
Discontinuation due to adverse events During treatment 6 Important	Based on data from 140 participants in 2 studies. [10] (Randomized controlled)			**Low** Due to very serious imprecision [11]	There were too few who discontinued due to adverse events to determine whether colchicine makes a difference (2 events).
Clinical progression Increase of 2 grades on 7-grade scale; 21 days after commencing treatment 6 Important	Relative risk 0.13 (CI 95% 0.02 — 1.02) Based on data from 105 participants in 1 studies. [12] (Randomized controlled)	140 per 1000 Difference:	18 per 1000 **122 fewer per 1000** (CI 95% 137 fewer — 3 more)	**Low** Due to very serious imprecision [13]	There were too few who experienced clinical deterioration to determine whether colchicine makes a difference (8 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Colchicine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Discharge from hospital End of treatment 6 Important	Relative risk 0.99 (CI 95% 0.97 — 1.01) Based on data from 11,375 participants in 2 studies. [14] (Randomized controlled)	704 per 1000 Difference:	697 per 1000 **7 fewer per 1000** (CI 95% 21 fewer — 7 more)	**High**	Colchicine has little or no impact on discharge from hospital.

Attached Images

7.2.4 Convalescent plasma

Not recommended

Do not use convalescent plasma for the treatment of COVID-19 in patients who require supplemental oxygen.

Additional information

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of convalescent plasma may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include convalescent plasma.

A related recommendation regarding the use of convalescent plasma in patients who do not require oxygen can be found here.

For a recent summary of the evidence, please see the Cochrane living systematic review of Convalescent plasma for people with COVID-19. The latest update published in February 2023 includes 33 randomised trials involving nearly 25 000 participants.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

General adult population
Evidence indicates no difference between convalescent plasma and standard care in incidence of death, requirement of mechanical ventilation or non-invasive ventilation, or discharge from hospital.

Although convalescent plasma may result in more adverse events and serious adverse events compared with standard care, it remains unclear if convalescent plasma is safe for the treatment of 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) *[95]*.

Certainty of the Evidence

Moderate

General adult population
Certainty of the evidence is moderate due to serious imprecision for mortality (wide confidence intervals) and non-invasive ventilation (reliance on a single study). Certainty is high for invasive mechanical ventilation and number of patients discharged from hospital.

Certainty of the evidence for the majority of remaining outcomes is low due to serious risk of bias (often as a result of poor reporting of baseline neutralising antibodies in included patients) and serious imprecision (wide confidence intervals). The exceptions are respiratory failure or ARDS, clinical recovery and negative PCR, for which certainty is very low (due to the above factors and also reliance on a single study).

For some outcomes, certainty has been downgraded due to the high prevalence of baseline neutralising antibodies (NAb) in trial participants. One study excluded patients with a NAb titer of 1:640 or lower *[96]*. Three studies did not report specific NAb titers of included patients *[100][104][106]*. The remaining studies detected NAb in 76% *[101]*, 49% *[99]*, 80% *[307]* and 54% *[103]* of patients at baseline. The RECOVERY trial measured neutralising antibodies in

81% of included patients at baseline, in which 62% were found to be SARS-CoV-2 seropositive *[107]*.

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.

Values and preferences

Substantial variability is expected or uncertain

General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this 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.

Resources

No important issues with the recommended alternative

As convalescent plasma is not recommended there are no resource considerations.

Equity

No important issues with the recommended alternative

As convalescent plasma is not recommended there are no equity considerations.

Acceptability

No important issues with the recommended alternative

As convalescent plasma is not recommended there are no acceptability considerations.

Feasibility

No important issues with the recommended alternative

As convalescent plasma is not recommended there are no feasibility considerations.

Clinical Question/ PICO

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

Summary

For the most recent summary of evidence, please see the Cochrane living systematic review of Convalescent plasma for people with COVID-19. The latest update published in February 2023 includes 33 randomised trials involving nearly 25 000 participants.

Evidence indicates that convalescent plasma is no more effective than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from 15 randomised trials that compared convalescent plasma with standard care in over 16,000 patients with COVID-19. The vast majority of data are from the RECOVERY trial, which included 11,558 adults hospitalised with mild-to-severe COVID-19 *[107]*, and REMAP-CAP, which included 2000 critically ill adults with COVID-19 *[368]*.

Publication status
One study is only available as a preprint and has therefore not been peer reviewed *[99]*.

Study characteristics
For a comprehensive description, see the study characteristics table.

Equity, diversity and inclusion

The characteristics of trial participants related to equity, diversity and inclusion (see technical report) were reported in minimal detail in the included studies. Ethnicity was reported in four studies and the reporting of ethnicity varied between trials. As a result, the specific population(s) to whom this data directly applies is unclear.

This participant data comes from Argentina, Australia, Bahrain, Brazil, Canada, Germany, India, Iran, Iraq, the Netherlands,, Saudi Arabia, Spain, United Kingdom and the United States.

The Taskforce will continue to extract and identify characteristics relevant to equity, diversity and inclusion where available.

What are the main results?
In the RECOVERY trial there was no significant difference in the primary endpoint of 28-day mortality in patients receiving convalescent plasma compared with usual care: 1399 (24%) of 5795 patients allocated to convalescent plasma and 1408 (24%) of 5763 patients allocated to usual care died within 28 days (RR 1.00, 95% CI 0.93 to 1.07). The 28-day mortality risk ratio was similar in all prespecified subgroups of patients.

When combined with data from the other included trials, results show that compared with standard care, convalescent plasma probably has little impact on risk of death (5 fewer per 1000; RR 0.98, CI 95% 0.93 to 1.04; 16,121 patients in 15 studies). In addition, convalescent plasma probably has little impact on the requirement of non-invasive ventilation and has no impact on the requirement of invasive mechanical ventilation or hospital discharge.

Convalescent plasma may increase the incidence of serious adverse events and adverse events, and also increase the rate of resolution of dyspnoea. We remain uncertain whether convalescent plasma has an impact on respiratory failure or acute respiratory distress syndrome (ARDS), admission to intensive care unit, clinical deterioration, clinical improvement, clinical recovery, negative polymerase chain reaction (PCR), time to improvement and time to discharge from hospital.

Our confidence in the results
Certainty of the evidence is high for invasive mechanical ventilation and number of patients discharged from hospital. Certainty is moderate due to serious imprecision for death (wide confidence intervals) and non-invasive ventilation (reliance on a single study).

Certainty for the majority of remaining outcomes is low due to serious risk of bias (often as a result of poor reporting of baseline neutralising antibodies in included patients) and serious imprecision (wide confidence intervals). The exceptions are respiratory failure or ARDS, clinical recovery and negative PCR, for which certainty is very low (due to the above factors and also reliance on a single study).

For some outcomes, certainty has been downgraded due to the high prevalence of baseline neutralising antibodies (NAb) in trial participants. One study excluded patients with a NAb titer of 1:640 or lower *[96]*. Eight studies did not report specific NAb titers of included patients *[100][104][106][336][337][338][356][368]*. Other studies detected NAb in 76% *[101]*, 49% *[99]*, 80% *[307]* and 54% *[103]* of patients at baseline. The RECOVERY trial measured neutralising antibodies in 81% of included patients at baseline, in which 62% were found to be SARS-CoV-2 seropositive *[107]*.

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence of these populations in the included studies).

Additional published studies
The following studies have been identified through our evidence surveillance processes. These studies are not included in the guideline but have been assessed by the evidence team as being highly unlikely to impact the current

recommendation(s). Although we have no current plans to include these studies, they may be incorporated in a future update of the guideline.

Trial and Source	Date	Number	Comparison & Population	Primary outcomes
Kirenga 2021 BMJ Open Respir Res	9 Aug	136	Convalescent plasma vs standard care in adults hospitalised with COVID-19	Time to viral clearance
Korley 2021 NEJM	18 Aug	511	Convalescent plasma vs placebo in high-risk outpatients with COVID-19	Disease progression
Devos 2021 Eur Respir J	26 Aug	483	Convalescent plasma vs standard care in adults hospitalised with COVID-19	Death or mechanical ventilation
Avendaño-Solá 2021 J Clin Invest	2 Sep	350	Convalescent plasma vs standard care in adults hospitalised with COVID-19	Disease progression
Bar 2021 J Clin Invest	17 Nov	80	Convalescent plasma vs standard care in adults hospitalised with COVID-19	Clinical severity score
Menichetti 2021 JAMA Netw Open	29 Nov	487	Convalescent plasma vs standard care in adults hospitalised with COVID-19	Death or mechanical ventilation
Ortigoza 2021 JAMA Intern Med	13 Dec	941	Convalescent plasma vs placebo in adults hospitalised with COVID-19	Clinical improvement

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Convalescent plasma	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.98 (CI 95% 0.93 — 1.04) Based on data from 16,121 participants in 15 studies. [1] (Randomized controlled)	256 per 1000 Difference:	251 per 1000 **5 fewer per 1000** (CI 95% 18 fewer — 10 more)	High	Convalescent plasma has no impact on death.
Invasive mechanical ventilation Within 28 days of commencing treatment 9 Critical	Relative risk 0.98 (CI 95% 0.89 — 1.08) Based on data from 11,898 participants in 4 studies. [2] (Randomized controlled)	124 per 1000 Difference:	122 per 1000 **2 fewer per 1000** (CI 95% 14 fewer — 10 more)	High	Convalescent plasma has no impact on invasive mechanical ventilation.
Respiratory failure or ARDS Within 28 days of commencing treatment 9 Critical	Relative risk 0.4 (CI 95% 0.08 — 2) Based on data from 160 participants in 1 studies. [3] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [4]	We are uncertain whether convalescent plasma increases or decreases respiratory failure or ARDS.
Non-invasive ventilation Within 28 days of commencing treatment	Relative risk 0.97 (CI 95% 0.89 — 1.05) Based on data from 7,005 participants in 1 studies. [5] (Randomized controlled)	239 per 1000 Difference:	232 per 1000 **7 fewer per 1000** (CI 95% 26 fewer — 12 more)	**Moderate** Due to serious imprecision [6]	Convalescent plasma probably has little or no impact on non-invasive ventilation.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Convalescent plasma	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important					
Serious adverse events Within 28 days of commencing treatment 6 Important	Relative risk 1.23 (CI 95% 0.95 — 1.6) Based on data from 3,420 participants in 5 studies. [7] (Randomized controlled)	102 per 1000 Difference:	125 per 1000 **23 more per 1000** (CI 95% 5 fewer — 61 more)	**Moderate** Due to serious imprecision [8]	Convalescent plasma probably has little impact on serious adverse events.
Adverse events Within 28 days of commencing treatment 6 Important	Relative risk 1.47 (CI 95% 0.38 — 5.74) Based on data from 457 participants in 3 studies. [9] (Randomized controlled)	395 per 1000 Difference:	581 per 1000 **186 more per 1000** (CI 95% 245 fewer — 1,872 more)	**Low** Due to serious risk of bias and serious imprecision [10]	Convalescent plasma may increase adverse events (222 events).
Clinical improvement Within 28 days of commencing treatment 6 Important	Relative risk 0.97 (CI 95% 0.86 — 1.1) Based on data from 595 participants in 3 studies. [11] (Randomized controlled)	668 per 1000 Difference:	648 per 1000 **20 fewer per 1000** (CI 95% 94 fewer — 67 more)	**Low** Due to serious risk of bias and serious imprecision [12]	Convalescent plasma may make little or no difference to clinical improvement at day 28 (388 events).
ICU admission Within 28 days of commencing treatment 6 Important	Relative risk 0.75 (CI 95% 0.36 — 1.59) Based on data from 493 participants in 2 studies. [13] (Randomized controlled)	373 per 1000 Difference:	280 per 1000 **93 fewer per 1000** (CI 95% 239 fewer — 220 more)	**Low** Due to serious risk of bias and imprecision [14]	Convalescent plasma may decrease ICU admission slightly (194 events).
Clinical deterioration (progression to severe/critical) [15] Within 28 days of commencing treatment 6 Important	Relative risk 0.71 (CI 95% 0.18 — 2.78) Based on data from 545 participants in 2 studies. [16] (Randomized controlled)	74 per 1000 Difference:	53 per 1000 **21 fewer per 1000** (CI 95% 61 fewer — 132 more)	**Low** Due to serious risk of bias and imprecision [17]	Convalescent plasma may have little impact on clinical deterioration (progression to severe/critical) at day 28 (37 events).
Clinical recovery	Relative risk 0.9 (CI 95% 0.76 — 1.06)			**Very low** Due to serious	We are uncertain whether convalescent

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Convalescent plasma	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Within 28 days of commencing treatment 6 Important	Based on data from 333 participants in 1 studies. [18] (Randomized controlled)			risk of bias and very serious imprecision [19]	plasma worsens clinical recovery (223 events).
Resolution of dyspnoea End of treatment 6 Important	Relative risk 1.21 (CI 95% 0.87 — 1.68) Based on data from 797 participants in 2 studies. [20] (Randomized controlled)	371 per 1000 Difference:	449 per 1000 **78 more per 1000** (CI 95% 48 fewer — 252 more)	**Low** Due to serious risk of bias and imprecision [21]	Convalescent plasma may increase resolution of dyspnoea slightly (285 events).
Viral nucleic acid negative 72 hours after commencing treatment 6 Important	Relative risk 2.33 (CI 95% 1.54 — 3.52) Based on data from 87 participants in 1 studies. [22] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [23]	Convalescent plasma may increase number of patients who are viral nucleic acid negative at 72 hours.
Hospital discharge Within 28 days of commencing treatment 6 Important	Relative risk 1 (CI 95% 0.97 — 1.02) Based on data from 12,233 participants in 5 studies. [24] (Randomized controlled)	666 per 1000 Difference:	666 per 1000 **0 fewer per 1000** (CI 95% 20 fewer — 13 more)	**High**	Convalescent plasma has little or no impact on hospital discharge.
Time to improvement Days 6 Important	Based on data from 382 participants in 2 studies. (Randomized controlled)	Rasheed 2020 (n=49) and Simonovich 2020 (n=333) both reported time to improvement, defined as a reduction of two or more points on an 8-point ordinal scale. Results in Rasheed favoured convalescent plasma (mean 4.5 days vs 8.5 days). Results in Simonovich showed no difference (12 days for both groups).		**Low** Due to serious risk of bias and imprecision [25]	We are uncertain whether convalescent plasma increases or decreases time to improvement.
Time to discharge from hospital Days 6 Important	Based on data from 797 participants in 2 studies. (Randomized controlled)	Agarwal 2020 (n=464) and Simonovich 2020 (n=333) both reported time to discharge from hospital. Both studies demonstrated slightly lower time to discharge in the control vs convalescent plasma group (median 13 days vs 14 days, and median 12 days vs 13 days, respectively).		**Low** Due to serious risk of bias and imprecision [26]	Convalescent plasma probably has little impact on time to discharge from hospital.

Attached Images

Only in research settings

Do not use convalescent plasma for the treatment of COVID-19 in patients who do not require oxygen outside of randomised trials with appropriate ethical approval.

Additional information

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 to treat COVID-19 in patients who do not require oxygen unless they are eligible to be enrolled in trials.

A related recommendation regarding the use of convalescent plasma in patients who require oxygen can be found here.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Convalescent plasma probably has little impact on all-cause mortality or the requirement of oxygen support, and may have little impact on mechanical ventilation or hospitalisation. We are uncertain whether convalescent plasma decreases incidence of acute respiratory failure or ICU admission.

Certainty of the Evidence

Moderate

Certainty of the evidence is moderate for all-cause mortality and requirement of oxygen support (due to reliance on a single study for the majority of outcome data), and low for mechanical ventilation and hospitalisation (due to wide confidence intervals and either few observed events or inconsistency in direction of effect).

Certainty is very low for ICU admission and acute respiratory failure due to reliance on a single study, wide confidence intervals and few observed events.

Values and preferences

Substantial variability is expected or uncertain

General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this 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

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

Equity

Important issues, or potential issues not investigated

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 may protect 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

Important issues, or potential issues not investigated

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

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

There is currently limited evidence about the impact of convalescent plasma on patient-relevant outcomes in the treatment of COVID-19 in patients who do not require oxygen. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that convalescent plasma should only be used to treat COVID-19 in patients who do not require oxygen the context of randomised trials with appropriate ethical approval.

Clinical Question/ PICO

Population: Patients with COVID-19 (no oxygen)
Intervention: Convalescent plasma
Comparator: Standard care

Summary

There remains uncertainty whether convalescent plasma is more effective and safer than standard care in treating patients with COVID-19 who do not require oxygen.

What is the evidence informing this recommendation?
Evidence comes from four randomised trials that compared convalescent plasma with standard care in 2634 adults with mild COVID-19 *[104][107][488][489]*.

Study characteristics
Mean age of participants ranged from 43 years (Sullivan 2022) to 77 years (Libster 2020). Only 8% of participants in the RECOVERY trial did not require supplemental oxygen at baseline—participant characteristics were not reported

separately for this population.

Median immunoglobulin G (IgG) titre ratios varied between trials. In Sullivan 2022 over 80% of participants received a single 250 ml infusion of plasma with a titre ratio of > 1:4860. Titres in the other studies were > 1:100 (RECOVERY; no mean/median provided for mild subgroup), > 1:1000 (Libster 2020) and median 1:1379 (Alemany 2022).

What are the main results?
Results demonstrate that convalescent plasma probably has little impact on all-cause mortality or the requirement of oxygen support, and may have little impact on mechanical ventilation or hospitalisation. We are uncertain whether convalescent plasma decreases incidence of acute respiratory failure or ICU admission.

Our confidence in the results
Certainty of the evidence is moderate for all-cause mortality and requirement of oxygen support (due to reliance on a single study for the majority of outcome data), and low for mechanical ventilation and hospitalisation (due to wide confidence intervals and either few observed events or inconsistency in direction of effect). Certainty is very low for ICU admission and acute respiratory failure due to reliance on a single study, wide confidence intervals and few observed events.

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Convalescent plasma	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Acute respiratory failure Within 28 days of treatment 9 Critical	Relative risk 0.4 (CI 95% 0.08 — 2) Based on data from 160 participants in 1 studies. [1] (Randomized controlled)	63 per 1000 Difference:	25 per 1000 **38 fewer per 1000** (CI 95% 58 fewer — 63 more)	**Very low** Due to extremely serious imprecision [2]	We are uncertain whether convalescent plasma increases or decreases acute respiratory failure (7 events).
Mechanical ventilation Within 28 days of treatment 9 Critical	Relative risk 0.5 (CI 95% 0.15 — 1.64) Based on data from 536 participants in 2 studies. [3] (Randomized controlled)	30 per 1000 Difference:	15 per 1000 **15 fewer per 1000** (CI 95% 25 fewer — 19 more)	**Low** Due to very serious imprecision [4]	Convalescent plasma may have little impact on mechanical ventilation (12 events).
Oxygen support required Within 28 days of treatment 6 Important	Relative risk 0.46 (CI 95% 0.23 — 0.9) Based on data from 1,181 participants in 1 studies. [5] (Randomized controlled)	44 per 1000 Difference:	20 per 1000 **24 fewer per 1000** (CI 95% 34 fewer — 4 fewer)	**Moderate** Due to serious imprecision [6]	Convalescent plasma probably has little impact on oxygen support required (38 events).
ICU admission Within 28 days of treatment	Relative risk 0.33 (CI 95% 0.07 — 1.6) Based on data from 160 participants in 1 studies.	75 per 1000 Difference:	25 per 1000 **50 fewer per**	**Very low** Due to extremely serious imprecision [8]	We are uncertain whether convalescent plasma increases or decreases ICU

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Convalescent plasma	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important	[7] (Randomized controlled)		**1000** (CI 95% 70 fewer — 45 more)		admission (8 events).
All-cause mortality Within 28 days of treatment 9 Critical	Relative risk 0.8 (CI 95% 0.58 — 1.11) Based on data from 2,238 participants in 3 studies. [9] (Randomized controlled)	68 per 1000 Difference:	54 per 1000 **14 fewer per 1000** (CI 95% 29 fewer — 7 more)	**Moderate** Due to serious imprecision [10]	Convalescent plasma probably has little impact on death (134 events).
Hospitalisation Within 28 days of treatment 6 Important	Relative risk 0.69 (CI 95% 0.31 — 1.56) Based on data from 1,557 participants in 2 studies. [11] (Randomized controlled)	75 per 1000 Difference:	52 per 1000 **23 fewer per 1000** (CI 95% 52 fewer — 42 more)	**Low** Due to serious imprecision and serious inconsistency [12]	Convalescent plasma may have little impact on hospitalisation (97 events).

Attached Images

7.2.5 Favipiravir

Not recommended

Do not use favipiravir for the treatment of COVID-19.

Additional information

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of favipiravir may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include favipiravir.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Important harms

Evidence demonstrates no benefit when using favipiravir to treat patients with COVID-19 with regards to mortality. Although incidence of serious adverse events is similar between groups, patients treated with favipiravir experienced a higher incidence of adverse events.

Certainty of the Evidence

Moderate

Certainty of evidence is moderate for all-cause mortality (due to serious imprecision based on limited events) and low for mechanical ventilation (due to very serious imprecision based on limited events and wide confidence intervals).

Certainty of evidence is high for adverse events, and moderate for hospitalisation, ICU admission and serious adverse events (due to wide confidence intervals and/or inconsistency in direction of effect). Certainty for all remaining outcomes was low or very low.

Values and preferences

Substantial variability is expected or uncertain

General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this 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.

Resources

No important issues with the recommended alternative

As favipiravir is not recommended there are no resource considerations.

Equity

No important issues with the recommended alternative

As favipiravir is not recommended there are no equity considerations.

Acceptability

No important issues with the recommended alternative

As favipiravir is not recommended there are no acceptability considerations.

Feasibility

No important issues with the recommended alternative

As favipiravir is not recommended there are no feasibility considerations.

Rationale

Based on the available evidence, favipiravir is no more effective than standard care in treating patients with COVID-19 and may increase the incidence of adverse events. We therefore recommend that favipiravir should not be used.

Clinical Question/ PICO

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

Summary

Evidence indicates that favipiravir is no more effective than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from 13 randomised trials that compared favipiravir with standard care or placebo in 3,360 participants *[542][543][544][545][546][547][548][549][550][551][552][553][563]*. Participants within included trials ranged in disease severity from mild to critical; however results demonstrated no difference in safety and/or effectiveness between these populations.

Study characteristics
The mean age of participants within included trials ranged from 36 to 63 years, and the proportion of females included within trials ranged from 33% to 55%. Trials varied considerably with regards to disease severity, presence of risk factors for disease progression and outcomes reported. All trials were in unvaccinated participants and all trials were conducted prior to Omicron becoming the dominant circulating variant.

Equity, diversity and inclusion

The characteristics of trial participants related to equity, diversity and inclusion (see technical report) were reported in minimal detail in the included studies. Ethnicity was reported in four studies and the reporting of ethnicity varied between trials. As a result, the specific population(s) to whom this data directly applies is unclear.

This participant data comes from Australia, Bahrain, Bangkok, Brazil, China, India, Japan, Kuwait, Malaysia, Mexico, Russia, Saudi Arabia, United Kingdom and the United States.

The Taskforce will continue to extract and identify characteristics relevant to equity, diversity and inclusion where available.

What are the main results?
Favipiravir probably has no impact on risk of death (4 more per 1000; RR 1.44, CI 95% 0.73 to 2.84; 2,982 participants in 10 studies), serious adverse events, hospitalisation or admission to ICU; however it increases the incidence of adverse events (75 more per 1000; RR 1.41 CI 95% 1.08 to 1.84; 3,091 participants in 10 studies). We are uncertain whether favipiravir has an impact on mechanical ventilation, respiratory failure/ ARDS, clinical improvement, discharge from hospital, or discontinuation due to adverse events.

Our confidence in the results
Certainty of the evidence is moderate for all-cause mortality (due to serious imprecision based on limited events). For other critical outcomes, certainty is low for mechanical ventilation (very serious imprecision based on low event

numbers and wide confidence intervals) and very low for respiratory failure or ARDS (extremely serious imprecision based on low event numbers, wide confidence intervals, reliance on a single study with few participants).

For important outcomes, certainty of the evidence is high for adverse events, moderate for hospitalisation and ICU admission (due to serious imprecision based on wide confidence intervals), and low for clinical improvement, discontinuation due to adverse events and discharge from hospital (all due to very serious imprecision, based on a combination of wide confidence intervals, low event numbers and/or inconsistency in direction of effect).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Favipiravir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality End of follow-up 9 Critical	Relative risk 1.44 (CI 95% 0.73 — 2.84) Based on data from 2,982 participants in 10 studies. [1] (Randomized controlled)	8 per 1000 Difference:	12 per 1000 **4 more per 1000** (CI 95% 2 fewer — 15 more)	**Moderate** Due to serious imprecision [2]	Favipiravir probably has little impact on death (34 events).
Mechanical ventilation End of follow-up 9 Critical	Relative risk 1.23 (CI 95% 0.41 — 3.71) Based on data from 687 participants in 3 studies. [3] (Randomized controlled)	16 per 1000 Difference:	20 per 1000 **4 more per 1000** (CI 95% 9 fewer — 43 more)	**Low** Due to very serious imprecision [4]	Favipiravir may have little impact on mechanical ventilation (12 events).
Respiratory failure or ARDS 28 days after commencing treatment 9 Critical	Relative risk 1.11 (CI 95% 0.39 — 3.19) Based on data from 19 participants in 1 studies. [5] (Randomized controlled)	400 per 1000 Difference:	444 per 1000 **44 more per 1000** (CI 95% 244 fewer — 876 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision [6]	We are uncertain whether favipiravir increases or decreases respiratory failure or ARDS (8 events).
Serious adverse events End of follow-up 6 Important	Relative risk 1.19 (CI 95% 0.74 — 1.92) Based on data from 2,162 participants in 6 studies. [7] (Randomized controlled)	28 per 1000 Difference:	33 per 1000 **5 more per 1000** (CI 95% 7 fewer — 26 more)	**Moderate** Due to serious imprecision [8]	Favipiravir probably has little impact on serious adverse events (67 events).
Adverse events End of follow-up 6 Important	Relative risk 1.41 (CI 95% 1.08 — 1.84) Based on data from 3,091 participants in 10 studies. [9] (Randomized controlled)	183 per 1000 Difference:	258 per 1000 **75 more per 1000** (CI 95% 15 more — 154 more)	**High**	Favipiravir increases adverse events.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Favipiravir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Discontinuation due to adverse events End of follow-up 6 Important	Relative risk 1.24 (CI 95% 0.25 — 6.25) Based on data from 228 participants in 2 studies. [10] (Randomized controlled)	26 per 1000 Difference:	32 per 1000 **6 more per 1000** (CI 95% 20 fewer — 137 more)	**Low** Due to very serious imprecision [11]	Favipiravir may have little impact on discontinuation due to adverse events (7 events).
Hospitalisation End of follow-up 6 Important	Relative risk 1.41 (CI 95% 0.75 — 2.68) Based on data from 703 participants in 4 studies. [12] (Randomized controlled)	51 per 1000 Difference:	72 per 1000 **21 more per 1000** (CI 95% 13 fewer — 86 more)	**Moderate** Due to serious imprecision [13]	Favipiravir probably has little impact on hospitalisation (40 events).
ICU admission End of follow-up 6 Important	Relative risk 1.07 (CI 95% 0.55 — 2.08) Based on data from 1,005 participants in 4 studies. [14] (Randomized controlled)	36 per 1000 Difference:	39 per 1000 **3 more per 1000** (CI 95% 16 fewer — 39 more)	**Moderate** Due to serious imprecision [15]	Favipiravir probably has little impact on ICU admission (37 events).
Discharge from hospital End of follow-up 6 Important	Relative risk 1.01 (CI 95% 0.94 — 1.08) Based on data from 394 participants in 2 studies. [16] (Randomized controlled)	879 per 1000 Difference:	888 per 1000 **9 more per 1000** (CI 95% 53 fewer — 70 more)	**Low** Due to serious imprecision and serious inconsistency [17]	Favipiravir may have little impact on discharge from hospital.
Clinical improvement End of follow-up 6 Important	Relative risk 1.16 (CI 95% 0.96 — 1.41) Based on data from 521 participants in 2 studies. [18] (Randomized controlled)	278 per 1000 Difference:	322 per 1000 **44 more per 1000** (CI 95% 11 fewer — 114 more)	**Low** Due to serious imprecision and serious inconsistency [19]	Favipiravir may increase clinical improvement slightly.

Attached Images

7.2.6 Hydroxychloroquine

Not recommended

Do not use hydroxychloroquine for the treatment of COVID-19.

Additional information

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of hydroxychloroquine may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include hydroxychloroquine.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Important harms

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.

Certainty of the Evidence

High

General adult population
Certainty of the evidence is high for death, number of patients requiring mechanical ventilation and number of patients discharged from hospital at day 28. Certainty is moderate for number of patients requiring ventilation (due to reliance on a single study), adverse events and serious adverse events (due to lack of blinding of patients and personnel). Certainty is low for hospitalisation (due to lack of blinding and low number of events) and for virological clearance and duration of hospital stay (due to low number of patients and reliance on a single/two small studies).

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

Values and preferences

We expect few to want the intervention

The Consumer Panel believes that as there is substantial evidence demonstrating well-known harms of hydroxychloroquine, informed patients would not choose this treatment.

Resources

No important issues with the recommended alternative

As hydroxychloroquine is not recommended there are no resource considerations.

Equity

No important issues with the recommended alternative

As hydroxychloroquine is not recommended there are no equity considerations.

Acceptability

No important issues with the recommended alternative

As hydroxychloroquine is not recommended there are no acceptability considerations.

Feasibility

No important issues with the recommended alternative

As hydroxychloroquine is not recommended there are no feasibility considerations.

Rationale

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 not be used.

Clinical Question/ PICO

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

Summary

Evidence indicates that hydroxychloroquine is potentially harmful and no more effective than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from 22 randomised trials that compared hydroxychloroquine with standard care in over 10,600 patients (see table for references). The majority of evidence comes from the RECOVERY and SOLIDARITY trials, which randomised 4716 and 1853 patients hospitalised with COVID-19, respectively *[127][49]*.

Publication status
Three studies, which contribute fewer than 150 patients to the results, are only available as preprints and have therefore not been peer reviewed *[111][116][304]*.

See table at the end of this summary for details of additional studies of hydroxychloroquine not yet included in the guideline.

Removal of studies
Version 44: Due to inconsistencies which have been identified in the data reported in the study by Abd-Elsalam et al. (Am J Med Hyg, 14 Aug 2020) *[123]*, this study has been removed from our analyses. The study contributed data to two outcomes (death and invasive mechanical ventilation) and the removal of these data did not change the strength or direction of the recommendation.

Study characteristics
Mean or median age across the trials ranged from 37 to 66 years, with the exception of one study in which the median age was 77 years *[131]*. The proportion of women ranged from 20 to 72% with the exception of one study in which only 1.5% of participants were women *[136]*. In the two largest trials, women comprised approximately 40% of included patients. There was significant variability in disease severity among patients included in the trials (see table).

Disease severity	Number of patients	References
Mild	1405	*[117][118][135][155][304]*
Mild-Moderate	916	*[122][130][131][136]*
Moderate	192	*[110][111][116][444]*
Mild-Moderate-Severe	2676	*[49][114][129]*
Moderate-Severe	4881	*[124][126][127]*

Severe	612	*[305][306][366]*

Equity, diversity and inclusion

The characteristics of trial participants related to equity, diversity and inclusion (see technical report) were reported in minimal detail in the included studies. Ethnicity was reported in eight studies and the reporting of ethnicity varied between trials. As a result, the specific population(s) to whom this data directly applies is unclear.

This participant data comes from Albania, Australia, Austria, Brazil, Canada, China, Colombia, Egypt, Finland, France, Honduras, India, Indonesia, Iran, Iceland, Ireland, Italy, Kuwait, India, Japan, Kuwait, Lebanon, Lithuania, Luxemburg, Malaysia, Mexico, Monaco, North Macedonia, Norway, Pakistan, Qatar, Saudi Arabia, South Africa, Spain, Switzerland, Taiwan and the united Kingdom.

The Taskforce will continue to extract and identify characteristics relevant to equity, diversity and inclusion where available.

What are the main results?
Hydroxychloroquine has little or no impact on the two critical outcomes of death and the need for mechanical ventilation. For every 1000 patients given hydroxychloroquine, 10 more are likely to die compared with those receiving standard care (RR 1.06, CI 95% 0.97 to 1.16; 10,382 patients in 19 studies) and seven more are likely to require mechanical ventilation (RR 1.08, CI 95% 0.91 to 1.28; 5701 patients in 8 studies). Hydroxychloroquine also has little or no impact on the number of patients requiring any form of ventilation (i.e. non-invasive ventilation, invasive mechanical ventilation and extracorporeal membrane oxygenation [ECMO]) or the number of patients discharged from hospital at day 28.

Hydroxychloroquine probably increases the risk of adverse events (216 more per 1000 patients (RR 1.67, CI 95% 1.21 to 2.30; 2077 patients in 11 studies)) but probably has little impact on serious adverse events (6 more per 1000 patients (RR 1.09, CI 95% 0.86 to 1.37; 2721 patients in 11 studies)).

For all other outcomes—virological clearance, hospitalisation and discharge from hospital—we are uncertain if hydroxychloroquine makes a difference compared with standard care.

Our confidence in the results
Certainty of the evidence is high for death, number of patients requiring mechanical ventilation and number of patients discharged from hospital at day 28. Certainty is moderate for number of patients requiring any form of ventilation (due to reliance on a single study), adverse or serious adverse events (due to lack of blinding of patients and personnel). Certainty is low for hospitalisation (due to lack of blinding and low number of events) and for virological clearance and duration of hospital stay (due to low number of patients and reliance on a single/two small studies).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
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 cardiomyopathy *[115]*. There are several known and potential interactions with other drugs *[115]*. Overdose of hydroxychloroquine may have potentially fatal complications. In pregnancy, it is only recommended when benefits outweigh harms *[115]*.

Paediatricians have considerable experience with hydroxychloroquine in **children and adolescents** for other indications. To date, no specific information on the benefits or harms of hydroxychloroquine use has been collected in this population.

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 *[119][120]*. There is no evidence to suggest that stillbirth, preterm birth, low birth weight or early childhood disability are more common following treatment with hydroxychloroquine *[119][120][121]*. While this evidence is reassuring, further research is needed.

Additional published studies
The following studies have been identified through our evidence surveillance processes. These studies are not included in the guideline but have been assessed by the evidence team as being highly unlikely to impact the current recommendation(s). Although we have no current plans to include these studies, they may be incorporated in a future update of the guideline.

Trial and Source	Date	Number	Comparison & Population	Primary outcomes
Schwartz 2021 CMAJ Open	18 Jun	148	HCQ vs placebo in community-dwelling individuals with confirmed COVID-19	Composite outcome of hospitalisation, IMV or death at 28 days
REMAP-CAP 2021 Intensive Care Med	12 Jul	412	HCQ vs standard care in critically ill patients	Organ support-free days
Gupta 2021 Med J Armed Forces India	26 Jul	110	HCQ vs standard care in moderate to severely ill patients	Days of hospitalisation until discharge or death
Byakika-Kibwika 2021 BMC Infect Dis	6 Dec	105	HCQ vs standard care in adults with non-severe COVID-19	Viral clearance; symptom resolution

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Hydroxychloroquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality End of follow-up 9 Critical	Relative risk 1.06 (CI 95% 0.97 — 1.16) Based on data from 10,188 participants in 18 studies. [1] (Randomized controlled)	169 per 1000 Difference:	179 per 1000 **10 more per 1000** (CI 95% 5 fewer — 27 more)	High	Hydroxychloroquine does not decrease death.
Invasive mechanical ventilation or ECMO End of follow-up 9 Critical	Relative risk 1.09 (CI 95% 0.9 — 1.32) Based on data from 5,507 participants in 7 studies. [2] (Randomized controlled)	86 per 1000 Difference:	94 per 1000 **8 more per 1000** (CI 95% 9 fewer — 28 more)	High	Hydroxychloroquine has no impact on the need for invasive mechanical ventilation or ECMO.
Patients requiring ventilation [3] Within 28 days of commencing treatment 6 Important	Relative risk 1.09 (CI 95% 0.79 — 1.49) Based on data from 1,686 participants in 1 studies. [4] (Randomized controlled)	80 per 1000 Difference:	87 per 1000 **7 more per 1000** (CI 95% 17 fewer — 39 more)	Moderate Due to serious imprecision [5]	Hydroxychloroquine probably has little impact on number of patients requiring ventilation (141 events).
Serious adverse events End of follow-up 6 Important	Relative risk 1.09 (CI 95% 0.86 — 1.37) Based on data from 2,721 participants in 11 studies. [6]	68 per 1000 Difference:	74 per 1000 **6 more per 1000** (CI 95% 10 fewer — 25 more)	Moderate Due to serious risk of bias	Hydroxychloroquine probably has little impact on serious adverse events

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Hydroxychloroquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Adverse events End of follow-up 6 Important	Relative risk 1.67 (CI 95% 1.21 — 2.3) Based on data from 2,077 participants in 11 studies. [7]	322 per 1000 Difference:	538 per 1000 **216 more per 1000** (CI 95% 68 more — 419 more)	**Moderate** Due to serious risk of bias	Hydroxychloroquine probably increases adverse events.
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.98 (CI 95% 0.96 — 1.01) Based on data from 7,365 participants in 5 studies. [8]	694 per 1000 Difference:	680 per 1000 **14 fewer per 1000** (CI 95% 28 fewer — 7 more)	**High**	Hydroxychloroquine has little impact on discharge from hospital.
Discontinuation due to adverse events During treatment 6 Important	Relative risk 2.13 (CI 95% 0.65 — 6.95) Based on data from 398 participants in 2 studies. [9]	20 per 1000 Difference:	43 per 1000 **23 more per 1000** (CI 95% 7 fewer — 119 more)	**Low** Due to very serious imprecision	We are uncertain whether hydroxychloroquine decreases or increases treatment discontinuation due to adverse events (12 events).
Clinical improvement Within 28 days after commencing treatment 6 Important	Relative risk 1.05 (CI 95% 0.91 — 1.2) Based on data from 247 participants in 1 studies. [10] (Randomized controlled)	756 per 1000 Difference:	794 per 1000 **38 more per 1000** (CI 95% 68 fewer — 151 more)	**Low** Due to very serious imprecision [11]	We are uncertain whether hydroxychloroquine improves or worsens clinical improvement (191 events).
Clinical deterioration Within 28 days after commencing treatment 6 Important	Relative risk 0.81 (CI 95% 0.35 — 1.89) Based on data from 247 participants in 1 studies. [12] (Randomized controlled)	89 per 1000 Difference:	72 per 1000 **17 fewer per 1000** (CI 95% 58 fewer — 79 more)	**Low** Due to very serious imprecision [13]	We are uncertain whether hydroxychloroquine improves or worsens clinical deterioration (20 events).
Virological clearance (negative PCR) Day 6-14 of treatment 6 Important	Relative risk 1.02 (CI 95% 0.93 — 1.11) Based on data from 750 participants in 5 studies. [14]	410 per 1000 Difference:	418 per 1000 **8 more per 1000** (CI 95% 29 fewer — 45 more)	**Low** Due to very serious imprecision	Hydroxychloroquine may have little impact on virological clearance (negative PCR).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Hydroxychloroquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Hospitalisation End of follow up 6 Important	Relative risk 0.68 (CI 95% 0.41 — 1.13) Based on data from 1,345 participants in 5 studies. [15]	55 per 1000 Difference:	37 per 1000 **18 fewer per 1000** (CI 95% 32 fewer — 7 more)	**Low** Due to serious imprecision and serious risk of bias	We are uncertain whether hydroxychloroquine decreases or increases hospitalisation (62 events).
Duration of hospital stay Days 6 Important	Based on data from 128 participants in 1 studies. [16] (Randomized controlled)	6.8 (Mean) Difference:	9.75 (Mean) **MD 2.95 higher** (CI 95% 0.07 higher — 5.83 higher)	**Low** Due to very serious imprecision [17]	We are uncertain whether hydroxychloroquine increases or decreases duration of hospital stay.

Attached Images

7.2.7 Hydroxychloroquine plus azithromycin

Not recommended

Do not use hydroxychloroquine plus azithromycin for the treatment of COVID-19.

Additional information

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Although certainty of the evidence is low, this recommendation is supported by the observation that neither hydroxychloroquine nor azithromycin as standalone treatments demonstrate a benefit when administered to patients with COVID-19.

This is a moderate priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Important harms

There are concerns regarding the safety of hydroxychloroquine plus azithromycin. Hydroxychloroquine has several known and potential interactions with other drugs. See the Summary for details of the adverse events of hydroxychloroquine and azithromycin when administered individually.

Certainty of the Evidence

Low

General adult population
Certainty of the evidence is low for the critical outcomes of death at day 15 and the need for invasive mechanical ventilation due to very serious imprecision (wide confidence intervals and reliance on a single study), and very low for death at the end of treatment due to serious risk of bias and very serious imprecision (wide confidence intervals and no events).

Certainty of the evidence is low for the important outcomes of adverse events, hospitalisation and virological clearance (negative PCR) due to serious risk of bias (lack of patient and personnel blinding) and serious imprecision (wide confidence intervals, few events or reliance on a single study). Certainty is very low for all remaining outcomes (serious adverse events, discharge from hospital and duration of hospital stay).

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 for all outcomes because of indirectness due to limited inclusion (or absence) of these populations in the trials.

Values and preferences

Substantial variability is expected or uncertain

General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this 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.

Resources

No important issues with the recommended alternative

As hydroxychloroquine plus azithromycin is not recommended there are no resource considerations.

Equity

No important issues with the recommended alternative

As hydroxychloroquine plus azithromycin is not recommended there are no equity considerations.

Acceptability

No important issues with the recommended alternative

As hydroxychloroquine plus azithromycin is not recommended there are no acceptability considerations.

Feasibility

No important issues with the recommended alternative

As hydroxychloroquine plus azithromycin is not recommended there are no feasibility considerations.

Rationale

General adult population

There is currently limited evidence about the effect of hydroxychloroquine plus azithromycin on patient-relevant outcomes in the treatment of COVID-19. However, when used individually, neither of these treatments has demonstrated improvements in clinical outcomes. We therefore recommend that hydroxychloroquine plus azithromycin should not be used to treat COVID-19.

Clinical Question/ PICO

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

Summary

There remains significant uncertainty whether hydroxychloroquine plus azithromycin is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?

Evidence comes from three randomised trials that compared hydroxychloroquine plus azithromycin with standard care. One trial included 444 adults hospitalised with moderate illness (345 with laboratory-confirmed COVID-19) *[122]* and two included 464 adult outpatients with mild COVID-19 *[135][136]*.

Study characteristics

Mean age of participants ranged from 37 to 50 years across the three studies. There were significant differences in the proportion of women enrolled: 43% in Cavalcanti et al., 57% in Johnston et al. and only 1% in Omrani et al. Pregnant women were ineligible in all studies.

Equity, diversity and inclusion

The characteristics of trial participants related to equity, diversity and inclusion (see technical report) were reported in minimal detail in the included studies. Ethnicity was reported in one study. As a result, the specific population(s) to whom this data directly applies is unclear.

None of these trials were conducted in Australia. This participant data comes from Brazil, Qatar and the United States.

The Taskforce will continue to extract and identify characteristics relevant to equity, diversity and inclusion where available.

What are the main results?

For death and serious adverse events, there were too few events (eight deaths and seven who experienced serious

adverse events) to determine whether hydroxychloroquine plus azithromycin makes a difference. We are uncertain whether hydroxychloroquine plus azithromycin increases or decreases the likelihood of invasive mechanical ventilation, discharge from hospital and incidence of hospitalisation, but it may increase slightly the duration of hospital stay and virological clearance (negative polymerase chain reaction [PCR]), and result in more adverse events.

Our confidence in the results
Certainty of the evidence is low or very low for all outcomes. This judgement is based on serious or very serious imprecision (wide confidence intervals, reliance on a single study and/or few observed events) and/or serious risk of bias (lack of blinding).

Additional information
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 cardiomyopathy. There are several known and potential interactions with other drugs. Overdose of hydroxychloroquine may have potentially fatal complications. In pregnancy, it is only recommended when benefits outweigh harms *[115]*.

For azithromycin, reported adverse events are generally mild or moderate and include rash, heart palpitations, urinary tract infection, dizziness, headache, fatigue and gastrointestinal symptoms such as dyspepsia and vomiting *[88]*.

In addition to the known harms associated with hydroxychloroquine and azithromycin, there are concerns regarding the safety of combination treatment using these two therapeutics.

Paediatricians have considerable experience with hydroxychloroquine in **children and adolescents** for other indications. To date, no specific information on the benefits or harms of hydroxychloroquine use has been collected in this population. The safety and effectiveness of azithromycin powder for solution for infusion for the treatment of infections in children has not been established. Infantile hypertrophic pyloric stenosis (IHPS) has been reported following the use of azithromycin in neonates (treatment up to 42 days of life) *[88]*.

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 *[119][120]*. There is no evidence to suggest that stillbirth, preterm birth, low birth weight or early childhood disability are more common following treatment with hydroxychloroquine *[119][120][121]*. While this evidence is reassuring, further research is needed. Azithromycin is classified as a Category B1 drug (drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed).

Additional published studies
The following studies have been identified through our evidence surveillance processes. These studies are not included in the guideline but have been assessed by the evidence team as being highly unlikely to impact the current recommendation(s). Although we have no current plans to include these studies, they may be incorporated in a future update of the guideline.

Trial and Source	Date	Number	Comparison & Population	Prima
Sivapalan 2021 Eur Respir J	3 Jun	117	Azithromycin plus hydroxychloroquine vs placebo in hospitalised adults	Alive hospi
Rodrigues 2021 Int J Antimicrob Agents	25 Aug	84	Azithromycin plus hydroxychloroquine vs placebo in outpatients with early and mild infection	Viral

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** HCQ+AZM	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 15 days of commencing treatment	Relative risk 0.6 (CI 95% 0.15 — 2.49) Based on data from 345 participants in 1 studies. [1] (Randomized	29 per 1000 Difference:	17 per 1000 **12 fewer per 1000**	**Low** Due to very serious imprecision [2]	There were too few who died to determine whether hydroxychloroquine plus azithromycin makes a difference (8 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** HCQ+AZM	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical	controlled)		(CI 95% 25 fewer — 43 more)		
All-cause mortality End of follow-up 9 Critical	Based on data from 459 participants in 2 studies. [3] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [4]	We are uncertain whether Hydroxychloroquine plus azithromycin increases or decreases all-cause mortality (0 events)
Invasive mechanical ventilation Within 15 days of commencing treatment 9 Critical	Relative risk 1.59 (CI 95% 0.8 — 3.18) Based on data from 345 participants in 1 studies. [5] (Randomized controlled)	**69** per 1000 Difference:	**110** per 1000 **41 more per 1000** (CI 95% 14 fewer — 150 more)	**Low** Due to very serious imprecision [6]	We are uncertain whether hydroxychloroquine plus azithromycin increases or decreases the need for invasive mechanical ventilation (31 events).
Adverse events End of follow-up 6 Important	Relative risk 2.38 (CI 95% 1.05 — 5.37) Based on data from 576 participants in 2 studies. [7] (Randomized controlled)	**173** per 1000 Difference:	**412** per 1000 **239 more per 1000** (CI 95% 9 more — 756 more)	**Low** Due to serious risk of bias and serious imprecision [8]	Hydroxychloroquine plus azithromycin may increase adverse events (158 events)
Serious adverse events End of follow-up 6 Important	Relative risk 1.85 (CI 95% 0.36 — 9.43) Based on data from 715 participants in 2 studies. [9] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [10]	There were too few who experienced a serious adverse event to determine whether hydroxychloroquine plus azithromycin makes a difference (7 events).
Discharge from hospital Within 15 days of commencing treatment 6 Important	Relative risk 0.96 (CI 95% 0.86 — 1.08) Based on data from 345 participants in 1 studies. [11] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [12]	Hydroxychloroquine plus azithromycin may have little impact on discharge from hospital (266 events).
Hospitalisation End of follow-up 6 Important	Relative risk 0.77 (CI 95% 0.09 — 6.83) Based on data from 459 participants in 2 studies. [13] (Randomized controlled)	**13** per 1000 Difference:	**10** per 1000 **3 fewer per 1000** (CI 95% 12 fewer — 76 more)	**Low** Due to very serious imprecision [14]	Hydroxychloroquine plus azithromycin may have little or no difference on hospitalisation (5 events)

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** HCQ+AZM	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Virological clearance (negative PCR) End of follow-up 6 Important	Relative risk 0.64 (CI 95% 0.43 — 0.96) Based on data from 292 participants in 1 studies. [15] (Randomized controlled)	315 per 1000 Difference:	202 per 1000 **113 fewer per 1000** (CI 95% 180 fewer — 13 fewer)	**Low** Due to very serious imprecision [16]	Hydroxychloroquine plus azithromycin may decrease virological clearance slightly (75 events)
Duration of hospital stay Days 6 Important	Based on data from 345 participants in 1 studies. [17] (Randomized controlled)	9.5 (Mean) Difference:	10.3 (Mean) **MD 0.8 higher** (CI 95% 0.85 lower — 2.45 higher)	**Very low** Due to serious risk of bias and very serious imprecision [18]	We are uncertain if hydroxychloroquine plus azithromycin increases duration of hospital stay.

Attached Images

7.2.8 Interferon beta-1a

Not recommended

Do not use subcutaneous or intravenous interferon β-1a for the treatment of COVID-19.

Additional information

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of subcutaneous or intravenous interferon β-1a may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include interferon β-1a.

Information regarding the use of inhaled interferon β-1a for the treatment of COVID-19 can be found here.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Important harms

General adult population
Subcutaneous and intravenous interferon β-1a does not impact on the incidence of death or number of patients requiring ventilation. Although included trials did not report on adverse or serious adverse events, 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

High

General adult population
Certainty of the evidence is high for death, patients requiring ventilation and discharge from hospital. For the remaining outcomes (septic shock and duration of hospital stay), certainty is very low due to non-blinding of patients and personnel, reliance on a single study, low patient and event numbers and wide confidence intervals.

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.

Values and preferences

Substantial variability is expected or uncertain

General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while

some patients may choose to participate in clinical trials of this 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.

Resources

Important issues, or potential issues not investigated

As interferon β-1a is not recommended there are no resource considerations.

Equity

Important issues, or potential issues not investigated

As interferon β-1a is not recommended there are no equity considerations.

Acceptability

Important issues, or potential issues not investigated

As interferon β-1a is not recommended there are no acceptability considerations.

Feasibility

Important issues, or potential issues not investigated

As interferon β-1a is not recommended there are no feasibility considerations.

Rationale

Based on the available evidence, interferon β-1a administered subcutaneously or intravenously is no more effective than standard care in treating patients with COVID-19. We therefore recommend that interferon β-1a should not be used.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Interferon β-1a
Comparator: Standard care

Summary

Evidence indicates that interferon β-1a given subcutaneously or intravenously is no more effective than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from four randomised trials that compared subcutaneous or intravenous interferon β-1a with standard care in 4646 patients hospitalised with COVID-19 *[49][140][452][477]*. The vast majority of data come from the WHO SOLIDARITY trial, which included 4100 adults hospitalised with moderate to critical COVID-19 *[49]*.

Study characteristics
In the SOLIDARITY trial, 35% of patients were under 50 years of age, 46% were aged 50–69 years, and 19% were 70 years or older; 37% were women.

In the SOLIDARITY trial, patients received three doses of interferon β-1a (44 µg subcutaneously) over 6 days, while patients on high-flow oxygen, ventilators or extracorporeal membrane oxygenation (ECMO) were given 10 µg intravenously once daily for 6 days.

Equity, diversity and inclusion

The characteristics of trial participants related to equity, diversity and inclusion (see technical report) were reported in minimal detail in the included studies. As a result, the specific population(s) to whom this data directly applies is unclear.

This participant data comes from Albania, Argentina, Australia, Austria, Belgium, Brazil, Canada, Colombia, Croatia, Egypt, Ethiopia, Finland, France, Georgia, Germany, Honduras, Hungry, India, Indonesia, Iran, Ireland, Italy, Kuwait, Japan, Lebanon, Lithuania, Malaysia, Mail, Nepal, the Netherlands, New Zealand, North Macedonia, Norway, Oman, Pakistan, Peru, Philippines, Portugal, Romania, Saudi Arabia, South Africa, Spain, Switzerland, United Kingdom and the United States.

The Taskforce will continue to extract and identify characteristics relevant to equity, diversity and inclusion where available.

What are the main results?
There were no differences in incidence of death, requirement of ventilation and discharge from hospital between interferon β-1a and standard care at day 28. We are uncertain whether treatment with interferon β-1a has an impact on the number of people experiencing septic shock and duration of hospital stay.

Our confidence in the results
Certainty of the evidence is high for risk of death, patients requiring ventilation and discharge from hospital. For incidence of septic shock and duration of hospital stay, certainty is very low due to non-blinding of patients and personnel, reliance on a single study, low patient and event numbers and wide confidence intervals.

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
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. Interferon β-1a is also associated with immune reactions that can produce flu-like symptoms *[137][138]*.

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.

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 *[139]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Interferon β-1a	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 1.05 (CI 95% 0.89 — 1.23) Based on data from 4,646 participants in 4 studies. [1] (Randomized controlled)	156 per 1000 Difference:	164 per 1000 **8 more per 1000** (CI 95% 17 fewer — 36 more)	High	Interferon β-1a does not impact death.
Patients requiring ventilation Within 28 days of commencing treatment 9 Critical	Relative risk 0.99 (CI 95% 0.83 — 1.17) Based on data from 3,912 participants in 2 studies. [2] (Randomized controlled)	116 per 1000 Difference:	115 per 1000 **1 fewer per 1000** (CI 95% 20 fewer — 20 more)	High	Interferon β-1a has no impact on number of patients requiring ventilation.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Interferon β-1a	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
ICU admission Within 28 days of commencing treatment 6 Important	Relative risk 1 (CI 95% 0.73 — 1.36) Based on data from 40 participants in 1 studies. [3] (Randomized controlled)	800 per 1000 Difference:	800 per 1000 **0 fewer per 1000** (CI 95% 216 fewer — 288 more)	**Very low** Due to extremely serious imprecision [4]	We are uncertain whether interferon β-1a increases or decreases ICU admission.
Septic shock Within 28 days of commencing treatment 6 Important	Relative risk 1.67 (CI 95% 0.7 — 3.99) Based on data from 91 participants in 1 studies. [5] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [6]	We are uncertain whether interferon β-1a improves or worsens septic shock (17 events).
Discharge from hospital Within 28 days of commencing treatment 6 Important	Relative risk 0.95 (CI 95% 0.92 — 0.99) Based on data from 4,181 participants in 2 studies. [7] (Randomized controlled)	778 per 1000 Difference:	739 per 1000 **39 fewer per 1000** (CI 95% 62 fewer — 8 fewer)	**High**	Interferon β-1a has no impact on number of patients discharged from hospital.
Duration of hospital stay Mean days to discharge 6 Important	Based on data from 81 participants in 1 studies. [8] (Randomized controlled)	12.3 (Mean) Difference:	14.8 (Mean) **MD 2.55 higher** (CI 95% 0.92 lower — 6.02 higher)	**Very low** Due to serious risk of bias and very serious imprecision [9]	We are uncertain whether interferon β-1a increases or decreases duration of hospital stay.
Time to improvement Days (median) 6 Important	Lower better Based on data from 40 participants in 1 studies. (Randomized controlled)	7 (Median) Difference:	5 (Median) **2 lower**	**Very low** Due to serious risk of bias and very serious imprecision [10]	We are uncertain whether interferon β-1a increases or decreases time to improvement.

Attached Images

7.2.9 Interferon beta-1a plus lopinavir-ritonavir

Not recommended

Do not use intravenous interferon β-1a plus lopinavir-ritonavir for the treatment of COVID-19.

Additional information

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Although certainty of the evidence is low, this recommendation is supported by the observation that neither intravenous interferon β-1a nor lopinavir-ritonavir as standalone treatments demonstrate a benefit when administered to patients with COVID-19.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Important harms

We are unclear whether interferon β-1a plus lopinavir-ritonavir increases or decreases incidence of death, adverse events or serious adverse events.

Subcutaneous and intravenous interferon β-1a does not impact on the incidence of death or number of patients requiring ventilation. Although included trials did not report on adverse or serious adverse events, 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.

With regards to lopinavir-ritonavir, evidence indicates no difference in incidence of death, requirement of mechanical ventilation or duration of hospital stay between lopinavir-ritonavir and standard care. Uncertainty remains regarding the incidence of serious adverse events and adverse events, however there are well-known side effects and harms associated with lopinavir-ritonavir, including gastrointestinal symptoms, hyperglycaemia, pancreatitis, QT and PR interval prolongation and hepatic impairment.

Certainty of the Evidence

Very low

General adult population
Certainty of the evidence is low for death due to very serious imprecision (wide confidence intervals and reliance on a single study), and very low for adverse and serious adverse events due to serious risk of bias (patients, personnel and outcome assessors unblinded) and very serious imprecision (wide confidence intervals 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 for all outcomes because of indirectness due to limited inclusion (or absence) of these populations in the trials.

Values and preferences

Substantial variability is expected or uncertain

General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this 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.

Resources

No important issues with the recommended alternative

As interferon β-1a plus lopinavir-ritonavir is not recommended there are no resource considerations.

Equity

No important issues with the recommended alternative

As interferon β-1a plus lopinavir-ritonavir is not recommended there are no equity considerations.

Acceptability

No important issues with the recommended alternative

As interferon β-1a plus lopinavir-ritonavir is not recommended there are no acceptability considerations.

Feasibility

No important issues with the recommended alternative

As interferon β-1a plus lopinavir-ritonavir is not recommended there are no feasibility considerations.

Rationale

General adult population
There is currently limited evidence about the effect of interferon β-1a plus lopinavir-ritonavir on patient-relevant outcomes in the treatment of COVID-19. However, when used individually, neither of these treatments has demonstrated improvements in clinical outcomes when administered to patients with COVID-19. We therefore recommend that interferon β-1a plus lopinavir-ritonavir should not be used to treat COVID-19.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Interferon β-1a plus lopinavir-ritonavir
Comparator: Standard care

Summary

There remains significant uncertainty whether inhaled interferon β-1a plus lopinavir-ritonavir is more effective and safer than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial that compared inhaled interferon β-1a plus lopinavir-ritonavir with placebo in 293 adults hospitalised with moderate or severe COVID-19 *[306]*.

Study characteristics
Median age of participants was ~63 years and 29% were women. Patients in the intervention group received 44 µg of subcutaneous IFN-ß1a on days 1, 3 and 6, and 400 mg lopinavir and 100 mg ritonavir every 12 hours for 14 days. Pregnant and breastfeeding women were ineligible.

What are the main results?
We are uncertain whether inhaled interferon β-1a plus lopinavir-ritonavir increases or decreases risk of death at day 28. Patients treated with interferon β-1a plus lopinavir-ritonavir had more adverse and serious adverse events.

Our confidence in the results
Certainty of the evidence is low for risk of death at day 28 due to very serious imprecision (low patient numbers and reliance on a single study). Certainty is very low for adverse and serious adverse events due to very serious imprecision (reliance on a single study, wide confidence intervals and few patients) and serious risk of bias (lack of blinding of participants and assessors).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included study).

Additional information
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. Interferon β-1a is also associated with immune reactions that can produce flu-like symptoms.

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.

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. 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Interferon β-1a plus lopinavir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 1.19 (CI 95% 0.57 — 2.49) Based on data from 293 participants in 1 studies. [1] (Randomized controlled)	81 per 1000 Difference:	96 per 1000 **15 more per 1000** (CI 95% 35 fewer — 121 more)	**Low** Due to very serious imprecision [2]	We are uncertain whether interferon β-1a plus lopinavir-ritonavir increases or decreases all-cause mortality (26 events)
Serious adverse events End of follow-up 6 Important	Relative risk 1.41 (CI 95% 1.09 — 1.81) Based on data from 292 participants in 1 studies. [3] (Randomized controlled)	385 per 1000 Difference:	543 per 1000 **158 more per 1000** (CI 95% 35 more — 312 more)	**Very low** Due to serious risk of bias and very serious imprecision [4]	We are uncertain whether interferon β-1a plus lopinavir-ritonavir increases serious adverse events (135 events).
Adverse events End of follow-up 6 Important	Relative risk 1.15 (CI 95% 1.01 — 1.3) Based on data from 292 participants in 1 studies. [5] (Randomized controlled)	709 per 1000 Difference:	815 per 1000 **106 more per 1000** (CI 95% 7 more — 213 more)	**Very low** Due to serious risk of bias and very serious imprecision [6]	We are uncertain whether interferon β-1a plus lopinavir-ritonavir increases adverse events (222 events).

Attached Images

7.2.10 Ivermectin

Not recommended

Do not use ivermectin for the treatment of COVID-19.

Additional information

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of ivermectin may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include ivermectin.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Important harms

Ivermectin probably has little impact on all-cause mortality, the need for invasive mechanical ventilation or hospitalisation, time to recovery or duration of hospitalisation; however it probably increases incidence of adverse events (RR 1.17, CI 95% 0.79 to 1.72; 146 more per 1000, moderate certainty). We are uncertain whether ivermectin increases or decreases the need for supplemental oxygen, ICU admission, serious adverse events or discontinuation due to adverse events, clinical recovery, clinical progression, clinical improvement or viral clearance.

Common side effects and harms associated with ivermectin, including diarrhoea, nausea and dizziness *[174]*.

Certainty of the Evidence

Moderate

General adult population

Certainty of the evidence is moderate for all-cause mortality, invasive mechanical ventilation, hospitalisation, time to recovery and duration of hospitalisation due to serious imprecision (inconsistent direction of effect and/or wide confidence intervals) and low for all remaining outcomes due to either very serious imprecision (clinical recovery and discontinuation due to adverse events; wide confidence intervals, reliance on a single study and/or few events) or due to serious imprecision and serious risk of bias.

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

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Values and preferences

Substantial variability is expected or uncertain

General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this 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.

Resources Important issues, or potential issues not investigated

As ivermectin is not recommended there are no resource considerations.

Equity Important issues, or potential issues not investigated

As ivermectin is not recommended there are no equity considerations.

Acceptability Important issues, or potential issues not investigated

As ivermectin is not recommended there are no acceptability considerations.

Feasibility Important issues, or potential issues not investigated

As ivermectin is not recommended there are no feasibility considerations.

Rationale

Based on the available evidence, ivermectin is no more effective than standard care in treating patients with COVID-19. We therefore recommend that ivermectin should not be used.

Clinical Question/ PICO

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

Summary

The available research evidence suggests that ivermectin does not decrease mortality, the need for mechanical ventilation or the need for hospitalisation in people with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from 19 randomised trials that compared ivermectin with standard care in over 3700 adults with COVID-19 *[172][176][177][178][179][180][182][324][326][329][335][357][431][444][450][494][495][518][522]*.

Publication status
Two studies are only available as preprints and have therefore not been peer reviewed (Shah Bukhari et al. posted to medRxiv on 5 February 2021 *[179]* and de la Rocha et al. posted to Res Sq on 23 May 2022 *[518]*).

See 'Removal of studies' section below for information on studies previously included in this recommendation.

Study characteristics
Mean/median age of participants across the studies ranged from 26 to 56 years and the proportion of women ranged from 27 to 61% (with the exception of two studies, in which the proportion of women ranged from 10 to 20% *[179][357]*). Pregnant and breastfeeding women were ineligible in all trials.

Equity, diversity and inclusion

The characteristics of trial participants related to equity, diversity and inclusion (see technical report) were reported in minimal detail in the included studies. Ethnicity was reported in two studies and the reporting of ethnicity varied between trials. As a result, the specific population(s) to whom this data directly applies is unclear.

None of these trials were conducted in Australia. This participant data comes from Argentina, Bangladesh, Brazil, Colombia, Georgia, India, Iran, Israel, Malaysia, Mexico, Pakistan, Spain, Thailand, and the United States of America.

The Taskforce will continue to extract and identify characteristics relevant to equity, diversity and inclusion where available.

What are the main results?
Ivermectin probably has little impact on all-cause mortality, the need for invasive mechanical ventilation or hospitalisation, time to recovery or duration of hospitalisation; however it probably increases incidence of adverse events (RR 1.17, CI 95% 0.79 to 1.72; 146 more per 1000, moderate certainty). We are uncertain whether ivermectin increases or decreases the need for supplemental oxygen, ICU admission, serious adverse events or discontinuation due to adverse events, clinical recovery, clinical progression, clinical improvement or viral clearance.

Our confidence in the results
Certainty of the evidence is moderate for all-cause mortality, invasive mechanical ventilation, hospitalisation, time to recovery and duration of hospitalisation due to serious imprecision (inconsistent direction of effect and/or wide confidence intervals) and low for all remaining outcomes due to either very serious imprecision (clinical recovery and discontinuation due to adverse events; wide confidence intervals, reliance on a single study and/or few events) or due to serious imprecision and serious risk of bias.

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
Common side effects and harms associated with ivermectin are diarrhoea, nausea and dizziness *[174]*.

Removal of studies
The following studies, previously included as part of the evidence informing this recommendation, have been removed. In all cases, removal of these studies did not change the strength or direction of the recommendation that was current at the time of their removal.

Removed from version 44:
Abd-Elsalam (J Med Virol, Jun 2021) *[322]* and Niaee (Asian Pacific J Trop Med, 25 June 2021) *[375]* were removed from our analyses due to inconsistencies that were identified in the reported data. Both studies contributed data to all-cause mortality, and Abd-Elsalam also contributed data to mechanical ventilation and duration of hospitalisation.

Removed from version 45:
Samaha (Viruses, May 2021) *[323]* was retracted by the journal on 26 Oct 2021 at the request of the authors following an error between files used for the statistical analysis. The study contributed data to the outcome on hospitalisation.

Removed from version 57:
Pott-Junior (Toxicol Rep, Mar 2021) *[181]* was retracted by the journal on 2 May 2022 "on the basis that there was clear evidence that the findings are unreliable. Additional external review of this published paper raised several concerns."

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days of commencing treatment 9 Critical	Relative risk 0.95 (CI 95% 0.75 — 1.21) Based on data from 6,800 participants in 12 studies. [1] (Randomized controlled)	100 per 1000 Difference:	95 per 1000 **5 fewer per 1000** (CI 95% 25 fewer — 21 more)	**Moderate** Due to serious imprecision [2]	Ivermectin probably has little impact on death (81 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Invasive mechanical ventilation End of follow-up 9 Critical	Relative risk 0.64 (CI 95% 0.43 — 0.94) Based on data from 3,682 participants in 8 studies. [3] (Randomized controlled)	100 per 1000 Difference:	64 per 1000 **36 fewer per 1000** (CI 95% 57 fewer — 6 fewer)	**Moderate** Due to serious imprecision [4]	Ivermectin probably has little impact on invasive mechanical ventilation (74 events).
Supplemental oxygen End of follow-up 6 Important	Relative risk 1.08 (CI 95% 0.5 — 2.32) Based on data from 114 participants in 2 studies. [5] (Randomized controlled)	158 per 1000 Difference:	171 per 1000 **13 more per 1000** (CI 95% 79 fewer — 209 more)	**Low** Due to serious risk of bias and serious imprecision [6]	We are uncertain whether ivermectin increases or decreases requirement of supplemental oxygen (19 events).
ICU admission End of follow-up 6 Important	Relative risk 0.86 (CI 95% 0.57 — 1.3) Based on data from 1,760 participants in 4 studies. [7] (Randomized controlled)	306 per 1000 Difference:	263 per 1000 **43 fewer per 1000** (CI 95% 132 fewer — 92 more)	**Low** Due to serious risk of bias and serious imprecision [8]	We are uncertain whether ivermectin increases or decreases admission to ICU (25 events)
Serious adverse events End of follow-up 6 Important	Relative risk 0.77 (CI 95% 0.58 — 1.03) Based on data from 3,018 participants in 10 studies. [9] (Randomized controlled)	22 per 1000 Difference:	17 per 1000 **5 fewer per 1000** (CI 95% 9 fewer — 1 more)	**Moderate** Due to serious risk of bias [10]	Ivermectin probably has little impact on serious adverse events.
Adverse events End of follow-up 6 Important	Relative risk 0.85 (CI 95% 0.72 — 1.02) Based on data from 5,239 participants in 14 studies. [11] (Randomized controlled)	159 per 1000 Difference:	135 per 1000 **24 fewer per 1000** (CI 95% 45 fewer — 3 more)	**High**	Ivermectin has little impact on adverse events.
Discontinuation due to adverse event End of treatment 6 Important	Relative risk 2.08 (CI 95% 0.92 — 4.71) Based on data from 1,595 participants in 4 studies. [12] (Randomized controlled)	11 per 1000 Difference:	23 per 1000 **12 more per 1000** (CI 95% 1 fewer — 41 more)	**Low** Due to very serious imprecision [13]	We are uncertain whether ivermectin increases or decreases discontinuation due to adverse event (20 events).
Hospitalisation End of follow-up	Relative risk 0.83 (CI 95% 0.66 — 1.04) Based on data from	122 per 1000	96 per 1000	**Moderate** Due to serious imprecision [15]	Ivermectin probably has little impact on hospitalisation (213

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important	2,888 participants in 5 studies. [14] (Randomized controlled)	Difference:	**26 fewer per 1000** (CI 95% 46 fewer — 2 more)		events).
Discharge from hospital End of follow-up 6 Important	Relative risk 1.06 (CI 95% 0.99 — 1.12) Based on data from 342 participants in 4 studies. [16] (Randomized controlled)	868 per 1000 Difference:	920 per 1000 **52 more per 1000** (CI 95% 9 fewer — 104 more)	**Low** Due to serious risk of bias and serious imprecision [17]	Ivermectin may increase discharge from hospital slightly (302 events).
Clinical recovery Within 21 days of commencing treatment 6 Important	Relative risk 1.03 (CI 95% 0.97 — 1.1) Based on data from 2,041 participants in 3 studies. [18] (Randomized controlled)	788 per 1000 Difference:	812 per 1000 **24 more per 1000** (CI 95% 24 fewer — 79 more)	**Low** Due to very serious imprecision [19]	We are uncertain whether ivermectin increases or decreases clinical recovery (320 events).
Clinical progression End of follow-up 6 Important	Relative risk 1.08 (CI 95% 0.82 — 1.42) Based on data from 2,132 participants in 7 studies. [20] (Randomized controlled)	87 per 1000 Difference:	93 per 1000 **6 more per 1000** (CI 95% 18 fewer — 39 more)	**Moderate** Due to serious imprecision [21]	Ivermectin probably has little impact on clinical progression.
Clinical improvement [22] End of follow-up 6 Important	Relative risk 1.07 (CI 95% 0.94 — 1.22) Based on data from 125 participants in 1 studies. [23] (Randomized controlled)	867 per 1000 Difference:	928 per 1000 **61 more per 1000** (CI 95% 52 fewer — 191 more)	**Low** Due to very serious imprecision [24]	We are uncertain whether ivermectin increases clinical improvement (113 events).
Viral clearance 7–12 days after treatment 6 Important	Relative risk 1.19 (CI 95% 0.94 — 1.52) Based on data from 1,318 participants in 6 studies. [25] (Randomized controlled)	752 per 1000 Difference:	895 per 1000 **143 more per 1000** (CI 95% 45 fewer — 391 more)	**Low** Due to serious risk of bias, Due to serious imprecision [26]	We are uncertain whether ivermectin increases or decreases viral clearance.
Time to recovery [27] Days (Lopez et al.)	Lower better Based on data from 398 participants in 1 studies. (Randomized controlled)	12 (Median)	10 (Median) CI 95%	**Low** Due to very serious imprecision [28]	We are uncertain whether ivermectin increases or decreases time to recovery.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important					
Time to recovery Days (TOGETHER trial) 6 Important	Lower better Based on data from 1,378 participants in 1 studies. (Randomized controlled)	14 (Median)	14 (Median) CI 95%	**Moderate** Due to serious imprecision [29]	Ivermectin probably has little impact on time to recovery.
Duration of hospitalisation Days (Lim, Shahbaznejad) 6 Important	Lower better Based on data from 559 participants in 2 studies. [30] (Randomized controlled)	7.42 (Mean) Difference:	7.04 (Mean) **MD 0.38 lower** (CI 95% 2.13 lower — 1.37 higher)	**Low** Due to serious imprecision and serious inconsistency [31]	Ivermectin may have little impact on duration of hospitalisation.
Duration of hospitalisation Days (TOGETHER) 6 Important	Lower better Based on data from 1,398 participants in 1 studies. (Randomized controlled)	6 (Median)	6 (Median) CI 95%	**Moderate** Due to serious imprecision [32]	Ivermectin probably has little impact on duration of hospitalisation.

Attached Images

7.2.11 Lopinavir-ritonavir

Not recommended

Do not use lopinavir-ritonavir for the treatment of COVID-19.

Additional information

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of lopinavir-ritonavir may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include lopinavir-ritonavir.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Important harms

General adult population
Evidence indicates no difference in incidence of death, requirement of mechanical ventilation or duration of hospital stay between lopinavir-ritonavir and standard care. Uncertainty remains regarding the incidence of serious adverse events and adverse events, however there are well-known side effects and harms associated with lopinavir-ritonavir.

Although most information on side effects 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 *[112][113][146]*. 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

Moderate

General adult population
Certainty of the evidence is high for death, mechanical ventilation or ECMO and discharge from hospital at day 28. Certainty is moderate for patients requiring ventilation (reliance on a single study), adverse events and serious adverse events (wide confidence intervals), and low for respiratory failure (inconsistency in direction of effect and wide confidence intervals), clinical improvement at day 14 (lack of blinding of patients/personnel and wide confidence intervals) and time to discharge from hospital (lack of blinding of patients/personnel 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 further downgraded because of indirectness due to limited inclusion (or absence) of these populations in the trials.

Values and preferences

Substantial variability is expected or uncertain

General adult population
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this 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 lopinavir-ritonavir during pregnancy and breastfeeding are unknown in the context of COVID-19.

Resources

Important issues, or potential issues not investigated

As lopinavir-ritonavir is not recommended there are no resource considerations.

Equity

Important issues, or potential issues not investigated

As lopinavir-ritonavir is not recommended there are no equity considerations.

Acceptability

Important issues, or potential issues not investigated

As lopinavir-ritonavir is not recommended there are no acceptability considerations.

Feasibility

Important issues, or potential issues not investigated

As lopinavir-ritonavir is not recommended there are no feasibility considerations.

Rationale

Based on the available evidence, lopinavir-ritonavir is no more effective than standard care in treating patients with COVID-19. We therefore recommend that lopinavir-ritonavir should not be used.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: Lopinavir-ritonavir
Comparator: Standard care

Summary

Evidence indicates that lopinavir-ritonavir is no more effective than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from nine randomised trials that compared lopinavir-ritonavir with standard care in over 9600 patients with COVID-19 *[112][113][146][152][155][306][478][479][480]*. The vast majority of data come from the RECOVERY and WHO SOLIDARITY trials, which included 5040 *[152]* and 2771 patients *[49][480]* with moderate-to-critical COVID-19. The SOLIDARITY trial was stopped early for reasons of futility.

Study characteristics
In the RECOVERY trial, mean age was 66 years and 40% were women. In the SOLIDARITY trial, 37% of patients were under 50 years of age, 43% were aged 50–69 years, and 20% were 70 years or older; 40% were women. For the five smaller trials, mean or median age ranged from 41 to 63 years and the proportion of women ranged from 28 to 59%. In the RECOVERY trial, six women were pregnant at randomisation—of the remaining studies, four excluded pregnant and breastfeeding women, and for two their eligibility was unclear *[146][155]*.

In the RECOVERY and SOLIDARITY trials, patients received lopinavir 400 mg plus ritonavir 100 mg orally twice daily for either 10 days or 14 days, respectively.

Equity, diversity and inclusion

The characteristics of trial participants related to equity, diversity and inclusion (see technical report) were reported in minimal detail in the included studies. Ethnicity was reported in two studies and the reporting of ethnicity varied between trials. As a result, the specific population(s) to whom this data directly applies is unclear.

This participant data comes from Albania, Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Colombia, Egypt, Ethiopia, Finland, France, Georgia, Germany, Honduras, India, Indonesia, Iran, Ireland, Italy, Kuwait, Lebanon, Lithuania, Malaysia, Mail, the Netherlands, New Zealand, North Macedonia, Norway, Oman, Pakistan, Peru, Philippines, Portugal,, Saudi Arabia, South Africa, Spain, Switzerland, United Kingdom and the United States.

The Taskforce will continue to extract and identify characteristics relevant to equity, diversity and inclusion where available.

What are the main results?
There were no differences in incidence of death, requirement of mechanical ventilation or extracorporeal membrane oxygenation (ECMO), discharge from hospital or time to discharge from hospital between lopinavir-ritonavir and standard care. Lopinavir-ritonavir probably increases incidence of adverse events and has little impact on serious adverse events, and may decrease the incidence of respiratory failure or acute respiratory distress syndrome. For all other outcomes, we are uncertain if lopinavir-ritonavir makes a difference.

Our confidence in the results
Certainty of the evidence is high for risk of death, invasive mechanical ventilation or ECMO and discharge from hospital at day 28. Certainty is moderate for patients requiring ventilation (reliance on a single study), serious adverse events and adverse events (wide confidence intervals). Certainty was low for respiratory failure (inconsistency in direction of effect and wide confidence intervals), clinical improvement at day 14 (lack of blinding of patients/personnel and wide confidence intervals) and time to discharge from hospital (lack of blinding of patients/personnel and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
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 *[145]*.

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.

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 have shown a favourable safety profile, with no increase in stillbirth, preterm birth, low birth weight or birth defects *[147][148][149][150][151]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Lopinavir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality End of treatment 9 Critical	Relative risk 1.04 (CI 95% 0.95 — 1.14) Based on data from 9,376 participants in 7 studies. [1] (Randomized controlled)	188 per 1000 Difference:	196 per 1000 **8 more per 1000** (CI 95% 9 fewer — 26 more)	High	Lopinavir-ritonavir has no impact on mortality.
Invasive mechanical ventilation or ECMO End of treatment 9 Critical	Relative risk 1.15 (CI 95% 0.95 — 1.38) Based on data from 5,074 participants in 3 studies. [2] (Randomized controlled)	84 per 1000 Difference:	97 per 1000 **13 more per 1000** (CI 95% 4 fewer — 32 more)	High	Lopinavir-ritonavir has no impact on patients requiring invasive mechanical ventilation or ECMO.
Non-invasive or invasive ventilation Within 28 days after commencing treatment 6 Important	Relative risk 1.02 (CI 95% 0.8 — 1.29) Based on data from 2,545 participants in 1 studies. [3] (Randomized controlled)	95 per 1000 Difference:	97 per 1000 **2 more per 1000** (CI 95% 19 fewer — 28 more)	Moderate Only one study [4]	Lopinavir-ritonavir probably has no impact on patients requiring non-invasive or invasive ventilation.
Serious adverse events End of treatment 6 Important	Relative risk 1.16 (CI 95% 0.77 — 1.76) Based on data from 1,583 participants in 5 studies. [5] (Randomized controlled)	135 per 1000 Difference:	157 per 1000 **22 more per 1000** (CI 95% 31 fewer — 103 more)	Moderate Due to serious imprecision [6]	Lopinavir-ritonavir probably has little impact on serious adverse events.
Adverse events End of treatment 6 Important	Relative risk 1.35 (CI 95% 1.06 — 1.73) Based on data from 1,151 participants in 6 studies. [7] (Randomized controlled)	423 per 1000 Difference:	571 per 1000 **148 more per 1000** (CI 95% 25 more — 309 more)	Moderate Due to serious imprecision [8]	Lopinavir-ritonavir probably increases adverse events.
Respiratory failure or ARDS	Relative risk 0.7 (CI 95% 0.49 — 1)	231	162	Low Due to serious	Lopinavir-ritonavir may decrease respiratory

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Lopinavir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
End of treatment 6 Important	Based on data from 540 participants in 3 studies. [9]	per 1000 Difference:	per 1000 **69 fewer per 1000** (CI 95% 118 fewer — 0 fewer)	inconsistency and serious imprecision	failure or ARDS (104 events).
Clinical improvement Day 14 after treatment 6 Important	Relative risk 1.15 (CI 95% 0.92 — 1.42) Based on data from 534 participants in 3 studies. [10]	324 per 1000 Difference:	373 per 1000 **49 more per 1000** (CI 95% 26 fewer — 136 more)	**Low** Due to serious risk of bias and serious imprecision [11]	Lopinavir-ritonavir may increase clinical improvement slightly.
Discharge from hospital 28 Days after commencing treatment 6 Important	Relative risk 1 (CI 95% 0.98 — 1.03) Based on data from 8,104 participants in 3 studies. [12]	742 per 1000 Difference:	742 per 1000 **0 fewer per 1000** (CI 95% 15 fewer — 22 more)	**High**	Lopinavir-ritonavir has no impact on discharge from hospital at 28 days.
Hospitalisation End of follow-up 6 Important	Relative risk 1.24 (CI 95% 0.6 — 2.56) Based on data from 471 participants in 1 studies. [13] (Randomized controlled)	53 per 1000 Difference:	66 per 1000 **13 more per 1000** (CI 95% 21 fewer — 83 more)	**Low** Due to very serious imprecision [14]	We are uncertain whether lopinavir-ritonavir increases or decreases hospitalisation.
Time to discharge from hospital Days 6 Important	Lower better Based on data from 5,040 participants in 1 studies. (Randomized controlled)	11 (Median)	11 (Median) CI 95%	**Low** Due to serious risk of bias and only one study [15]	Lopinavir-ritonavir may have little impact on time to discharge from hospital.

Attached Images

7.2.12 Sodium-glucose transport protein 2 inhibitors

Not recommended

New

Do not use empagliflozin or dapagliflozin for the treatment of COVID-19.

Additional information

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of empagliflozin or dapagliflozin for treatment of COVID-19 may still be considered in the context of randomised trials with appropriate ethical approval.

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

This is a moderate priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Evidence indicates no difference between empagliflozin or dapagliflozin and standard care in incidence of death or hospital discharge. Uncertainty remains regarding the incidence of serious adverse events.

Certainty of the Evidence

Moderate

Certainty of the evidence is moderate for all-cause mortality and hospital discharge due to serious imprecision (wide confidence intervals) and low for serious adverse events due to very serious imprecision (single study and wide confidence intervals).

Values and preferences

Substantial variability is expected or uncertain

General adult population

We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this 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.

Resources

No important issues with the recommended alternative

As empagliflozin or dapagliflozin are not recommended there are no resource considerations.

Equity

No important issues with the recommended alternative

As empagliflozin and dapagliflozin are not recommended there are no equity considerations.

Acceptability

No important issues with the recommended alternative

As empagliflozin and dapagliflozin are not recommended there are no acceptability considerations.

Feasibility

No important issues with the recommended alternative

As empagliflozin and dapagliflozin are not recommended there are no feasibility considerations.

Clinical Question/ PICO

Population: Patients with COIVD 19
Intervention: Empagliflozin or dapagliflozin
Comparator: Standard care

Summary

Evidence indicates that empagliflozin or dapagliflozin is no more effective than standard care in treating patients with COVID-19.

What is the evidence informing this recommendation?
Evidence comes from two randomised trials—the RECOVERY trial that compared empagliflozin with standard care in 4271 adults hospitalised with moderate-to-severe COVID-19 *[594]* and the DARE-19 trial that compared dapagliflozin with standard care in 1250 adults hospitalised with moderate COVID-19 *[593]*.

Study characteristics
In the RECOVERY trial of empagliflozin the mean age of participants was 61 years and the proportion of women was 38%. Just over two-thirds of patients required either no oxygen or simple (low-flow) oxygen, 24% required non-invasive ventilation and 1% required invasive mechanical ventilation. Most patients (90%) received concomitant corticosteroids.
In the DARE-19 trial of empagliflozin the mean age of participants was 61 years and the proportion of women was 43%. All patients were on simple (low-flow) oxygen and just over half (58%) received concomitant corticosteroids.

What are the main results?
Empagliflozin or dapagliflozin probably has no impact on risk of death (6 fewer per 1000; RR 0.91, CI 95% 0.71 to 1.17; 5521 patients from 2 studies) or hospital discharge (16 more per 1000; RR 1.02, CI 95% 1.00 to 1.05; 5521 patients from 2 studies). There is probably little difference between empagliflozin or dapagliflozin and standard care for death or discharge from hospital at 28 days.

Our confidence in the results
Certainty of the evidence is moderate for all-cause mortality and hospital discharge due to serious imprecision (wide confidence intervals). Certainty of evidence is low for serious adverse events due to very serious imprecision (wide confidence intervals and single study).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Empagliflozin or dapagliflozin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 28 days after commencement of treatment	Relative risk 0.91 (CI 95% 0.71 — 1.17) Based on data from 5,521 participants in 2 studies. [1] (Randomized controlled)	**67** per 1000 Difference:	**61** per 1000 **6 fewer per 1000** (CI 95% 19 fewer — 11 more	**Moderate** Due to serious imprecision [2]	Empagliflozin or dapagliflozin probably has little or no difference on death.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Empagliflozin or dapagliflozin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical			)		
Hospital discharge Within 28 days of commencing treatment 6 Important	Relative risk 1.02 (CI 95% 1 — 1.05) Based on data from 5,521 participants in 2 studies. [3] (Randomized controlled)	802 per 1000 Difference:	818 per 1000 **16 more per 1000** (CI 95% 0 fewer — 40 more)	**Moderate** Due to serious imprecision [4]	Empagliflozin or dapagliflozin probably has little or no difference on hospital discharge.
Serious adverse events Within 28 days of commencing treatment 6 Important	Relative risk 0.8 (CI 95% 0.59 — 1.08) Based on data from 1,229 participants in 1 studies. [5] (Randomized controlled)	133 per 1000 Difference:	106 per 1000 **27 fewer per 1000** (CI 95% 55 fewer — 11 more)	**Low** Due to very serious imprecision [6]	Empagliflozin or dapagliflozin may increase serious adverse events slightly.

Attached Images

7.3 Drug treatments not recommended outside of clinical trials

Info Box

The Taskforce has reviewed high quality evidence for a number of drug treatments used to treat COVID-19. Since the start of the pandemic over 4500 randomised trials have been registered (see COVID-NMA Initiative). We continually monitor new research for randomised trials that evaluate any disease-modifying treatments for COVID-19. As each new trial is published, our panels assess and make recommendations on whether the treatment should be used in the clinical care of patients.

For many of these, there is insufficient data to determine whether they are safe and/or effective in treating COVID-19. As a result, the Taskforce has recommended that these treatments are not used to treat COVID-19 until more definitive evidence is available, except where indicated for conditions other than COVID-19. For further information regarding these treatments and the evidence base underlying the recommendation, please click on the treatment of interest below.

Treatment category	Treatment
Antiandrogens	Dutasteride
Antineoplastics	Angiotensin 2 receptor agonist (C21) Camostat mesilate Opaganib
Antiparasitic, antifungals and other anti-infective agents	Chloroquine Doxycycline Ivermectin plus doxycycline Nitazoxanide
Antihypertensives	Telmisartan
Antithrombotic, antiplatelets and related therapies	Sulodexide
Antivirals	Baloxavir marboxil Darunavir-cobicistat Enisamium Ensovibep Sofosbuvir-daclatasvir Triazavirin Umifenovir
Human and blood derived products	Human umbilical cord mesenchymal stem cells Intravenous immunoglobulin Intravenous immunoglobulin plus methylprednisolone
Immunomodulating drugs	Anakinra CD24Fc Lenzilumab Ruxolitinib Tofacitinib

Interferons	Interferon beta-1a (inhaled) Interferon beta-1b Interferon gamma Interferon kappa plus trefoil factor 2 (IFN-κ plus TFF2) Peginterferon lambda
Other antibody related therapies	Bamlanivimab Bamlanivimab plus etesevimab Bebtelovimab
Other therapies	Almitrine Aprepitant Bromhexine hydrochloride Fluvoxamine Metformin Recombinant human granulocyte colony-stimulating factor Sabizabulin
Vitamins, supplements and cofactors	Combined metabolic activators (CMA) N-acetylcysteine Vitamin C Vitamin D analogues (calcifediol / cholecalciferol) Zinc

7.3.1 Other drug treatments

Consensus recommendation

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

Additional information

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 drug treatments in these populations unless they are eligible to be enrolled in trials.

Evidence To Decision

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.

Values and preferences

Substantial variability is expected or uncertain

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.

The NC19CET Consumer Panel believes that informed patients may prefer to wait until there is available evidence, while other informed patients may choose to participate in clinical trials.

Resources

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

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.

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 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 *[18][20][108][109]*, 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.

7.4 Drug treatments under review

Info Box

We are continually monitoring new research for randomised trials that evaluate any disease-modifying treatments for COVID-19. As each new trial is published, our panels assess and make recommendations on whether the treatment should be used in the clinical care of patients. This section provides details of studies that are currently under review by our panels. Recommendations on whether these treatments should be used in the clinical care of patients will be included in a future update of the guideline.

7.5 Drug treatments not currently under review

Info Box

Many randomised trials of COVID-19 have been published that include small numbers of patients and/or report no outcomes of clinical relevance. A comprehensive list of randomised trials that do not meet our inclusion criteria, and which are not currently being reviewed by the Taskforce, can be found here.

8. Chemoprophylaxis

Updated

Info Box

The Drug Treatment Panel is responsible for developing recommendations specific to pre- and post-exposure prophylaxis.

Recommendations are subsequently reviewed by the Guidelines Leadership Group and approved by the Steering Committee prior to publication. In addition, all recommendations are reviewed by the Consumer Panel to establish acceptability to the patient population for which they are relevant.

Currently there are no recommended chemoprophylaxis for COVID-19 pre or post-exposure prophylaxis

8.1 Casirivimab plus imdevimab (Ronapreve) for post-exposure prophylaxis

Consensus recommendation

New

Do not routinely use casirivimab plus imdevimab (Ronapreve) for post-exposure prophylaxis of COVID-19.

Additional information

The Taskforce has previously recommended the prophylactic use of casirivimab plus imdevimab (Ronapreve) to reduce the risk of symptomatic and asymptomatic COVID-19 infection in seronegative household contacts of individuals with confirmed COVID-19. The recommendations were based on one trial (COVID-19 Phase 3 Prevention Trial), in which casirivimab plus imdevimab was administered subcutaneously to close household contacts of individuals with confirmed COVID-19 [361]. Participants were healthy individuals aged 12 years or older who were seronegative for SARS-CoV-2 antibodies at the time of treatment.

The COVID-19 Phase 3 Prevention Trial was conducted before the emergence of Omicron as the dominant variant. Since the development of the initial recommendations, a significant body of in vitro evidence has emerged demonstrating a significant reduction in activity of casirivimab plus imdevimab against the Omicron BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that casirivimab plus imdevimab (Ronapreve) is effective as prophylaxis in individuals exposed to currently circulating variants of COVID-19.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

In close household contacts of individuals with confirmed COVID-19, casirivimab plus imdevimab probably has little impact on the incidence of symptomatic and confirmed COVID-19 infection (symptomatic plus asymptomatic).

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
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.

Pregnant or breastfeeding women
There is uncertainty around the benefits and harms of casirivimab plus imdevimab for pregnant or breastfeeding women with COVID-19 as no details were reported in the trials for these populations.

Children or adolescents
Children aged 12 years and over were eligible for inclusion in the study on casirivimab plus imdevimab, but results were not presented separately for this subgroup and it is unclear how many children were included. As a result, there remains uncertainty around the benefits and harms of casirivimab plus imdevimab for children and adolescents at risk of COVID-19 infection.

Certainty of the Evidence

Moderate

Certainty of the evidence is moderate for symptomatic COVID-19 infection, confirmed COVID-19 infection and adverse events (due to serious imprecision based on reliance on a single study), and low for all-cause mortality and serious adverse events (due to very serious imprecision based on reliance on a single study, few events and wide confidence intervals).

Values and preferences

Substantial variability is expected or uncertain

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

Resources

Important issues, or potential issues not investigated

The unavailability of casirivimab plus imdevimab, as well as the high cost of treatment, are limiting factors preventing widespread use of this treatment.

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity; however as casirivimab plus imdevimab is not currently available in Australia it is not currently accessible to patients or clinicians.

Acceptability

Important issues, or potential issues not investigated

Although we have no systematically collected evidence regarding acceptability.

Feasibility

Important issues, or potential issues not investigated

On 15 October, the Therapeutic Goods Administration granted provisional approval to use casirivimab plus imdevimab in adults who have been exposed to SARS-CoV-2 and who either have a medical condition making them unlikely to respond to or be protected by vaccination or who have not been vaccinated against COVID-19. Casirivimab plus imdevimab as prophylaxisis not feasible in patients who do not meet eligibility as specified by the Australian Government Department of Health.

Clinical Question/ PICO

Population: Casirivimab-imdevimab prophylaxis for COVID-19
Intervention: Casirivimab plus imdevimab
Comparator: Placebo

Summary

Post-exposure prophylactic casirivimab plus imdevimab probably reduces symptomatic and asymptomatic COVID-19 infection in seronegative close household contacts of confirmed COVID-19 patients.

What is the evidence informing this recommendation?
Evidence comes from one randomised trial that compared casirivimab plus imdevimab with placebo in 1505 household contacts of confirmed COVID-19 patients *[361]*.

Study characteristics
Median age of participants was 43 years and 55% were women. Individuals received a single subcutaneous 1200 mg dose of REGEN-COV (600 mg casirivimab plus 600 mg imdevimab) or placebo. Pregnant and breastfeeding women were ineligible. Adolescents (12-17 years of age) were eligible for inclusion, however results were not reported separately.

What are the main results?
Results demonstrate that casirivimab plus imdevimab probably reduces incidence of symptomatic COVID-19 infection (RR 0.19 CI 95% 0.10 to 0.35; 1505 patients in 1 study) and confirmed COVID-19 infection (symptomatic plus asymptomatic; RR 0.34 CI 95% 0.23 to 0.48; 1505 patients in 1 study). In addition, results demonstrate a reduction in incidence of adverse events in individuals treated with prophylactic casirivimab plus imdevimab (RR 0.70 CI 95% 0.61 to 0.80; 2617 patients in 1 study).

We are unsure whether casirivimab plus imdevimab has an impact on death, serious adverse events or discontinuation

due to adverse events.

Our confidence in the results
Certainty of the evidence is moderate for symptomatic COVID-19 infection, confirmed COVID-19 infection (symptomatic plus asymptomatic infection) and adverse events (due to serious imprecision based on reliance on a single study), and low for all-cause mortality and serious adverse events (due to very serious imprecision based on reliance on a single study, few events and wide confidence intervals).

For pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
As of 20 August 2021, REGEN-COV (casirivimab plus imdevimab) has been granted provisional determination by the Australian Register of Therapeutic Goods allowing an application for provisional registration. Currently casirivimab plus imdevimab is not available for use within Australia.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Casirivimab plus imdevimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality End of follow-up 9 Critical	Relative risk 1 (CI 95% 0.14 — 7.06) Based on data from 2,617 participants in 1 studies. [1] (Randomized controlled)	2 per 1000 Difference:	2 per 1000 **0 fewer per 1000** (CI 95% 2 fewer — 12 more)	**Low** Due to very serious imprecision [2]	There were too few deaths to determine if casirivimab plus imdevimab makes a difference (4 deaths).
Symptomatic COVID-19 infection Within 28 days of treatment 6 Important	Relative risk 0.19 (CI 95% 0.1 — 0.35) Based on data from 1,505 participants in 1 studies. [3] (Randomized controlled)	78 per 1000 Difference:	15 per 1000 **63 fewer per 1000** (CI 95% 70 fewer — 51 fewer)	**Moderate** Due to serious imprecision [4]	Casirivimab pus imdevimab probably decreases symptomatic COVID-19 (70 events).
Confirmed COVID-19 infection Within 28 days of treatment 6 Important	Relative risk 0.34 (CI 95% 0.23 — 0.48) Based on data from 1,505 participants in 1 studies. [5] (Randomized controlled)	142 per 1000 Difference:	48 per 1000 **94 fewer per 1000** (CI 95% 109 fewer — 74 fewer)	**Moderate** Due to serious imprecision [6]	Casirivimab plus imdevimab probably decreases confirmed COVID-19 infection (143 events).
Adverse events Within 28 days of treatment 6 Important	Relative risk 0.7 (CI 95% 0.61 — 0.8) Based on data from 2,617 participants in 1 studies. [7] (Randomized controlled)	290 per 1000 Difference:	203 per 1000 **87 fewer per 1000** (CI 95% 113 fewer — 58 fewer)	**Moderate** Due to serious imprecision [8]	Casirivimab plus imdevimab probably decreases adverse events (644 events).
Serious adverse	Relative risk 0.66	11	7	**Low**	Casirivimab plus

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Casirivimab plus imdevimab	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
events Within 28 days of treatment 6 Important	(CI 95% 0.3 — 1.47) Based on data from 2,617 participants in 1 studies. [9] (Randomized controlled)	per 1000 Difference:	per 1000 **4 fewer per 1000** (CI 95% 8 fewer — 5 more)	Due to very serious imprecision [10]	imdevimab may have little impact on serious adverse events (35 events).
Discontinuation due to adverse events End of treatment 6 Important	Based on data from 2,617 participants in 1 studies. [11]				No participants discontinued treatment due to an adverse event.

Attached Images

8.2 Hydroxychloroquine for pre-exposure prophylaxis

Not recommended

For healthcare workers with no active COVID-19, do not use hydroxychloroquine for pre-exposure prophylaxis outside of randomised trials with appropriate ethical approval.

Additional information

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 for pre-exposure prophylaxis in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Important harms

General adult population
In addition to uncertainty around the benefits for people at high risk of being exposed to individuals 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.

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
There may be additional concerns regarding harms in these populations.

Certainty of the Evidence

Low

General adult population
Certainty of the evidence is low for laboratory-confirmed diagnosis, moderate for adverse events and confirmed or probable infection (due to included studies terminating early), low for serious adverse events and symptoms compatible with COVID-19 (due to studies being terminated early and few events), and very low for discontinuation due to aderse events.

Children and adolescents, pregnant women, people requiring palliative care and older people living with frailty or cognitive impairment
Certainty of the evidence was downgraded further for all outcomes due to indirectness, as these special populations were not included in the trials.

Values and preferences

Substantial variability is expected or uncertain

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 take risks.

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.

Resources

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

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 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
Since these populations are particularly at risk from COVID-19, we encourage trials that include these populations (with appropriate baseline measurement of frailty and cognitive impairment). Given the absence of trials and uncertain benefit-to-harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

Implementability of the recommendation 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 hydroxychloroquine for pre-exposure prophylaxis on the prevention of COVID-19 in healthcare workers. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that hydroxychloroquine for pre-exposure prophylaxis should only be used to prevent COVID-19 infection 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 once-weekly hydroxychloroquine for pre-exposure prophylaxis for the prevention of COVID-19 infection in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

Population: Healthcare workers (with no active or prior COVID-19)
Intervention: Pre-exposure hydroxychloroquine
Comparator: Placebo

Summary

Pre-exposure prophylactic hydroxychloroquine may be no more effective at preventing COVID-19 infection in high-risk healthcare workers than placebo and may result in more adverse events.

What is the evidence informing this recommendation?
Evidence comes from three randomised trials that compared hydroxychloroquine as pre-exposure prophylaxis with placebo in 1884 high-risk healthcare workers with no active or prior COVID-19 *[188][189][394]*.

We have found two new studies comparing hydroxychloroquine as pre-exposure prophylaxis with placebo among healthcare workers at high risk (Syed et al. medRxiv doi: 10.1101/2021.05.17.21257012 and Naggie et al. medRxiv doi: 10.1101/2021.08.19.21262275). These studies are currently under review and will be incorporated in a future version of the guideline.

Study characteristics
Two studies reported comparatively low doses of hydroxychloroquine: in Rajasingham et al. participants were given a loading dose of 400 mg (two 200 mg tablets) of hydroxychloroquine twice separated by 6-8 hours, followed by 400 mg (two 200 mg tablets) either once or twice weekly for 12 weeks *[189]*. Participants in Grau-Pujol et al. were given 400 mg hydroxychloroquine daily for 4 days, followed by 400 mg once weekly for one month *[?]*. In the study by Abella et al. participants received 600 mg of hydroxychloroquine daily for 8 weeks *[188]*.

Median age ranged from 31 to 42 years in the hydroxychloroquine arms and from 34 to 40 years in the placebo arms. The proportion of women ranged from 53% to 83% in the hydroxychloroquine arms and 49% to 73% in the placebo arms. One study explicitly excluded pregnant women *[?]*, one study did not specify whether pregnant or breastfeeding women were eligible *[188]*, and no pregnant women enrolled in the third study, although 30 women reported breastfeeding at baseline *[189]*.

What are the main results?
Pre-exposure prophylactic hydroxychloroquine probably increases incidence of adverse events (108 more per 1000 healthcare workers; RR 1.45 CI 95% 1.14 to 1.84; 1801 participants in 3 studies). Pre-exposure prophylactic hydroxychloroquine may make little or no difference to the number of people who contract laboratory-confirmed COVID-19, experience symptoms compatible with COVID-19, develop confirmed or probable infection, experience serious adverse events or who discontinue treatment due to adverse events.

Our confidence in the results
Certainty of the evidence is low for laboratory-confirmed diagnosis, moderate for adverse events and confirmed or probable infection (due to included studies terminating early), low for serious adverse events and symptoms compatible with COVID-19 (due to studies being terminated early and few events), and very low for discontinuation due to adverse events.

Additional information
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 [52]. There are several known and potential interactions with other drugs [52]. 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 [52].

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Pre-exp HCQ	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Laboratory-confirmed diagnosis End of treatment 9 Critical	Relative risk 0.87 (CI 95% 0.4 — 1.88) Based on data from 1,877 participants in 3 studies. [1] (Randomized controlled)	16 per 1000 Difference:	14 per 1000 **2 fewer per 1000** (CI 95% 10 fewer — 14 more)	**Low** Due to serious risk of bias and serious imprecision [2]	Hydroxychloroquine pre-exposure prophylaxis may have little impact on laboratory-confirmed diagnosis in healthcare workers (26 events).
All-cause mortality End of treatment 6 Important	Based on data from 1,608 participants in 2 studies. [3]				There were no deaths.
Serious adverse events End of treatment 6 Important	Relative risk 0.78 (CI 95% 0.31 — 2.01) Based on data from 1,752 participants in 2 studies. [4] (Randomized controlled)	11 per 1000 Difference:	9 per 1000 **2 fewer per 1000** (CI 95% 8 fewer — 11 more)	**Low** Due to serious risk of bias and serious imprecision [5]	Hydroxychloroquine pre-exposure prophylaxis may have little impact on serious adverse events in healthcare workers (18 events).
Adverse events End of treatment 6 Important	Relative risk 1.45 (CI 95% 1.14 — 1.84) Based on data from 1,801 participants in 3 studies. [6] (Randomized controlled)	241 per 1000 Difference:	349 per 1000 **108 more per 1000** (CI 95% 34 more — 202 more)	**Moderate** Due to serious risk of bias [7]	Hydroxychloroquine pre-exposure prophylaxis probably increases adverse events in healthcare workers.
Symptoms compatible with COVID-19 12 weeks 6 Important	Relative risk 0.75 (CI 95% 0.5 — 1.11) Based on data from 1,483 participants in 1 studies. [8] (Randomized controlled)	77 per 1000 Difference:	58 per 1000 **19 fewer per 1000** (CI 95% 39 fewer — 8 more)	**Low** Due to serious risk of bias and serious imprecision [9]	Hydroxychloroquine pre-exposure prophylaxis may have little impact on development of symptoms compatible with COVID-19 in healthcare workers (95 events).
Confirmed or probable infection 12 weeks 6 Important	Relative risk 0.87 (CI 95% 0.6 — 1.27) Based on data from 1,483 participants in 1 studies. [10] (Randomized controlled)	79 per 1000 Difference:	69 per 1000 **10 fewer per 1000** (CI 95% 32 fewer — 21 more)	**Moderate** Due to serious risk of bias [11]	Hydroxychloroquine pre-exposure prophylaxis probably has little or no impact on confirmed or probable infection (107 events).
Discontinuation due to adverse events 8 weeks	Relative risk 0.95 (CI 95% 0.2 — 4.54) Based on data from 125 participants in 1 studies. [12] (Randomized controlled)			**Very low** Due to serious risk of bias and very serious imprecision [13]	There were too few events (6 events) to determine whether hydroxychloroquine pre-exposure prophylaxis increases or decreases discontinuation due to

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Pre-exp HCQ	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important					adverse events.

Attached Images

8.3 Hydroxychloroquine for post-exposure prophylaxis

Not recommended

For people exposed to individuals with SARS-CoV-2 infection, do not use hydroxychloroquine for post-exposure prophylaxis outside of randomised trials with appropriate ethical approval.

Additional information

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 for post-exposure prophylaxis in these populations unless they are eligible to be enrolled in trials.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Important harms

General adult population
In addition to uncertainty around the benefits for people exposed to individuals 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.

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
There may be additional concerns regarding harms in these populations.

Certainty of the Evidence

Very low

General adult population
Certainty of the evidence for the primary outcome of laboratory-confirmed diagnosis is moderate. Certainty is high for adverse events and low for all other outcomes, due either to serious risk of bias and serious imprecision (symptoms compatible with COVID-19, confirmed or probable infection and discontinuation due to adverse events) or very serious imprecision (all-cause mortality and serious adverse events).

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
Certainty of the evidence was downgraded further for all outcomes due to indirectness, as it is unclear whether these special populations were included in the trials.

Values and preferences

We expect few to want the intervention

The Consumer Panel believes that as there is evidence of harm but no evidence of benefit, informed individuals would not choose to use hydroxychloroquine for prophylaxis.

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 take risks.

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.

Resources

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

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 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
These populations are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). Given the absence of trials and uncertain benefit-to-harm ratio, this recommendation protects these more vulnerable populations.

Acceptability

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

Implementability of the recommendation 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 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 hydroxychloroquine chemoprophylaxis 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, the use of hydroxychloroquine as post-exposure prophylaxis in these populations should be avoided until evidence becomes available.

Clinical Question/ PICO

Population: People exposed to COVID-19
Intervention: Hydroxychloroquine post-exposure prophylaxis
Comparator: Placebo

Summary

Based on the available evidence, post-exposure prophylactic hydroxychloroquine is probably no more effective at preventing COVID-19 infection than placebo, and results in more adverse events.

What is the evidence informing this recommendation?
Evidence informing this recommendation comes from two randomised trials that compared post-exposure prophylaxis using hydroxychloroquine to placebo in 3135 asymptomatic people *[190][192]*. All study participants were exposed to a person with a confirmed COVID-19 infection and were asymptomatic when treatment started.

We have found two new studies comparing post-exposure prophylactic hydroxychloroquine with placebo—one in direct household contacts of patients with COVID-19 (Barnabas et al. Ann Intern Med doi: 10.7326/M20-6519) and the other in healthcare workers exposed to patients infected by SARS-CoV-2 (Rojas-Serrano et al. PLoS One doi: 10.1371/journal.pone.0261980). These studies are currently under review and an updated recommendation will be included in a future version of the guideline.

Study characteristics
In the first trial of 821 people, median age was 40 years and 52% were women *[190]*. In the second trial of 2314 people, mean age was 49 years and 73% were women *[192]*.

Our confidence in the results
Certainty of the evidence is moderate for laboratory-confirmed diagnosis and adverse events (due to imprecision). Certainty is low for all other outcomes either due to serious inconsistency and serious risk of bias (symptoms compatible with COVID-19, confirmed or probable infection and discontinuation due to adverse events) or very serious imprecision (all-cause mortality and serious adverse events).

Additional information
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 *[115]*. There are several known and potential interactions with other drugs *[115]*. 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 *[115]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Hydroxychloroquine post-exposure prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Laboratory-confirmed diagnosis 14 days after commencing	Relative risk 0.96 (CI 95% 0.71 — 1.3) Based on data from 3,135 participants in 2 studies. [1] (Randomized	52 per 1000 Difference:	50 per 1000 **2 fewer per 1000** (CI 95% 15 fewer	**Moderate** Due to serious imprecision [2]	Hydroxychloroquine post-exposure prophylaxis probably has no effect on the number of laboratory-confirmed diagnoses.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Hydroxychloroquine post-exposure prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
treatment 9 Critical	controlled)		— 16 more)		
Symptoms compatible with COVID-19 14 days after commencing treatment 6 Important	Relative risk 0.98 (CI 95% 0.82 — 1.18) Based on data from 3,135 participants in 2 studies. [3] (Randomized controlled)	128 per 1000 Difference:	125 per 1000 **3 fewer per 1000** (CI 95% 23 fewer — 23 more)	**Low** Due to serious risk of bias and imprecision [4]	Hydroxychloroquine post-exposure prophylaxis may have no effect on the number of symptoms compatible with COVID-19.
Confirmed or probable infection 14 days after commencing treatment 6 Important	Relative risk 0.83 (CI 95% 0.58 — 1.18) Based on data from 821 participants in 1 studies. [5] (Randomized controlled)	143 per 1000 Difference:	119 per 1000 **24 fewer per 1000** (CI 95% 60 fewer — 26 more)	**Low** Due to serious risk of bias and imprecision [6]	Hydroxychloroquine post-exposure prophylaxis may have no effect on the number of patients with confirmed or probable infection.
All-cause mortality End of treatment 6 Important	Relative risk 0.68 (CI 95% 0.22 — 2.07) Based on data from 3,318 participants in 2 studies. [7] (Randomized controlled)	5 per 1000 Difference:	3 per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 5 more)	**Low** Due to very serious imprecision [8]	We are uncertain whether hydroxychloroquine post-exposure prophylaxis improves or worsens all-cause mortality (13 events).
Serious adverse events End of treatment 6 Important	Relative risk 0.89 (CI 95% 0.44 — 1.81) Based on data from 2,497 participants in 1 studies. [9] (Randomized controlled)	13 per 1000 Difference:	12 per 1000 **1 fewer per 1000** (CI 95% 7 fewer — 11 more)	**Low** Due to very serious imprecision [10]	We are uncertain whether hydroxychloroquine post-exposure prophylaxis increases or decreases serious adverse events (31 events).
Adverse events End of treatment 6 Important	Relative risk 4.76 (CI 95% 1.19 — 19.1) Based on data from 3,197 participants in 2 studies. [11] (Randomized controlled)	82 per 1000 Difference:	390 per 1000 **308 more per 1000** (CI 95% 16 more — 1,484 more)	**Moderate** Due to serious risk of bias [12]	Hydroxychloroquine post-exposure prophylaxis probably increases the number of adverse events.
Discontinuation due to adverse events End of treatment	Relative risk 4.1 (CI 95% 0.52 — 32.23) Based on data from 3,346 participants in 2 studies. [13] (Randomized	5 per 1000 Difference:	20 per 1000 **15 more per 1000** (CI 95% 2 fewer	**Very low** Due to serious risk of bias and very serious imprecision [14]	We are uncertain whether hydroxychloroquine post-exposure prophylaxis increases

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Hydroxychloroquine post-exposure prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important	controlled)		— 156 more)		discontinuation due to adverse events (33 events).

Attached Images

Clinical Question/ PICO

Population: Special populations
Intervention: Hydroxychloroquine post-exposure prophylaxis
Comparator: Placebo

Summary

Based on the available evidence, post-exposure prophylactic hydroxychloroquine is probably no more effective at preventing COVID-19 infection than placebo, and results in more adverse events.

What is the evidence informing this recommendation?
Evidence informing this recommendation comes from two randomised trials that compared post-exposure prophylaxis using hydroxychloroquine to placebo in 3135 asymptomatic people *[190][192]*. All study participants were exposed to a person with a confirmed COVID-19 infection and were asymptomatic when treatment started.

We have found one new study comparing post-exposure prophylactic hydroxychloroquine with placebo in direct household contacts of patients with COVID-19 (Barnabas et al. Ann Intern Med doi: 10.7326/M20-6519). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

Study characteristics
In the first trial of 821 people, median age was 40 years and 52% were women *[190]*. In the second trial of 2314 people, mean age was 49 years and 73% were women *[192]*.

Our confidence in the results
Certainty of the evidence is moderate for laboratory-confirmed diagnosis and adverse events (due to imprecision). Certainty is low for all other outcomes either due to serious inconsistency and serious risk of bias (symptoms compatible with COVID-19, confirmed or probable infection and discontinuation due to adverse events) or very serious imprecision (all-cause mortality and serious adverse events).

Additional information
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 *[115]*. There are several known and potential interactions with other drugs *[115]*. 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 *[115]*.

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 *[119][120]*. There is no evidence to suggest that stillbirth, preterm birth, low birth weight or early childhood disability are more common following treatment with hydroxychloroquine *[119][120][121]*. While this evidence is reassuring, further research is needed.

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 on the use of hydroxychloroquine as post-exposure prophylaxis in this population.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Hydroxychloroquine post-exposure prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Laboratory-confirmed diagnosis 14 days after commencing treatment 9 Critical	Relative risk 0.96 (CI 95% 0.71 — 1.3) Based on data from 3,135 participants in 2 studies. [1] (Randomized controlled)	52 per 1000 Difference:	50 per 1000 **2 fewer per 1000** (CI 95% 15 fewer — 16 more)	**Low** Due to serious imprecision and indirectness [2]	Hydroxychloroquine post-exposure prophylaxis may have no effect on the number of laboratory-confirmed diagnoses.
Symptoms compatible with COVID-19 14 days after commencing treatment 6 Important	Relative risk 0.98 (CI 95% 0.82 — 1.18) Based on data from 3,135 participants in 2 studies. [3] (Randomized controlled)	128 per 1000 Difference:	125 per 1000 **3 fewer per 1000** (CI 95% 23 fewer — 23 more)	**Very low** Due to serious risk of bias, imprecision and indirectness [4]	Hydroxychloroquine post-exposure prophylaxis may have no effect on the number of symptoms compatible with COVID-19.
Confirmed or probable infection 14 days after commencing treatment 6 Important	Relative risk 0.83 (CI 95% 0.58 — 1.18) Based on data from 821 participants in 1 studies. [5] (Randomized controlled)	143 per 1000 Difference:	119 per 1000 **24 fewer per 1000** (CI 95% 60 fewer — 26 more)	**Very low** Due to serious risk of bias, imprecision and indirectness [6]	Hydroxychloroquine post-exposure prophylaxis may have no effect on the number of patients with confirmed or probable infection.
All-cause mortality End of treatment 6 Important	Relative risk 0.68 (CI 95% 0.22 — 2.07) Based on data from 3,318 participants in 2 studies. [7] (Randomized controlled)	5 per 1000 Difference:	3 per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 5 more)	**Very low** Due to very serious imprecision and serious indirectness [8]	We are uncertain whether hydroxychloroquine post-exposure prophylaxis improves or worsens all-cause mortality (13 events).
Serious adverse events End of treatment 6 Important	Relative risk 0.89 (CI 95% 0.44 — 1.81) Based on data from 2,497 participants in 1 studies. [9] (Randomized controlled)	13 per 1000 Difference:	12 per 1000 **1 fewer per 1000** (CI 95% 7 fewer — 11 more)	**Very low** Due to very serious imprecision and serious indirectness [10]	We are uncertain whether hydroxychloroquine post-exposure prophylaxis increases or decreases serious adverse events (31 events).
Adverse events End of treatment 6 Important	Relative risk 4.76 (CI 95% 1.19 — 19.1) Based on data from 3,197 participants in 2 studies. [11] (Randomized controlled)	82 per 1000 Difference:	390 per 1000 **308 more per 1000** (CI 95% 16 more — 1,484 more)	**Low** Due to serious risk of bias and indirectness [12]	Hydroxychloroquine post-exposure prophylaxis may increase the number of adverse events.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Hydroxychloroquine post-exposure prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Discontinuation due to adverse events End of treatment 6 Important	Relative risk 4.1 (CI 95% 0.52 — 32.23) Based on data from 3,346 participants in 2 studies. [13] (Randomized controlled)	5 per 1000 Difference:	20 per 1000 **15 more per 1000** (CI 95% 2 fewer — 156 more)	**Very low** Due to serious risk of bias, indirectness and very serious imprecision [14]	We are uncertain whether hydroxychloroquine post-exposure prophylaxis increases or decreases discontinuation due to adverse events (33 events).

Attached Images

8.4 Tixagevimab plus cilgavimab (Evusheld) for pre-exposure prophylaxis

Consensus recommendation

New

Do not routinely use tixagevimab plus cilgavimab (Evusheld) for pre-exposure prophylaxis of COVID-19.

Additional information

The Taskforce previously recommended that tixagevimab plus cilgavimab (Evusheld) should not be routinely used for pre-exposure prophylaxis, but that use may be considered in individuals who are severely immunocompromised. This recommendation was based on the PROVENT trial [454], in which 5197 unvaccinated adults were administered a single 300 mg dose of Evusheld consisting of two intramuscular injections (150 mg tixagevimab and 150 mg cilgavimab).

The PROVENT trial was conducted before the emergence of Omicron as the dominant variant. Since the development of the initial recommendations, a significant body of in vitro evidence has emerged demonstrating a significant reduction in activity of tixagevimab plus cilgavimab (Evusheld) against the Omicron BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that tixagevimab plus cilgavimab (Evusheld) is effective as pre-exposure prophylaxis due to currently circulating variants of COVID-19; however, use maybe considered in exceptional circumstances, in individuals who are severely immunocompromised where risk of infection with the BA2 variant is more likely, as in vitro evidence suggests that some efficacy remains for Omicron BA2 variant.

In the absence of reliable evidence, the Taskforce has developed this recommendation based on their clinical expertise and experience.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Tixagevimab plus cilgavimab probably has little impact on incidence of positive SARS-CoV-2 infection, emergency department visits, adverse events or serious adverse events. We are unsure if tixagevimab plus cilgavimab impacts all-cause mortality or progression to severe disease.

Certainty of the Evidence

Moderate

Certainty is moderate for positive SARS-CoV-2 infection, emergency department visits, adverse events and serious adverse events due to serious imprecision (reliance on a single study). Certainty is low for all-cause mortality and progression to severe disease due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Values and preferences

Substantial variability is expected or uncertain

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

Resources

Important issues, or potential issues not investigated

The limited availability of tixagevimab plus cilgavimab, as well as the high cost of treatment, are limiting factors preventing widespread use of this treatment.

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity; however any limitations on availability and the significant cost of tixagevimab plus cilgavimab may affect equity based on geographic area and access to tixagevimab plus cilgavimab.

Acceptability

Important issues, or potential issues not investigated

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

Feasibility

No important issues with the recommended alternative

The Therapeutic Goods Administration provisionally approved the use of tixagevimab plus cilgavimab for use as pre-exposure prophylaxis on 24 February 2022 for the following indications:

- individuals who have moderate-to-severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments that make it likely that they will not mount an adequate immune response to COVID-19 vaccination; or
- individuals for whom vaccination is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine or COVID-19 vaccine component (TGA).

Clinical Question/ PICO

Population: Evusheld for COVID-19 prophylaxis
Intervention: Evusheld
Comparator: Placebo – pre-exposure prophylaxis

Summary

Evidence indicates that tixagevimab plus cilgavimab likely has little impact in reducing SARS-CoV-2 infection when used as pre-exposure prophylaxis, however it may be of benefit in treating patients who are severely immunocompromised.

What is the evidence informing this recommendation?
Evidence comes from the PROVENT trial *[454]* that compared tixagevimab plus cilgavimab (Evusheld) with placebo in 5197 adults who were expected to benefit from having received treatment due to either increased risk of inadequate response to vaccination, or increased risk of exposure due to a high density work and/or living environment.

Study characteristics
Mean age of participants was 53 years and 46% were women. Approximately 25% of participants were aged 65 years or over. Participants received a single dose of Evusheld, consisting of two simultaneous intramuscular injections (150 mg tixagevimab and 150 mg cilgavimab). Pregnant and breastfeeding women and children and adolescents were ineligible.

What are the main results?
Tixagevimab plus cilgavimab probably has little impact on incidence of positive SARS-CoV-2 infection, emergency department visits, adverse events or serious adverse events. We are unsure if tixagevimab plus cilgavimab impacts all-cause mortality or progression to severe disease.

Our confidence in the results
Certainty of the evidence is moderate for positive SARS-CoV-2 infection, emergency department visits, adverse events and serious adverse events due to serious imprecision (reliance on a single study). Certainty is low for all-cause mortality and progression to severe disease due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information
The Therapeutic Goods Administration has granted provisional determination for Evusheld. As of 24 February 2022,

Evusheld is not approved for use for the prevention of SARS-CoV-2 infection.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo – pre-exp prophylaxis	**Intervention** Evusheld	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Positive SARS-CoV-2 infection 9 Critical	Relative risk 0.24 (CI 95% 0.1 — 0.55) Based on data from 5,172 participants in 1 studies. [1] (Randomized controlled)	10 per 1000 Difference:	2 per 1000 **8 fewer per 1000** (CI 95% 9 fewer — 4 fewer)	**Moderate** Due to serious imprecision [2]	Evusheld probably has little impact on positive SARS-CoV-2 infection (25 events)
Severe COVID-19 6 Important	Relative risk 0.17 (CI 95% 0.01 — 4.12) Based on data from 5,172 participants in 1 studies. [3] (Randomized controlled)	1 per 1000 Difference:	0 per 1000 **1 fewer per 1000** (CI 95% 1 fewer — 3 more)	**Low** Due to very serious imprecision [4]	We are uncertain whether evusheld increases or decreases severe COVID-19 (1 event)
Emergency department visits 6 Important	Relative risk 1.54 (CI 95% 0.92 — 2.57) Based on data from 5,172 participants in 1 studies. [5] (Randomized controlled)	11 per 1000 Difference:	17 per 1000 **6 more per 1000** (CI 95% 1 fewer — 17 more)	**Moderate** Due to serious imprecision [6]	Evusheld probably has little or no difference on emergency department visits (77 events)
Adverse events 6 Important	Relative risk 1.03 (CI 95% 0.95 — 1.12) Based on data from 5,197 participants in 1 studies. [7] (Randomized controlled)	342 per 1000 Difference:	352 per 1000 **10 more per 1000** (CI 95% 17 fewer — 41 more)	**Moderate** Due to serious imprecision [8]	Evusheld probably has little or no difference on adverse events
Serious adverse events 6 Important	Relative risk 1.09 (CI 95% 0.67 — 1.78) Based on data from 5,197 participants in 1 studies. [9] (Randomized controlled)	13 per 1000 Difference:	14 per 1000 **1 more per 1000** (CI 95% 4 fewer — 10 more)	**Moderate** Due to serious imprecision [10]	Evusheld probably has little or no difference on serious adverse events (73 events)
All-cause mortality 9 Critical	Relative risk 0.5 (CI 95% 0.13 — 2) Based on data from 5,197 participants in 1 studies. [11] (Randomized controlled)	2 per 1000 Difference:	1 per 1000 **1 fewer per 1000** (CI 95% 2 fewer — 2 more)	**Low** Due to very serious imprecision [12]	We are uncertain whether evusheld increases or decreases all-cause mortality (8 events)

Attached Images

8.5 Tixagevimab plus cilgavimab (Evusheld) for post-exposure prophylaxis

Only in research settings

For people exposed to individuals with SARS-CoV-2 infection, do not use tixagevimab plus cilgavimab for post-exposure prophylaxis outside of randomised trials with appropriate ethical approval.

Additional information

Evidence suggests that administration of tixagevimab plus cilgavimab has little impact on preventing SARS-CoV-2 infection when administered as post-exposure prophylaxis in people who have been in close contact with an individual with confirmed COVID-19.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Tixagevimab plus cilgavimab probably decreases incidence of adverse events (RR 0.72, CI 95% 0.59, 0.89; 1121 participants in 1 study) but probably has little impact on incidence of positive SARS-CoV-2 infection. We are unsure if tixagevimab or cilgavimab impacts progression to severe disease. No participants died.

Certainty of the Evidence

Moderate

Confidence is moderate for positive SARS-CoV-2 infection and adverse events due to serious imprecision (reliance on a single study), and low for progression to severe disease and serious adverse events due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Values and preferences

Substantial variability is expected or uncertain

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

Resources

Important issues, or potential issues not investigated

The limited availability of tixagevimab plus cilgavimab, as well as the high cost of treatment, are limiting factors preventing widespread use of this treatment.

Equity

Important issues, or potential issues not investigated

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.

Acceptability

Important issues, or potential issues not investigated

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

patients and clinicians.

Feasibility

Intervention is likely difficult to implement

As of 24 March 2022, tixagevimab plus cilgavimab is not approved for use as post-exposure prophylaxis.

Rationale

General adult population

In adults exposed to an individual with confirmed COVID-19, tixagevimab plus cilgavimab has little impact on prevention of SARS-CoV-2 infection. Because of this, the Taskforce recommends that tixagevimab plus cilgavimab should only be used as post-exposure prophylaxis in the context of randomised trials with appropriate ethical approval.

Clinical Question/ PICO

Population:	Evusheld for COVID-19 prophylaxis
Intervention:	Evusheld
Comparator:	Placebo – post-exposure prophylaxis

Summary

Evidence indicates that tixagevimab plus cilgavimab likely has little impact in reducing SARS-CoV-2 infection when used as post-exposure prophylaxis.

What is the evidence informing this recommendation?

Evidence comes from a single clinical study report (STORM CHASER trial) that compared tixagevimab plus cilgavimab (Evusheld) with placebo in 1,121 adults within 8 days of being exposed to an individual with laboratory confirmed COVID-19 and who were in high-density settings.

Study characteristics

Mean age of participants was 46 years and 49% were women. Approximately one quarter of participants were aged 65 years or over. One fifth of patients were aged 60 years or over, with only 3.5% of participants being over 75 years of age. Participants received a single dose of Evusheld, consisting of two simultaneous intramuscular injections (150mg tixagevimab and 150mg cilgavimab). Pregnant and breastfeeding women and children and adolescents were ineligible.

What are the main results?

Tixagevimab plus cilgavimab probably decreases incidence of adverse events (RR 0.72, CI 95% 0.59, 0.89; 1121 participants in 1 study) but probably has little impact on incidence of positive SARS-CoV-2 infection. We are unsure if tixagevimab or cilgavimab impacts progression to severe disease. No participants died.

Our confidence in the results

Confidence is moderate for positive SARS-CoV-2 infection and adverse events due to serious imprecision (reliance on a single study), and low for progression to severe disease and serious adverse events due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

Additional information

The Therapeutic Goods Administration have granted provisional determination for Evusheld. As of 24 February 2022, Evusheld is not approved for use for the prevention of SARS-CoV-2 infection.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo – post-exp prophylaxis	**Intervention** Evusheld	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality 9 Critical	Relative risk Based on data from 1,121 participants in 1 studies. [1]				No patients died
Positive SARS-CoV-2 infection 9 Critical	Relative risk 0.67 (CI 95% 0.36 — 1.24) Based on data from 1,121 participants in 1 studies. [2] (Randomized controlled)	46 per 1000 Difference:	31 per 1000 **15 fewer per 1000** (CI 95% 29 fewer — 11 more)	**Moderate** Due to serious imprecision [3]	Evusheld probably has little or no difference on positive SARS-CoV-2 infection (40 events)
Severe COVID-19 6 Important	Relative risk 0.17 (CI 95% 0.01 — 4.06) Based on data from 1,121 participants in 1 studies. [4] (Randomized controlled)	3 per 1000 Difference:	1 per 1000 **2 fewer per 1000** (CI 95% 3 fewer — 9 more)	**Low** Due to very serious imprecision [5]	We are uncertain whether evusheld increases or decreases severe COVID-19 (1 event)
Adverse events 6 Important	Relative risk 0.72 (CI 95% 0.59 — 0.89) Based on data from 1,121 participants in 1 studies. [6] (Randomized controlled)	298 per 1000 Difference:	215 per 1000 **83 fewer per 1000** (CI 95% 122 fewer — 33 fewer)	**Moderate** Due to serious imprecision [7]	Evusheld probably decreases adverse events (273 events)
Serious adverse events 6 Important	Relative risk 0.83 (CI 95% 0.2 — 3.45) Based on data from 1,121 participants in 1 studies. [8] (Randomized controlled)	8 per 1000 Difference:	7 per 1000 **1 fewer per 1000** (CI 95% 6 fewer — 20 more)	**Low** Due to very serious imprecision [9]	We are uncertain whether evusheld increases or decreases serious adverse events (8 events)

Attached Images

9. Respiratory support in adults

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 *[193]*. Direct evidence suggests that CPAP therapy is preferred for patients with persistent hypoxaemia associated with COVID-19 (defined as requiring an $FiO2 \geq 0.4$ to maintain oxygen saturation in their target range). Currently insufficient direct evidence available to support the use of bilevel positive pressure support in the setting of COVID-19. High-flow nasal oxygen (HFNO) may be an alternative to CPAP in certain situation.

Panels responsible for the recommendations in this section:

Recommendations	Primary Panel
HFNO and NIV	Acute and Critical Care Panel
Respiratory management of the deteriorating patient, video-laryngoscopy, neuromuscular blockers, PEEP, prone positioning, recruitment manoeuvres and ECMO	Acute and Critical Care Panel
Respiratory support for pregnant and postpartum women	Pregnancy and Perinatal Care Panel
Recommendations are reviewed by the Guidelines Leadership Group and approved by the Steering Committee before being published. The remaining panels review recommendations when relevant to their specific population group. In addition, all our recommendations are reviewed by the Consumer Panel.	

Info Box

The Acute and Critical Care Panel is responsible for developing recommendations specific to respiratory support for the general population. The Pregnancy and Perinatal Care Panel is responsible for developing recommendations specific to respiratory support for pregnant and postpartum women.

Recommendations are subsequently reviewed by the Guidelines Leadership Group and approved by the Steering Committee prior to publication. In addition, all recommendations are reviewed by the Consumer Panel to establish acceptability to the patient population for which they are relevant.

9.1 Respiratory management

Consensus recommendation

Guiding principles of care

For patients with COVID-19 receiving respiratory support, use single and negative pressure rooms wherever possible. If none are available, other alternatives are single rooms, or shared ward spaces with cohorting of confirmed COVID-19 patients. Ensure contact, droplet and airborne precautions are in place. Healthcare workers should be fully vaccinated and wearing fit-tested N95 masks.

Additional information

The additional relative risk of infection to healthcare workers associated with specific oxygen therapies and respiratory support is uncertain but is thought to add minimal additional risk in an environment where transmission of infection with COVID-19 is already high.

Info Box

When caring for patients with COVID-19, clinicians need to determine a target range of oxygen saturation to titrate oxygen therapy. Advisable target ranges of oxygen saturation are:

- 92–96% in most patients
- 88–92% in patients at risk of hypercapnia

All awake patients receiving respiratory support should be educated on proning (see section 8.7) and should be encouraged/assisted to prone for as long as is practicable.

Conventional oxygen therapy can be delivered by:

- Nasal prongs at 1–4 L/min (FiO2 approx. 0.24-0.36) to maintain oxygen saturation within the target range.
- Mask at 6–10 L/min (FiO2 approx. 0.35-0.60) to maintain oxygen saturation within the target range.
- Non-rebreather mask 15L/min (FiO2 approx. 1.00) to maintain oxygen saturation within the target range.
- High-flow nasal oxygen (HFNO) therapy with flow rates up to 60L/min with an oxygen/air blender supplying oxygen at FiO2, 0.21-1.00 to maintain oxygen saturation within the target range. It delivers high flow oxygen that is humidified and heated, via large diameter nasal cannula.

Non-invasive ventilation can be delivered by:

- Continuous positive airway pressure (CPAP), a mode of non-invasive ventilation which applies continuous positive airway pressure (with or without entrained oxygen). It can aid in alveolar recruitment and optimise oxygen delivery. CPAP is generally used for hypoxaemic respiratory failure.
- Bilevel positive pressure support (e.g. BiPAP), another mode of non-invasive ventilation which provides a higher level of pressure during the inspiratory phase to enhance ventilation, while a lower level of positive pressure is delivered during the expiratory phase (known as positive end-expiratory pressure [PEEP]). Supplemental oxygen can also be delivered through the device. Bilevel positive pressure support is generally used when there is hypercapnia with or without hypoxaemia.

Conditional recommendation

For patients with COVID-19 who have hypoxaemic respiratory failure and are unable to maintain oxygen saturations within target range despite oxygen delivery by nasal prongs or mask, consider using continuous positive airway pressure (CPAP).

The evidence suggests that CPAP therapy is preferred for patients with persistent hypoxaemia associated with COVID-19 (defined as requiring an FiO2 ≥ 0.4 to maintain oxygen saturation in their target range). Adjust continuous positive airway pressure as required, most patients require pressures of 10 to 12 cmH2O. Excessive pressures may increase the risk of pneumothorax. Titrate oxygen to maintain oxygen saturation in the target range. There is currently insufficient direct evidence available to support the use of bilevel positive pressure support in the setting of COVID-19.

If CPAP is not available or not tolerated, consider high-flow nasal oxygen (HFNO) as an alternative to conventional oxygen delivery, using the same safety parameters.

Patients receiving CPAP (and/or HFNO) for COVID-19, monitor closely at all times and liaise with ICU in case of deterioration. Do not delay endotracheal intubation and invasive mechanical ventilation in patients with COVID-19 who are deteriorating despite optimised, less invasive respiratory therapies.

Clinical Question/ PICO

Population: Patients with COVID-19 patients
Intervention: Continuous positive airway pressure
Comparator: Conventional oxygen therapy

Outcome Timeframe	**Study results and measurements**	**Comparator** Conventional oxygen therapy	**Intervention** CPAP	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality or trachael intubation [composite] Within 30 days 9 Critical	Relative risk 0.82 (CI 95% 0.69 — 0.98) Based on data from 733 participants in 1 studies. [1] (Randomized controlled)	444 per 1000 Difference:	364 per 1000 **80 fewer per 1000** (CI 95% 138 fewer — 9 fewer)	**Moderate** Due to serious imprecision [2]	CPAP probably decreases death or trachael intubation [composite] (295 events).
Trachael intubation Within 30 days 9 Critical	Relative risk 0.81 (CI 95% 0.67 — 0.98) Based on data from 733 participants in 1 studies. [3] (Randomized controlled)	413 per 1000 Difference:	335 per 1000 **78 fewer per 1000** (CI 95% 136 fewer — 8 fewer)	**Moderate** Due to serious imprecision [4]	CPAP probably decreases trachael intubation (273 events).
All-cause mortality Within 30 days 9 Critical	Relative risk 0.87 (CI 95% 0.64 — 1.18) Based on data from 737 participants in 1 studies. [5] (Randomized controlled)	192 per 1000 Difference:	167 per 1000 **25 fewer per 1000** (CI 95% 69 fewer — 35 more)	**Low** Due to very serious imprecision [6]	CPAP may decrease all-cause mortality slightly (132 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** Conventional oxygen therapy	**Intervention** CPAP	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Admission to critical care 6 Important	Relative risk 0.88 (CI 95% 0.78 — 1) Based on data from 733 participants in 1 studies. [7] (Randomized controlled)	615 per 1000 Difference:	541 per 1000 **74 fewer per 1000** (CI 95% 135 fewer — 0 fewer)	**Moderate** Due to serious imprecision [8]	CPAP probably decreases admission to critical care (424 events).
Critical care length of stay Mean 6 Important	Lower better Based on data from 882 participants in 1 studies. [9] (Randomized controlled)	9.6 (Mean) Difference:	9.5 (Mean) **MD 0.1 lower** (CI 95% 2.03 lower — 1.83 higher)	**Low** Due to very serious imprecision [10]	CPAP may have little impact on critical care length of stay.
Hospital length of stay Mean 6 Important	Lower better Based on data from 882 participants in 1 studies. [11] (Randomized controlled)	17.3 (Mean) Difference:	16.4 (Mean) **MD 0.9 lower** (CI 95% 3.26 lower — 1.46 higher)	**Low** Due to very serious imprecision [12]	CPAP may have little impact on hospital length of stay.

Attached Images

Clinical Question/ PICO

Population: Patients with COVID-19 patients
Intervention: High-flow nasal oxygen therapy
Comparator: Conventional oxygen therapy

Outcome Timeframe	**Study results and measurements**	**Comparator** standard oxygen therapy	**Intervention** HFNO	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality or trachael intubation [composite] Within 30 days 9 Critical	Relative risk 1 (CI 95% 0.85 — 1.17) Based on data from 770 participants in 1 studies. [1] (Randomized controlled)	444 per 1000 Difference:	444 per 1000 **0 fewer per 1000** (CI 95% 67 fewer — 75 more)	**Moderate** Due to serious imprecision [2]	HFNO probably has little impact on all-cause mortality or tracheal intubation [composite] (342 events).
All-cause mortality	Relative risk 0.77 (CI 95% 0.44 — 1.35)	192	148	**Moderate** Due to serious	HFNO probably decreases new all-cause

Outcome Timeframe	**Study results and measurements**	**Comparator** standard oxygen therapy	**Intervention** HFNO	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Within 30 days of commencing treatment 9 Critical	Based on data from 982 participants in 2 studies. [3] (Randomized controlled)	per 1000 Difference:	per 1000 **44 fewer per 1000** (CI 95% 108 fewer — 67 more)	imprecision [4]	mortality slightly (176 deaths)
Tracheal intubation Within 30 days of commencing treatment 9 Critical	Relative risk 0.84 (CI 95% 0.58 — 1.22) Based on data from 981 participants in 2 studies. [5] (Randomized controlled)	**436** per 1000 Difference:	**366** per 1000 **70 fewer per 1000** (CI 95% 183 fewer — 96 more)	**Low** Due to serious risk of bias and serious imprecision [6]	HFNO may decrease new tracheal intubation (408 events).
Admission to critical care 6 Important	Relative risk 0.99 (CI 95% 0.89 — 1.11) Based on data from 770 participants in 1 studies. [7] (Randomized controlled)	**615** per 1000 Difference:	**609** per 1000 **6 fewer per 1000** (CI 95% 68 fewer — 68 more)	**Moderate** Due to serious imprecision [8]	HFNO probably has little impact on admission to critical care (472 events).
Critical care length of stay Mean 6 Important	Lower better Based on data from 882 participants in 1 studies. [9] (Randomized controlled)	**9.6** (Mean) Difference:	**10.5** (Mean) **MD 0.9 higher** (CI 95% 1.03 lower — 2.83 higher)	**Low** Due to very serious imprecision [10]	HFNO may have little impact on critical care length of stay.
Hospital length of stay Mean 6 Important	Lower better Based on data from 882 participants in 1 studies. [11] (Randomized controlled)	**17.3** (Mean) Difference:	**18.3** (Mean) **MD 1 higher** (CI 95% 1.51 lower — 3.51 higher)	**Low** Due to very serious imprecision [12]	HFNO may have little impact on hospital length of stay.

Attached Images

Clinical Question/ PICO

Population: Patients with hypoxaemia associated with COVID-19

Intervention: Non-invasive ventilation (helmet or face mask)

Comparator: High-flow nasal oxygen (HFNO) or supplementary oxygen therapy (SOT)

Summary

See the Summary in the NIV recommendation for consider using in negative pressure rooms, single rooms or shared ward spaces with cohorting of confirmed COVID-19 patients.

Outcome Timeframe	**Study results and measurements**	**Comparator** HFNO or SOT	**Intervention** Helmet or face mask NIV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
See summary	Based on data from 3,804 participants in 25 studies. (Randomized controlled)	See summary for findings on all-cause mortality and endotracheal intubation.			

Attached Images

9.2 Respiratory management of the deteriorating patient

Consensus recommendation

Do not delay endotracheal intubation and mechanical ventilation in patients with COVID-19 who are deteriorating despite optimised, less invasive respiratory therapies.

Additional information

Patients can deteriorate rapidly 5 to 10 days after onset of symptoms.

The net clinical benefit for each patient should be considered on a case-by-case basis, as factors such as frailty, advanced illness or comorbidity may lessen the benefit and increase potential harms.

Decisions around proceeding to more invasive forms of therapy should be discussed with the patient, healthcare decision-maker or family/carers. The goals of patient care need to balance the preferences and values of the patient, based on discussion and an advance care directive or plan if available, and consideration of the patient's expected short- and long-term responses to more invasive forms of treatment.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Benefits and harms should be considered on a case-by-case basis as the net clinical benefit is likely to vary for each patient. Frailty, advanced illness or comorbidity may lessen the benefit and increase potential harms. Benefits can include a decrease in self-inflicted lung injury and rapid decline. Harms relevant to transmission should also be considered, as there may be different risks of transmission associated with different settings, for example ICU compared to the emergency department.

Certainty of the Evidence

No studies were identified in COVID-19 patients that address the interventions, comparators and outcomes of interest.

Values and preferences

Substantial variability is expected or uncertain

There is no systematically collected information regarding patients' preferences and values at this point. In some patients, comfort, sedation and intubation may lead to symptom management improvement. However, in other patients intubation may not be feasible or considered suitable. Some patients may decline intubation if offered. Decisions around proceeding to more invasive forms of ventilation should be made collaboratively with the patient or their medical treatment decision-maker.

People requiring palliative care and older people living with frailty or cognitive impairment
Consider the preferences and values of the patient and whether they have an advanced care directive or plan.

The Consumer Panel believes that in line with available evidence, some informed patients/carers would wish to have more invasive treatment initiated if this is consistent with their goals of care. The Panel recognises that some informed patients/carers may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel also believes that most informed patients/carers would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. However, there are likely to be resource issues associated with different settings.

Equity

Important issues, or potential issues not investigated

There are likely no important equity issues.

Acceptability

Important issues, or potential issues not investigated

Although we have no systematically collected evidence regarding acceptability, we expect some patients may decline intubation if offered.

Feasibility

Important issues, or potential issues not investigated

More invasive ventilation options may be very limited in patients with frailty or underlying health issues, and in other circumstances where clinical judgement deems patients may be unlikely to benefit from intubation. In some situations and settings (where deterioration occurs outside the hospital), intensification of treatment may be further limited by access to suitably experienced clinicians.

Adaptation

The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign *[193]*. Wording has been adapted for clarity and applicability to the Australian context.

9.3 Videolaryngoscopy

Conditional 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.

Additional information

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Time to intubation varies 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.

Values and preferences

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.

The Consumer Panel believes that in line with available evidence, most informed patients would agree with the recommendation for this treatment for COVID-19. The Panel also believes that most informed patients would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources

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

No important issues with the recommended alternative

Videolaryngoscopy is generally a well-accepted intervention, and there are no important issues regarding acceptability.

Feasibility

Important issues, or potential issues not investigated

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 *[207]*. A simulation study is also included that evaluated the distance between a dummy's mouth and physician's face during intubation *[212]*.

Effectiveness and adverse events

Study design	Randomised trials
Population	Critically ill patients requiring emergency intubation in emergency departments or intensive care units. No studies available in patients with COVID-19.
Intervention	Videolaryngoscopy
Comparison	Direct laryngoscopy
Synthesis method	Meta-analysis
Results	We included six of the eight randomised trials (1023 patients) in the Rombey review *[205][206][208][209][210][211]*. (Two were excluded because patients were intubated before hospital admission.) We included an additional randomised trial of 163 patients that was published after the Rombey review *[204]*. This study did not change the overall results for the outcomes, but did improve the precision of the estimate for inadvertent oesophageal intubation. 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)

Study design	Crossover study
Population	25 doctors of mixed experience performing tracheal intubation on a high-fidelity manikin.
Intervention	Videolaryngoscopy
Comparison	Direct laryngoscopy
Results	Videolaryngoscopy may extend the mouth-to-mouth distance from laryngoscopist to patient compared

Certainty of the evidence is low to very low due to indirectness (not based on COVID-19 patients or exclusively patients

with acute respiratory distress syndrome), risk of bias, lack of precision in some outcomes and small number of adverse events.

Outcome Timeframe	**Study results and measurements**	**Comparator** Direct laryngoscopy	**Intervention** Videolaryngoscopy	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
First-pass intubation success	Relative risk 1.05 (CI 95% 0.94 — 1.17) Based on data from 1,186 participants in 7 studies. [1] (Randomized controlled)	716 per 1000 Difference:	752 per 1000 **36 more per 1000** (CI 95% 43 fewer — 122 more)	**Very low** Due to serious risk of bias, inconsistency and indirectness [2]	We are uncertain whether videolaryngoscopy increases or decreases first-pass intubation success.
Oesophageal intubation	Relative risk 0.4 (CI 95% 0.17 — 0.93) Based on data from 795 participants in 4 studies. [3] (Randomized controlled)	50 per 1000 Difference:	20 per 1000 **30 fewer per 1000** (CI 95% 41 fewer — 3 fewer)	**Low** Due to serious risk of bias and indirectness [4]	Videolaryngoscopy may decrease oesophageal intubation.
Operator distance in cm [5] 8 Critical	Measured by: distance analysed from videorecording High better Based on data from 25 participants in 1 studies. [6] (Randomized controlled)	16.4 centimetres (Mean) Difference:	35.6 centimetres (Mean) **MD 19.2 higher** (CI 95% 13.28 lower — 25.12 higher)	**Very low** Due to serious risk of bias, indirectness and imprecision [7]	Videolaryngoscopy may increase the operator distance.
Time to successful intubation 7 Critical	Based on data from 988 participants in 6 studies. [8] (Randomized controlled)	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.		**Very low** Due to serious risk of bias, indirectness and imprecision, and very serious inconsistency [9]	We are uncertain whether videolaryngoscopy increases or decreases time to successful intubation.

Attached Images

9.4 Neuromuscular blockers

Info Box

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.

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 NMBA

Comparator: No continuous infusion of NMBA

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 (NMBAs) with cisatracurium for up to 48 hours to no continuous infusions of NMBAs *[214][215][216][217][218]*.

For all critical outcomes, it is uncertain whether infusion of NMBAs makes a difference. The ROSE trial, which had a different sedation strategy to the other trials and implemented a higher positive end-expiratory pressure (PEEP) strategy, is the largest (1006 participants) and most recent trial, and may be the most reflective of current practice *[215]*. There were no differences for the mortality outcomes, but the trial found a small increase in muscle weakness at 28 days in the NMBA group.

Outcome Timeframe	**Study results and measurements**	**Comparator** No NMBA	**Intervention** NMBA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
28-day mortality 6 Important	Relative risk 0.78 (CI 95% 0.58 — 1.06) Based on data from 1,461 participants in 5 studies. [1] (Randomized controlled)	372 per 1000 Difference:	290 per 1000 **82 fewer per 1000** (CI 95% 156 fewer — 22 more)	Very low Due to serious inconsistency, indirectness and imprecision [2]	We are uncertain whether neuromuscular blockers improve or worsen 28-day mortality (513 events).
90-day mortality 9 Critical	Relative risk 0.81 (CI 95% 0.62 — 1.06) Based on data from 1,461 participants in 5 studies. [3] (Randomized controlled)	441 per 1000 Difference:	357 per 1000 **84 fewer per 1000** (CI 95% 168 fewer — 26 more)	Very low Due to serious inconsistency, indirectness and imprecision [4]	We are uncertain whether neuromuscular blockers improve or worsen 90-day mortality (612 events).
ICU mortality 6 Important	Relative risk 0.72 (CI 95% 0.57 — 0.91) Based on data from 455 participants in 4 studies. [5] (Randomized	438 per 1000 Difference:	315 per 1000 **123 fewer per**	Very low Due to serious imprecision and very serious indirectness [6]	We are uncertain whether neuromuscular blockers increase or decrease ICU mortality (171 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** No NMBA	**Intervention** NMBA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	controlled)		**1000** (CI 95% 188 fewer — 39 fewer)		
ICU weakness at day 28 9 Critical	Relative risk 1.23 (CI 95% 0.81 — 1.88) Based on data from 356 participants in 4 studies. [7] (Randomized controlled)	**230** per 1000 Difference:	**283** per 1000 **53 more per 1000** (CI 95% 44 fewer — 202 more)	**Very low** Due to serious risk of bias and imprecision, and very serious indirectness [8]	We are uncertain whether neuromuscular blockers increase or decrease ICU weakness at day 28 (91 events).
Barotrauma 6 Important	Relative risk 0.55 (CI 95% 0.35 — 0.85) Based on data from 1,426 participants in 4 studies. [9] (Randomized controlled)	**74** per 1000 Difference:	**41** per 1000 **33 fewer per 1000** (CI 95% 48 fewer — 11 fewer)	**Very low** Due to serious risk of bias, indirectness and indirectness [10]	We are uncertain whether neuromuscular blockers improve or worsen barotrauma (81 events).
Mechanical ventilation duration Days 6 Important	Measured by: Days Based on data from 92 participants in 2 studies. [11] (Randomized controlled)	**18** (Median) Difference:	**20** (Median) **2 higher**	**Very low** Due to serious risk of bias, inconsistency and indirectness, and very serious imprecision [12]	We are uncertain whether neuromuscular blockers increase or decrease mechanical ventilation duration.
Ventilator-free days at day 28 6 Important	Measured by: Days Based on data from 1,462 participants in 5 studies. [13] (Randomized controlled)	**9.6** (Median) Difference:	**9.9** (Median) **0.3 higher**	**Very low** Due to serious risk of bias, indirectness and imprecision [14]	We are uncertain whether neuromuscular blockers improve or worsen ventilator-free days at day 28.
MRC score at day 28 6 Important	Measured by: Medical Research Council (MRC) scale Scale: 0 — 60 High better Based on data from 1,346 participants in 2 studies. [15] (Randomized controlled) Follow up: 28 days.	**49.8** muscle strength (Median) Difference:	**45.9** muscle strength (Median) **MD 4.1 lower**	**Very low** Due to serious risk of bias and indirectness, and very serious inconsistency [16]	We are uncertain whether neuromuscular blockers improve or worsen MRC score at day 28.

Attached Images

Conditional recommendation against

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

Additional information

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.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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

Very low

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.

Values and preferences

Substantial variability is expected or uncertain

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.

The Consumer Panel believes that in line with available evidence, most informed patients would agree with the recommendation for this treatment for COVID-19. The Panel also believes that most informed patients would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

There is a risk of creating inequity as some populations may have limited access to neuromuscular blockers, particularly if there is a shortage.

Acceptability

Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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 NMBA

Comparator: No continuous infusion of NMBA

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 (NMBAs) with cisatracurium for up to 48 hours to no continuous infusions of NMBAs *[214][215][216][217][218]*.

For all critical outcomes, it is uncertain whether infusion of NMBAs makes a difference. The ROSE trial, which had a different sedation strategy to the other trials and implemented a higher positive end-expiratory pressure (PEEP) strategy, is the largest (1006 participants) and most recent trial, and may be the most reflective of current practice *[215]*. There were no differences for the mortality outcomes, but the trial found a small increase in muscle weakness at 28 days in the NMBA group.

Outcome Timeframe	**Study results and measurements**	**Comparator** No NMBA	**Intervention** NMBA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
28-day mortality 6 Important	Relative risk 0.78 (CI 95% 0.58 — 1.06) Based on data from 1,461 participants in 5 studies. [1] (Randomized controlled)	372 per 1000 Difference:	290 per 1000 **82 fewer per 1000** (CI 95% 156 fewer — 22 more)	**Very low** Due to serious inconsistency, indirectness and imprecision [2]	We are uncertain whether neuromuscular blockers improve or worsen 28-day mortality (513 events).
90-day mortality 9 Critical	Relative risk 0.81 (CI 95% 0.62 — 1.06) Based on data from 1,461 participants in 5 studies. [3] (Randomized controlled)	441 per 1000 Difference:	357 per 1000 **84 fewer per 1000** (CI 95% 168 fewer — 26 more)	**Very low** Due to serious inconsistency, indirectness and imprecision [4]	We are uncertain whether neuromuscular blockers improve or worsen 90-day mortality (612 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** No NMBA	**Intervention** NMBA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
ICU mortality 6 Important	Relative risk 0.72 (CI 95% 0.57 — 0.91) Based on data from 455 participants in 4 studies. [5] (Randomized controlled)	438 per 1000 Difference:	315 per 1000 **123 fewer per 1000** (CI 95% 188 fewer — 39 fewer)	**Very low** Due to serious imprecision and very serious indirectness [6]	We are uncertain whether neuromuscular blockers increase or decrease ICU mortality (171 events).
ICU weakness at day 28 9 Critical	Relative risk 1.23 (CI 95% 0.81 — 1.88) Based on data from 356 participants in 4 studies. [7] (Randomized controlled)	230 per 1000 Difference:	283 per 1000 **53 more per 1000** (CI 95% 44 fewer — 202 more)	**Very low** Due to serious risk of bias and imprecision, and very serious indirectness [8]	We are uncertain whether neuromuscular blockers increase or decrease ICU weakness at day 28 (91 events).
Barotrauma 6 Important	Relative risk 0.55 (CI 95% 0.35 — 0.85) Based on data from 1,426 participants in 4 studies. [9] (Randomized controlled)	74 per 1000 Difference:	41 per 1000 **33 fewer per 1000** (CI 95% 48 fewer — 11 fewer)	**Very low** Due to serious risk of bias, indirectness and indirectness [10]	We are uncertain whether neuromuscular blockers improve or worsen barotrauma (81 events).
Mechanical ventilation duration Days 6 Important	Measured by: Days Based on data from 92 participants in 2 studies. [11] (Randomized controlled)	18 (Median) Difference:	20 (Median) **2 higher**	**Very low** Due to serious risk of bias, inconsistency and indirectness, and very serious imprecision [12]	We are uncertain whether neuromuscular blockers increase or decrease mechanical ventilation duration.
Ventilator-free days at day 28 6 Important	Measured by: Days Based on data from 1,462 participants in 5 studies. [13] (Randomized controlled)	9.6 (Median) Difference:	9.9 (Median) **0.3 higher**	**Very low** Due to serious risk of bias, indirectness and imprecision [14]	We are uncertain whether neuromuscular blockers improve or worsen ventilator-free days at day 28.
MRC score at day 28 6 Important	Measured by: Medical Research Council (MRC) scale Scale: 0 — 60 High better Based on data from 1,346 participants in 2 studies. [15] (Randomized controlled) Follow up: 28 days.	49.8 muscle strength (Median) Difference:	45.9 muscle strength (Median) **MD 4.1 lower**	**Very low** Due to serious risk of bias and indirectness, and very serious inconsistency [16]	We are uncertain whether neuromuscular blockers improve or worsen MRC score at day 28.

Attached Images

9.5 Positive end-expiratory pressure

Consensus recommendation

For mechanically ventilated adults with COVID-19 and moderate-to-severe acute respiratory distress syndrome, consider using a higher positive end-expiratory pressure (PEEP) strategy (PEEP > 10 cm H2O) over a lower PEEP strategy.

Additional information

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

While there is no current evidence for using a higher positive end-expiratory pressure (PEEP) strategy in patients with COVID-19 and moderate-to-severe acute respiratory distress syndrome (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.

Values and preferences

No substantial variability expected

We have no systematically collected information regarding patients' preferences and values at this point.

The Consumer Panel believes that in line with expert consensus and the limited available evidence, some informed patients would agree with the recommendation and consider this treatment. The Panel recognises that some informed patients may choose not to have this treatment based on reasons unrelated to COVID-19.

The Consumer Panel also believes that most informed patients/carers would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources

No important issues with the recommended alternative

We have no systematically collected evidence regarding cost-benefit.

Equity

No important issues with the recommended alternative

There are likely no important equity issues.

Acceptability

Factor not considered

We are uncertain if a higher PEEP ventilation strategy would be acceptable to both patients and healthcare providers.

Feasibility

No important issues with the recommended alternative

There are likely no important feasibility issues.

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 *[193]*.

9.6 Prone positioning

Info Box

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

9.6.1 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.

Additional information

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 which minimises the risk of adverse events, e.g. accidental extubation.

Net clinical benefit for each patient should be considered on a case-by-case basis, as factors such as frailty, advanced illness or comorbidity may lessen the benefit and increase potential harms.

Decisions around proceeding to more invasive forms of therapy should consider the preferences and values of the patient and whether they have an advanced care directive or plan, and should be discussed with the patient, healthcare decision-maker or family/carers.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

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.

People requiring palliative care and older people living with frailty or cognitive impairment
Net clinical benefit for each patient should be considered on a case-by-case basis. For example, older people living with frailty may be at particular risk of harm from proning. The symptom benefits of proning in palliative patients remain unclear.

Certainty of the Evidence

No studies were identified in COVID-19 patients that address the interventions or outcomes of interest.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values at this point.

People requiring palliative care and older people living with frailty or cognitive impairment
Consider the preferences and values of the patient and whether they have an advanced care directive or plan. Decisions around proceeding to more invasive forms of ventilation should be discussed with the patient or their medical treatment decision-maker.

The Consumer Panel believes that in line with expert consensus and the limited available evidence, most informed patients/carers would agree with the recommendation for this treatment. The Panel recognises that some informed patients/carers may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel also believes that most informed patients/carers would agree that infection control precautions are

optimised to minimise the risk of infection for others.

Resources

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

There is the potential for inequity as some healthcare facilities may not have sufficient staff to offer prone positioning.

Acceptability

Important issues, or potential issues not investigated

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

No important issues with the recommended alternative

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.

People requiring palliative care and older people living with frailty or cognitive impairment
It may not be feasible to prone patients in this population as they may be at particular risk of harm from proning.

Adaptation

The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign *[193]*. Wording has been adapted for clarity and applicability to the Australian context.

Conditional 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 for at least 3 hours per day as tolerated. When positioning a patient in prone, ensure proning is used with caution and accompanied by close monitoring of the patient. Use of prone positioning should not delay endotracheal intubation and mechanical ventilation in patients with COVID-19 who are deteriorating despite optimised less invasive respiratory therapies.

Additional information

For adults with COVID-19 and respiratory symptoms who are receiving any form of supplemental oxygen therapy and have not yet been intubated, prone positioning for as long as tolerated may increase benefits.

Vulnerable people who are treated outside the ICU, for example people who are older and living with frailty, cognitive impairment or unable to communicate, may especially be at increased risk of harm from proning. Despite the potential risks of awake proning associated with frailty, there may be benefits for this group. The net clinical benefit for each individual patient should be considered on a case-by-case basis.

Currently, the evidence indicates that prone positioning probably decreases treatment failure and the need for intubation, with no increase in harms. Prone positioning 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.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Prone positioning is recommended in mechanically ventilated patents with moderate-to-severe acute respiratory distress syndrome of other aetiologies. In these patients prone positioning improves the rates of treatment failure and reduces the need for intubation within 28 to 30 days. The randomised controlled trials have indicated no increase in harms, but possible pressure injury should be monitored.

People requiring palliative care and older people living with frailty or cognitive impairment
Net clinical benefit for each individual patient should be considered on a case-by-case basis. For example, older people living with frailty who are treated outside the intensive care unit (ICU) and patients who are unable to communicate may be at particular risk of harm from proning.

Certainty of the Evidence

Moderate

The certainty of the evidence is low. Outcomes ranged from moderate to low, with important outcomes such as admission to ICU, all-cause mortality, adverse events, including pressure sores. Outcomes were downgraded because of methodological limitations of included studies and serious imprecision due to few events and participants in included studies.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values at this point. However, patients in one small prospective cohort study who received proning rated their comfort levels as acceptable, good or excellent.

The Consumer Panel believes that in line with expert consensus and the limited available evidence, most informed patients/carers would agree with the recommendation for this treatment. The Panel recognises that some informed patients/carers may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel also believes that most informed patients/carers would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Proning is associated with significant cost as additional staff are needed to move and monitor those in prone position. Healthcare workers must be trained to facilitate safe practice.

Equity

Important issues, or potential issues not investigated

Staff carrying out prone positioning need to move and monitor those who are in the prone position, which may be resource intensive. This may result in potential inequity as some healthcare facilities may not be able to offer prone positioning.

Acceptability

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding acceptability of prone positioning. Clear communication from health professionals regarding the possible benefits and harms of prone positioning is essential.

Feasibility

No important issues with the recommended alternative

Prone positioning 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.

People requiring palliative care and older people living with frailty or cognitive impairment
It may not be feasible to prone patients in this population as older people living with frailty and patients who are unable to communicate may be at particular risk of harm from proning. Feasibility may vary depending on setting and may be less feasible when patients are treated outside the ICU.

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.

Clinical Question/ PICO

Population: Patients with COVID-19 on supplementary oxygen who are not yet intubated
Intervention: Prone positioning
Comparator: No prone positioning

Summary

Evidence for this recommendation comes from five randomised trials of 2274 adults with acute hypoxaemic respiratory failure requiring respiratory support with high-flow nasal cannula or non-invasive ventilation. The trials compared the use of prone positioning (either 16 hours per day or as long and as frequently as possible) with standard care where prone positioning was not encouraged *[354][355]*.

Patient age ranged from 18 to 74 years (mean 61 years) and two-thirds were men. Many patients had comorbidities, with around a third with diabetes mellitus or obesity.

Outcome Timeframe	**Study results and measurements**	**Comparator** Not proning	**Intervention** Proning	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality Within 30 days 9 Critical	Relative risk 0.89 (CI 95% 0.76 — 1.06) Based on data from 1,874 participants in 4 studies. [1] (Randomized controlled)	231 per 1000 Difference:	206 per 1000 **25 fewer per 1000** (CI 95% 55 fewer — 14 more)	**Moderate** Due to serious imprecision [2]	Prone positioning probably has little or no difference on all-cause mortality (410 deaths)
Trachael intubation Within 30 days 9 Critical	Relative risk 0.8 (CI 95% 0.72 — 0.9) Based on data from 2,026 participants in 4 studies. [3] (Randomized controlled)	405 per 1000 Difference:	324 per 1000 **81 fewer per 1000** (CI 95% 113 fewer — 41 fewer)	**Moderate** Due to serious risk of bias [4]	Prone positioning probably decreases trachael intubation (739 events)
All-cause mortality within 60 days 9 Critical	Relative risk 0.95 (CI 95% 0.66 — 1.36) Based on data from 400 participants in 1 studies. [5] (Randomized controlled)	236 per 1000 Difference:	224 per 1000 **12 fewer per 1000** (CI 95% 80 fewer — 85 more)	**Low** Due to very serious imprecision [6]	Prone positioning may have little or no difference on all-cause mortality (92 deaths)
Admission to ICU 28 days 6 Important	Relative risk 1.08 (CI 95% 0.82 — 1.44) Based on data from 75 participants in 1 studies. [7] (Randomized controlled)	692 per 1000 Difference:	747 per 1000 **55 more per 1000** (CI 95% 125 fewer — 304 more)	**Low** Due to serious risk of bias and serious imprecision [8]	We are uncertain whether proning impacts admission to ICU.
Adverse events End of follow-up 4 Important	Relative risk 4.16 (CI 95% 0.02 — 981.19) Based on data from 475 participants in 2 studies. [9] (Randomized controlled)	43 per 1000 Difference:	179 per 1000 **136 more per 1000** (CI 95% 42 fewer — 42,148 more)	**Low** Due to serious imprecision and serious risk of bias [10]	Prone positioning may have little or no difference on adverse events

Outcome Timeframe	**Study results and measurements**	**Comparator** Not proning	**Intervention** Proning	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Pressure sores 28–30 days 6 Important See Summary	Relative risk 0.5 (CI 95% 0.16 — 1.56) Based on data from 1,196 participants in 2 studies. [11] (Randomized controlled)	32 per 1000 Difference:	16 per 1000 **16 fewer per 1000** (CI 95% 27 fewer — 18 more)	**Low** Due to serious risk of bias and serious imprecision [12]	Proning may have little or no difference on pressure sores.

Attached Images

9.6.2 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.

Additional information

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.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

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.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding the preferences and values of pregnant and breastfeeding women with COVID-19 at this point.

The Consumer Panel believes that in line with expert consensus and the limited available evidence, most informed pregnant or postpartum women in this group of COVID-19 patients would agree with the recommendation and consider this treatment. The Panel recognises that some pregnant or postpartum women may choose not to have this treatment based on reasons unrelated to COVID-19.

The Consumer Panel also believes that most informed patients would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

There is the potential for inequity as some healthcare facilities may not have sufficient staff to offer prone positioning.

Acceptability

Important issues, or potential issues not investigated

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.

Additional information

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.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

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.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding the preferences and values of pregnant and breastfeeding women with COVID-19 at this point.

The Consumer Panel believes that in line with expert consensus and the limited available evidence, some informed pregnant or postpartum women in this group of COVID-19 patients would agree with the recommendation and consider this treatment. The Panel recognises that some pregnant or postpartum women may choose not to have this treatment based on reasons unrelated to COVID-19.

The Consumer Panel also believes that most informed patients would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

There is the potential for inequity as some healthcare facilities may not have sufficient staff to offer prone positioning.

Acceptability

Important issues, or potential issues not investigated

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.

9.6.3 Prone positioning and CPR

Consensus recommendation

For patients with COVID-19 in prone position requiring cardiopulmonary resuscitation (CPR), where safe and feasible, return the patient to supine position and commence resuscitation.

If returning the patient to supine position is not safe and feasible, commence CPR in prone position. Once it is safe and feasible, return the patient to supine position and continue the resuscitation process.

Additional information

When caring for patients with COVID-19, consider the options available for providing cardiopulmonary resuscitation (CPR) when instituting prone positioning.

It is reasonable to provide CPR in the prone position when supine CPR cannot be feasibly or safely implemented, and the airway is secured.

Returning the patient to supine position should only be performed when there are suitable resources to minimise risk of harm to staff and patients, e.g. accidental extubation, venous or arterial line dislodgement.

Provision of CPR for patients in prone position should be performed where there are hospital guidelines, and training in provision of prone CPR has been undertaken.

Decisions to commence CPR should consider the preferences and values of the patient and whether they have an advanced care directive or plan, and should be discussed with the patient, healthcare decision-maker or family/carersin advance of need.

Consideration should also be given to whether prone positioning has contributed to the need for CPR, for example by including abdominal compression and obstruction to venous return.

9.7 Recruitment manoeuvres

Info Box

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 positive end-expiratory pressure [PEEP]) recruitment manoeuvres.

Additional information

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

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.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values at this point.

The Consumer Panel believes that in line with expert consensus and the limited available evidence, most informed patients would agree with the recommendation for this treatment. The Panel recognises that some informed patients may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel also believes that most informed patients would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. However, patients receiving recruitment manoeuvres

may require more intensive monitoring.

Equity No important issues with the recommended alternative

There are likely no important equity issues.

Acceptability Important issues, or potential issues not investigated

We are uncertain if recruitment manoeuvres would be acceptable to both patients and healthcare providers.

Feasibility No important issues with the recommended alternative

There are likely no important feasibility issues.

Adaptation

The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign *[193]*. Wording has been adapted for clarity and applicability to the Australian context.

9.8 Extracorporeal membrane oxygenation

Info Box

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.

9.8.1 ECMO for adults

Conditional recommendation

Consider early referral to an extracorporeal membrane oxygenation (ECMO) centre for patients developing refractory respiratory failure in mechanically ventilated adults with COVID-19 (despite optimising ventilation, including proning and neuromuscular blockers).

Additional information

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 acute respiratory distress syndrome.

Net clinical benefit for each patient should be considered on a case-by-case basis, as factors such as frailty, advanced illness or comorbidity may lessen the benefit and increase potential harms.

Decisions around proceeding to more invasive forms of therapy should consider the preferences and values of the patient and whether they have an advanced care directive or plan, and should be discussed with the patient, healthcare decision-maker or family/carers.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Extracorporeal membrane oxygenation (ECMO) is only used as a form of life support in patients who are severely ill—it may increase oxygenation and reduce ventilator-induced lung injuries, which may assist to increase recovery and decrease mortality. However, ECMO may be associated with risk of serious side effects, such as major bleeding, disseminated intravascular coagulation and injuries from cannulation. ECMO is only used in carefully selected patients who are at decreased risk of harms from receiving ECMO and may benefit the most from the potential survival benefits of ECMO.

People requiring palliative care and older people living with frailty or cognitive impairment
Net clinical benefit for each patient should be considered on a case-by-case basis. For example, older people living with frailty may be at particular risk of harm from more invasive forms of therapy, and the symptom benefits in palliative patients remain unclear.

Certainty of the Evidence

Very low

Two non-comparative observational studies were identified in COVID-19 patients receiving ECMO.

Values and preferences

Substantial variability is expected or uncertain

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.

People requiring palliative care and older people living with frailty or cognitive impairment
Consider the preferences and values of the patient and whether they have an advanced care directive or plan. Decisions around proceeding to more invasive forms of therapy should be discussed with the patient or their medical treatment decision-maker.

The Consumer Panel believes that in line with the limited available evidence, some informed patients/carers may prefer

to wait until the available evidence is clearer, while others may agree to have more invasive treatment initiated if this is consistent with their goals of care. The Panel recognises that some patients/carers may still choose not to have this treatment based on reasons unrelated to COVID-19.

The Consumer Panel also believes that most informed patients/carers would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. ECMO is resource-intensive and requires experienced centres, healthcare workers and infrastructure.

Equity

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

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 *[193]*. Wording has been adapted for clarity and applicability to the Australian context.

Clinical Question/ PICO

Population: Patients with COVID-19
Intervention: ECMO
Comparator: No ECMO

Summary

We are uncertain if extracorporeal membrane oxygenation (ECMO) is more effective than no ECMO in patients who are critically ill with COVID-19. ECMO may be associated with risk of serious side effects.

Systematic reviews of ECMO for acute respiratory failure in non-COVID-19 patients suggest there may be a benefit, but that ECMO may also be associated with significant harms. Data comparing ECMO to no ECMO in patients with COVID-19 are still lacking.

What is the evidence informing this recommendation?
Evidence comes from two non-comparative observational studies in critically ill patients with COVID-19 receiving ECMO. One study included 1035 patients *[220]* and the other included 83 patients *[221]*.

Study characteristics
The Extracorporeal Life Support Organization (ELSO) Registry included 1035 patients (median age of 49 years) from 213 hospitals in 36 countries *[220]*. The proportion of women was 26%, of whom 22 were pregnant. Ninety-four percent of patients received venovenous ECMO. Before initiation of ECMO, 72% of patients received neuromuscular blockers, 60% were placed in prone position and 99% were ventilated. Before ventilation, 59% of patients received non-invasive ventilation and 35% high-flow nasal oxygen therapy. Patients received pharmacological therapies for COVID-19, including chloroquine or hydroxychloroquine (52%), glucocorticoids (41%), anticytokine (28%), lopinavir–ritonavir (11%), remdesivir (8%) and intravenous immunoglobulin (3%).

In the retrospective cohort of 83 patients from five intensive care units (ICUs) in France, median age was 49 years and the proportion of women was 27% *[221]*. Ninety-seven percent of patients received venovenous ECMO. Before initiation of ECMO, 96% of patients received neuromuscular blockers and 94% were placed in prone position. Patients received pharmacological therapies for COVID-19, including lopinavir-ritonavir (23%), hydroxychloroquine (19%), high-dose corticosteroids (14%), tocilizumab (10%) and remdesivir (10%).

What are the main results?
In the ELSO registry study, at 90 days following initiation of ECMO, 37% of patients had died in hospital, 30% were discharged home or to an acute rehabilitation centre, 17% were discharged to another hospital, 10% were discharged to a long-term acute care centre or unspecified location, and 6% either remained in ICU or hospital.

A subgroup analysis found that the risk of in-hospital mortality increased with age. Acute kidney injury, chronic respiratory insufficiency, an immunocompromised state, or a pre-ECMO cardiac arrest were also associated with an increased risk of in-hospital mortality. Conversely, higher PaO2:FiO2 was associated with lower mortality. Renal replacement therapy was used in 44% of patients. Complications other than renal replacement therapy were reported in 55% of patients.

The retrospective cohort of five ICUs in France reported that at 90 days 36% of patients had died, 56% were discharged from ICU, 6% were in ICU but no longer receiving ECMO and 1% were still receiving ECMO. Renal replacement therapy was used in 46% of patients. The most common ECMO-related complications were massive haemorrhage (42% of patients) and ECMO-circuit changes (27%). Other complications were also observed.

Our confidence in the results
Certainty of the evidence is very low due to reliance on non-comparative observational data.

Additional information
While the ELSO registry included data from many countries, it may not be generalisable to the Australian setting. Death rates in Australia have been lower than most other countries and Australia's health system has been operating within its capacity, unlike in other parts of the world where resource considerations may have contributed to adverse outcomes.

Of note, patients received therapies for COVID-19 that are not currently recommended by our guideline, with 19 to 54% of patients receiving chloroquine or hydroxychloroquine and 11 to 23% receiving lopinavir-ritonavir. Our guideline recommends corticosteroids in patients requiring oxygen, which includes all patients receiving ECMO—only 14 to 41% of patients in these studies received steroids.

Outcome Timeframe	**Study results and measurements**	**Comparator** No ECMO	**Intervention** ECMO	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality at 90 days [1] 90 days 9 Critical	Based on data from 1,118 participants in 2 studies. (Observational (non-randomized))	Please see summary		Very low Due to very serious risk of bias and very serious indirectness. [2]	We are uncertain whether ECMO increases or decreases mortality at 90 days.

Attached Images

9.8.2 ECMO for pregnant and postpartum women

Consensus recommendation

Consider referral to an extracorporeal membrane oxygenation (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.

Additional information

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 acute respiratory distress syndrome.

The decision on whether to use ECMO should be taken in consultation with the patient, healthcare decision-maker or family/carers, 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.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The benefit of extracorporeal membrane oxygenation (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; it aims to increase oxygenation and reduce ventilator-induced lung injuries. However, it may be associated with 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 administrated 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 compare ECMO to no ECMO.

Values and preferences

Substantial variability is expected or uncertain

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.

The Consumer Panel believes that in line with the limited available evidence, some informed patients/carers may prefer to wait until the available evidence is clearer, while others may agree to have more invasive treatment initiated if this is consistent with their goals of care. The Panel recognises that some patients/carers may still choose not to have this treatment based on reasons unrelated to COVID-19.

The Consumer Panel also believes that most informed patients/carers would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. ECMO is resource-intensive and requires experienced centres, healthcare workers and infrastructure.

Equity Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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 Important issues, or potential issues not investigated

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.

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.

10. Respiratory support in neonates, children and adolescents

Info Box

The Paediatric and Adolescent Care Panel is responsible for developing recommendations specific to respiratory support in neonates, children and adolescents.

Recommendations are subsequently reviewed by the Guidelines Leadership Group and approved by the Steering Committee prior to publication. In addition, all recommendations are reviewed by the Consumer Panel to establish acceptability to the patient population for which they are relevant.

10.1 Requiring non-invasive respiratory support

10.1.1 High-flow nasal oxygen and non-invasive ventilation

Info Box

High-flow nasal oxygen (HFNO) therapy is a form of respiratory support where warmed, humidified oxygen is delivered at high-flow rates.

Non-invasive ventilation (NIV) refers to any type of positive pressure support delivered without an endotracheal tube during spontaneous breathing. Supplemental oxygen can also be delivered through the device.

HFNO or NIV should be considered when low-flow oxygen is unable to maintain target peripheral oxygen saturation and/or to treat respiratory distress. Target peripheral oxygen saturations may vary in neonates, children and adolescents with co-morbid conditions, such as preterm birth, cyanotic congenital heart disease or chronic lung disease.

Practical Info

High-flow nasal oxygen
The concentration of oxygen can be titrated (using a blender) between 21% and 100%. Flow rates can be given up to 60 L/min in adults. In children, flow rates are typically 2 L/kg/min (maximum 50 L/min), except in neonates ≤ 4 kg where flow rates of 4 to 8 L/min are typically used.

Consensus recommendation

Consider using high-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV) therapy for neonates, children and adolescents with hypoxaemia or respiratory distress associated with COVID-19 and not responding to low-flow oxygen. Use it with caution and pay strict attention to staff safety, including the use of appropriate personal protective equipment (PPE).

Additional information

The preferred location for high-flow nasal oxygen is a negative pressure room or a single room with the door closed. If these locations are not immediately available then HFNO or NIV should not be withheld if indicated. However, it should be recognised that this therapy may pose an aerosol risk to staff and other patients, and appropriate precautions should be used.

In children and adolescents with COVID-19 for whom HFNO or NIV is appropriate for an alternate clinical presentation (e.g. concomitant bronchiolitis or severe asthma), ensure airborne and other infection control precautions are also optimised.

Consider early transfer in the deteriorating neonate, child or adolescent to a specialised paediatric or neonatal critical care unit.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Evidence from non-COVID neonates with acute hypoxaemic respiratory failure shows a reduction in endotracheal intubation and chronic lung disease. Non-invasive ventilation (NIV)/ high-flow nasal oxygen (HFNO) may be helpful for children with severe bronchiolitis or asthma and may reduce the need for intubation. Since NIV/HFNO is a known aerosol-generating procedure, with possible increased risk of aerosolisation with poor mask fit *[18]*, harms associated with a potential risk of transmission to healthcare workers need to be considered and the procedure used with caution, with strict attention paid to staff safety. Benefits and harms need to be considered in the context of the relevant alternate clinical presentation.

Certainty of the Evidence

No studies were identified in neonates, children and adolescents with COVID-19 that address the interventions, comparators and outcomes of interest.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians.

The Consumer Panel believes that in line with expert consensus and the available evidence, most informed patients, parents, carers, families and guardians would agree with the recommendation for this treatment. The panel recognises that some informed patients, parents, carers, families and guardians may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel believes that most informed patients, parents, carers, families and guardians would agree with the recommendation that infection control precautions are optimised to minimise the risk of infection for others.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. NIV/HFNO requires less staffing and equipment than mechanical ventilation via an endotracheal tube. There are likely to be resource issues associated with different settings. There are limited negative pressure rooms in private and some public hospitals, although some hospitals have converted rooms into negative pressure rooms.

There are additional resource considerations for hospital spaces where caution needs to be applied and strict attention paid to staff safety. In single rooms or shared ward spaces with cohorting of neonates, children and adolescents with confirmed COVID-19, there are additional resource considerations for use of PPE and performing NIV/HFNO safely.

Equity

Important issues, or potential issues not investigated

There may be equity issues due to the availability of negative pressure rooms and hospital spaces that are able to perform NIV/HFNO safely. NIV/HFNO can be provided in hospital settings outside an intensive care unit.

Acceptability

Important issues, or potential issues not investigated

We have no systematically collected information regarding acceptability. NIV/HFNO is generally a well-accepted practice by neonates, children and adolescents, their families and healthcare providers in non-COVID-19 conditions.

Feasibility

Important issues, or potential issues not investigated

There may be feasibility issues due to the availability of negative pressure rooms and hospital spaces that are able to perform NIV/HFNO safely.

10.1.2 Prone positioning (non-invasive)

Consensus recommendation

For neonates, children and adolescents with COVID-19 and respiratory symptoms who are receiving non-invasive respiratory support, consider prone positioning if patient co-operation is possible. When positioning a patient prone, ensure it is used with caution and close monitoring of the patient.

Additional information

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

While there is no current evidence for using prone positioning in neonates, children and adolescents with COVID-19, it is recommended for ventilated, children and adolescents with moderate-to-severe acute respiratory distress syndrome due to non-COVID causes, and is frequently used in neonates requiring mechanical ventilation. In these patients it may have a survival benefit but may also increase the risk of harms from complications, such as pressure injury, endotracheal tube obstruction or accidental extubation. Younger children who are awake and not receiving mechanical ventilation are less likely to comply with prolonged periods of prone positioning.

Certainty of the Evidence

No studies were identified in neonates, children and adolescents with COVID-19 that address the interventions or outcomes of interest.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians. Children with milder respiratory disease and not receiving sedation may not comply with prone positioning.

The Consumer Panel believes that in line with expert consensus and the available evidence, most informed patients, parents, carers, families and guardians would agree with the recommendation for this treatment. The panel recognises that some informed patients, parents, carers, families and guardians may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel believes that most informed patients, parents, carers, families and guardians would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Prone positioning is not associated with significant cost for infants and small children who require minimal nursing care to position. In larger children and adolescents, additional staff are needed to move and monitor in prone position, which will increase costs. Healthcare workers must be trained to facilitate safe practice in larger children and adolescents.

Equity Important issues, or potential issues not investigated

There is the potential for inequity as some healthcare facilities may not have sufficient staff or training to offer prone positioning.

Acceptability Important issues, or potential issues not investigated

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 No important issues with the recommended alternative

Prone positioning of mechanically ventilated neonates, children and adolescents is 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.

Adaptation

The recommendation is adapted from published recommendations by the Surviving Sepsis Campaign *[193]*. Wording has been adapted for clarity and applicability to the Australian context.

10.1.3 Respiratory management of the deteriorating child

Consensus recommendation

Consider endotracheal intubation and mechanical ventilation in neonates, children and adolescents with COVID-19 who are deteriorating despite optimised, non-invasive respiratory support.

Additional information

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Benefits and harms should be considered on a case-by-case basis before undertaking invasive respiratory support, especially in children with a pre-existing life-limiting illness. There are well-known benefits of invasive ventilation, including improved oxygenation and reduced mortality in ARDS due to causes other than COVID-19. Harms relevant to SARS-CoV-2 transmission should be considered as with all children with respiratory failure—there may be complications related to invasive mechanical ventilation. There may also be accentuated risks of COVID-19 transmission to other patients or staff in critical care settings.

Certainty of the Evidence

No studies in neonates, children and adolescents with COVID-19 were identified that address the interventions, comparators and outcomes of interest.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians.

The Consumer Panel believes that in line with expert consensus and the available evidence, most informed patients, parents, carers, families and guardians would agree with the recommendation for this treatment. The panel recognises that some informed patients, parents, carers, families and guardians may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel believes that most informed patients, parents, carers, families and guardians would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. However, there are likely to be resource issues associated with different settings.

Equity

Important issues, or potential issues not investigated

We recognise that access to staff trained in paediatric critical care is not equitable, and Is concentrated in tertiary metropolitan hospitals or retrieval services. Some children may therefore not have immediate access to a clinician with skills and experience intubating a critically ill child.

Acceptability No important issues with the recommended alternative

Although we have no systematically collected evidence regarding acceptability, we do not expect acceptability issues in neonates, children and adolescents.

Feasibility Important issues, or potential issues not investigated

Access to staff trained in paediatric critical care in rural and remote areas may impact on feasibility for intubation.

Rationale

Evidence for management of severe COVID-19 in children is limited. However, there are no data to suggest modifications to standard respiratory care are necessary.

10.2 Requiring invasive mechanical ventilation

10.2.1 Prone positioning (mechanical ventilation)

Consensus recommendation

For mechanically ventilated neonates, children and adolescents with COVID-19 and hypoxaemia despite optimising ventilation, consider prone positioning if there are no contraindications.

Additional information

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

While there is no current evidence for using prone positioning in neonates, children and adolescents with COVID-19, it is recommended for ventilated children and adolescents with moderate to severe ARDS due to non-COVID causes, and is frequently used in neonates requiring mechanical ventilation. In these patients it may have a survival benefit but may also increase the risk of harms from complications such as pressure injury, endotracheal tube obstruction or accidental extubation. Younger children are less likely to comply with prolonged periods of prone positioning.

Certainty of the Evidence

No studies were identified in neonates, children or adolescents with COVID-19 that address the interventions or outcomes of interest.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians.

The Consumer Panel believes that in line with expert consensus and the available evidence, informed patients, parents, carers, families and guardians would agree with the recommendation for this treatment. The panel recognises that some informed patients, parents, carers, families and guardians may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel believes that most informed patients, parents, carers, families and guardians would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Prone positioning is not associated with significant cost for infants and small children since they require minimal nursing care to position. In larger children and adolescents, additional staff are needed to move and monitor in prone position, which will increase costs. Healthcare workers must be trained to facilitate safe practice in larger children and adolescents.

Equity

Important issues, or potential issues not investigated

There is the potential for inequity as some healthcare facilities may not have sufficient staff or training to offer prone positioning.

Acceptability

Important issues, or potential issues not investigated

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

No important issues with the recommended alternative

Prone positioning of mechanically ventilated children and adolescents is 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.

Rationale

Current reports suggest prone ventilation is effective in improving hypoxia associated with COVID-19 in adults. 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.

10.2.2 Positive end-expiratory pressure (PEEP)

Consensus recommendation

For mechanically ventilated neonates, children and adolescents with COVID-19 and moderate-to-severe acute respiratory distress syndrome with atelectasis, consider using a higher positive end-expiratory pressure (PEEP) strategy over a lower PEEP strategy. The absolute PEEP values that constitute a high and low PEEP strategy will depend on age and patient size.

Additional information

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

While there is no current evidence for using a higher positive end-expiratory pressure (PEEP) strategy in neonates, children and adolescents with COVID-19 and moderate-to-severe acute respiratory distress syndrome (ARDS), higher PEEP levels are recommended for ventilated neonates, children and adolescents with moderate to severe ARDS of other aetiologies. A high PEEP level may be associated with potential harms, including increased work of breathing, hypotension and air leaks.

Certainty of the Evidence

No studies were identified in neonates, children or adolescents with COVID-19 that address the question of lower versus higher PEEP strategy.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians.

The Consumer Panel believes that in line with expert consensus and the available evidence, some informed patients, parents, carers, families and guardians would agree with the recommendation and consider this treatment. The panel recognises that some informed patients, parents, carers, families and guardians may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel believes that most informed patients, parents, carers, families and guardians would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

Equity

No important issues with the recommended alternative

There are likely no important equity issues.

Acceptability

Important issues, or potential issues not investigated

We are uncertain if a higher PEEP ventilation strategy would be acceptable to neonates, children, adolescents and their families, and healthcare providers.

Feasibility

No important issues with the recommended alternative

There are likely no important feasibility issues.

10.2.3 Recruitment manoeuvres

Info Box

Neonates, children and adolescents 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 (PEEP) at a constant driving pressure, or the use of escalating mean airway pressure during high-frequency oscillatory ventilation (incremental PEEP, stepwise or staircase); and high driving pressures.

Consensus recommendation

For mechanically ventilated neonates, children and adolescents with COVID-19 and hypoxic respiratory failure characterised by severe atelectasis unresponsive to other ventilation strategies, consider using recruitment manoeuvres.

Additional information

In neonates and infants, staircase or stepwise incremental recruitment manoeuvres should only be performed using mean airway pressure in a high-frequency oscillatory ventilation mode. Staircase or stepwise (incremental positive end-expiratory pressure [PEEP]) recruitment manoeuvres should not be performed during conventional ventilation.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Recruitment manoeuvres may benefit mechanically ventilated children and adolescents with severe hypoxaemia due to COVID-19 by opening collapsed lung units and improving oxygenation and lung mechanics during mechanical ventilation. However, they may also be associated with harms, such as the increased risk of volutrauma/barotrauma and hypotension.

Certainty of the Evidence

No studies were identified in neonates, children or adolescents with COVID-19 that compare recruitment manoeuvres to no recruitment manoeuvres or variations on recruitment manoeuvres.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians.

The Consumer Panel believes that in line with expert consensus and the available evidence, some informed patients, parents, carers, families and guardians would agree with the recommendation and consider this treatment. The Panel recognises that some informed patients, parents, carers, families and guardians may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel believes that most informed patients, parents, carers, families and guardians would agree that

infection control precautions are optimised to minimise the risk of infection for others.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. However, neonates, children and adolescents receiving recruitment manoeuvres may require more intensive monitoring.

Equity

No important issues with the recommended alternative

Due to the potential to cause transient cardiovascular instability, and the requirement for intensive monitoring, recruitment manoeuvres in neonates, children and adolescents will usually only be performed in a dedicated paediatric critical care setting by an experienced clinician familiar with the intervention.

Acceptability

Important issues, or potential issues not investigated

We are uncertain if recruitment manoeuvres would be acceptable to neonates, children, adolescents and their families, and healthcare providers.

Feasibility

No important issues with the recommended alternative

There are likely no important feasibility issues.

10.2.4 Neuromuscular blockers

Conditional recommendation against

For intubated neonates, children and adolescents with COVID-19, do not routinely use continuous infusions of neuromuscular blocking agents (NMBAs).

However, if effective lung-protective ventilation cannot be achieved, consider targeted intermittent use of NMBAs. If indicated, the choice of NMBA should be guided by the age group and regional practice.

Additional information

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

There is no substantial net benefit to using neuromuscular blockers. Prolonged use of neuromuscular blocking agents (NMBAs) could have negative effects on intubated neonates, children and adolescents, such as muscle weakness, oedema and difficulty weaning from mechanical ventilation.

Certainty of the Evidence

Very low

Outcomes identified as most critical were 90-day mortality and muscle weakness at 28 days. No studies were identified that included neonates, children or adolescents 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 involving adults with COVID-19.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families and guardians. Since there is uncertainty regarding the critical outcome of muscle weakness, some might consider NMBAs unacceptable. The inability to move or communicate while being treated with neuromuscular blockers is likely to be an additional consideration for children and adolescents.

The Consumer Panel believes that in line with the available evidence, informed patients, parents, carers, families and guardians would agree with the recommendation; however, some informed patients, parents, carers, families and guardians may consider this treatment as a short-term intervention. The panel recognises that some informed patients, parents, carers, families and guardians may choose not to have this treatment based on reasons unrelated to COVID-19.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. There are potential resource considerations due to supply issues for some neuromuscular blockers.

Equity

Important issues, or potential issues not investigated

There is a risk of creating inequity as some facilities may have limited access to neuromuscular blockers suitable for neonates, children and adolescents.

Acceptability

Important issues, or potential issues not investigated

As the indication for NMBAs in severe or critical COVID-19 disease is to improve critical care delivery, generally NMBAs will be acceptable to neonates, children, adolescents and their families. The potential harms and effects of NMBAs may be less acceptable to some children, adolescents and their families, especially being paralysed and non-responsive. Clinicians should weigh the risks and benefits in decision making.

Feasibility

Important issues, or potential issues not investigated

Feasibility may be affected by potential supply issues for some neuromuscular blockers.

Rationale

Routine use of continuous infusions of neuromuscular blockers could have negative effects on intubated neonates, children and adolescents, such as muscle weakness, oedema and difficulty weaning from mechanical ventilation.

Clinical Question/ PICO

Population: Mechanically ventilated children and adolescents with COVID-19 and persistent ventilator dyssynchrony, the need for ongoing deep sedation, prone ventilation or persistently high plateau pressures

Intervention: Continuous infusion of NMBA

Comparator: No continuous infusion of NMBA

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 (NMBAs) with cisatracurium for up to 48 hours to no continuous infusions of NMBAs *[214][215][216][217][218]*.

For all critical outcomes, it is uncertain whether infusion of NMBAs makes a difference. The ROSE trial, which had a different sedation strategy to the other trials and implemented a higher positive end-expiry pressure (PEEP) strategy, is the largest (1006 participants) and most recent trial, and may be the most reflective of current practice *[215]*. 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** No NMBA	**Intervention** NMBA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
28-day mortality 6 Important	Relative risk 0.78 (CI 95% 0.58 — 1.06) Based on data from 1,461 participants in 5 studies. [1] (Randomized controlled)	372 per 1000 Difference:	290 per 1000 **82 fewer per 1000** (CI 95% 156 fewer — 22 more)	**Very low** Due to serious inconsistency, indirectness and imprecision [2]	We are uncertain whether neuromuscular blockers improve or worsen 28-day mortality (513 events).
90-day mortality 9 Critical	Relative risk 0.81 (CI 95% 0.62 — 1.06) Based on data from 1,461 participants in 5 studies. [3] (Randomized controlled)	441 per 1000 Difference:	357 per 1000 **84 fewer per 1000**	**Very low** Due to serious inconsistency, indirectness and imprecision [4]	We are uncertain whether neuromuscular blockers improve or worsen 90-day mortality (612 events).

Outcome Timeframe	**Study results and measurements**	**Comparator** No NMBA	**Intervention** NMBA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
			(CI 95% 168 fewer — 26 more)		
ICU mortality 6 Important	Relative risk 0.72 (CI 95% 0.57 — 0.91) Based on data from 455 participants in 4 studies. [5] (Randomized controlled)	438 per 1000 Difference:	315 per 1000 **123 fewer per 1000** (CI 95% 188 fewer — 39 fewer)	**Very low** Due to serious imprecision and very serious indirectness [6]	We are uncertain whether neuromuscular blockers increase or decrease ICU mortality (171 events).
ICU weakness at day 28 9 Critical	Relative risk 1.23 (CI 95% 0.81 — 1.88) Based on data from 356 participants in 4 studies. [7] (Randomized controlled)	230 per 1000 Difference:	283 per 1000 **53 more per 1000** (CI 95% 44 fewer — 202 more)	**Very low** Due to serious risk of bias and imprecision, and very serious indirectness [8]	We are uncertain whether neuromuscular blockers increase or decrease ICU weakness at day 28 (91 events).
Barotrauma 6 Important	Relative risk 0.55 (CI 95% 0.35 — 0.85) Based on data from 1,426 participants in 4 studies. [9] (Randomized controlled)	74 per 1000 Difference:	41 per 1000 **33 fewer per 1000** (CI 95% 48 fewer — 11 fewer)	**Very low** Due to serious risk of bias, indirectness and indirectness [10]	We are uncertain whether neuromuscular blockers improve or worsen barotrauma (81 events).
Mechanical ventilation duration Days 6 Important	Measured by: Days Based on data from 92 participants in 2 studies. [11] (Randomized controlled)	18 (Median) Difference:	20 (Median) **2 higher**	**Very low** Due to serious risk of bias, inconsistency and indirectness, and very serious imprecision [12]	We are uncertain whether neuromuscular blockers increase or decrease duration of mechanical ventilation.
Ventilator-free days at day 28 6 Important	Measured by: Days Based on data from 1,462 participants in 5 studies. [13] (Randomized controlled)	9.6 (Median) Difference:	9.9 (Median) **0.3 higher**	**Very low** Due to serious risk of bias, indirectness and imprecision [14]	We are uncertain whether neuromuscular blockers improve or worsen ventilator-free days at day 28.
MRC score at day 28 6 Important	Measured by: Medical Research Council (MRC) scale Scale: 0 — 60 High better Based on data from 1,346 participants in 2 studies. [15] (Randomized	49.8 muscle strength (Median) Difference:	45.9 muscle strength (Median) **MD 4.1 lower**	**Very low** Due to serious risk of bias and indirectness, and very serious inconsistency [16]	We are uncertain whether neuromuscular blockers improve or worsen MRC score at day 28.

Outcome Timeframe	**Study results and measurements**	**Comparator** No NMBA	**Intervention** NMBA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	controlled) Follow up: 28 days.				

Attached Images

10.2.5 High-frequency oscillatory ventilation (HFOV)

Info Box

High-frequency oscillatory ventilation (HFOV) is a specialised mode of respiratory support via an endotracheal tube that delivers very small tidal volumes at a rate much faster than normal breathing rates (> 2 Hz). It is used as a rescue therapy in neonates and children for severe respiratory failure when conventional mechanical ventilation is not effective. In neonates with severe respiratory failure, HFOV reduces need for ECMO. HFOV requires specialist equipment, and nursing and medical expertise.

Consensus recommendation

Do not routinely use high-frequency oscillatory ventilation (HFOV) as a first line mode of mechanical ventilation in neonates, children and adolescents with severe COVID-19. HFOV should be limited to a rescue therapy in neonates and children not responding to conventional mechanical ventilation in a specialist centre with experience with HFOV.

HFOV delivers gas at very high flow rates. This may increase the aerosol-generating potential compared to other forms of respiratory support used in intensive care. This may limit the suitability of HFOV in patients with COVID-19 unless strict attention to staff safety and infection control measures can be applied.

Additional information

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

While there is no current evidence for using high-frequency oscillatory ventilation (HFOV) in neonates, children or adolescents with COVID-19, it is recommended as a rescue therapy for ventilated neonates, children and adolescents with moderate to severe respiratory failure, including acute respiratory distress syndrome of other aetiologies. In these patients, it may have a survival benefit but may also increase the risk of harms from complications, such as cardiac compromise, barotrauma, endotracheal tube obstruction or accidental extubation. Infection prevention and staff safety should also be considered.

Certainty of the Evidence

No studies were identified in neonates, children or adolescents with COVID-19 that address the interventions or outcomes of interest.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians.

The Consumer Panel believes that in line with expert consensus, informed patients, parents, carers, families and guardians would agree to initiate this more invasive treatment if consistent with their goals of care. The panel recognises that some informed patients, parents, carers, families and guardians may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

The Consumer Panel believes that most informed patients, parents, carers, families and guardians would agree that

infection control precautions are optimised to minimise the risk of infection for others.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

Equity

HFOV can only be used in specialist critical care settings with appropriate equipment and staff, which may cause equity issues.

Acceptability

Important issues, or potential issues not investigated

We are uncertain if HFOV would be acceptable to neonates, children or adolescents with COVID-19 or their families and healthcare providers. However, HFOV is an established intensive care therapy in neonates and children that has been accepted other aetiologies.

Feasibility

Important issues, or potential issues not investigated

Different types of HFOV ventilators exist and some may not be compliant with infection control measures, which could impact the feasibility of this intervention.

Rationale

While there is no current evidence for using HFOV in neonates, children or adolescents with COVID-19 and severe respiratory failure, HFOV is used for ventilated neonates, children and adolescents with severe respiratory failure of other aetiologies, such as rescue therapy when conventional ventilation is not effective.

10.2.6 Videolaryngoscopy

Conditional recommendation

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

Additional information

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Laryngoscopy is a specialist medical procedure. Time to intubation varies depending on the experience of the operator and the setting, irrespective of the method of laryngoscopy. In non-COVID-19 neonates and children, videolaryngoscopy may reduce intubation failure rates. 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.

Values and preferences

No substantial variability expected

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families and guardians. Although there is uncertainty regarding the time to successful intubation, we are reasonably confident that they would find videolaryngoscopy an acceptable intervention compared to direct laryngoscopy.

The Consumer Panel believes that in line with the available evidence, most informed patients, parents, carers, families and guardians would agree with the recommendation for this treatment, if available and the operator is trained in its use. The panel also believes that most informed patients, parents, carers, families and guardians would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources

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 panels noted that rural and remote hospitals may 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 panels clarified in the recommendation that videolaryngoscopy should only be considered if available and operators are trained in its use.

The Paediatric Panel noted that intubation of infants and young children is a specialist procedure. Clinicians experienced in intubating adults may not be trained to perform intubation in infants and young children. This may reduce equity outside of dedicated paediatric centres.

Acceptability

No important issues with the recommended alternative

Videolaryngoscopy is generally a well-accepted intervention, and there are no important issues regarding acceptability.

Feasibility

Important issues, or potential issues not investigated

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, and may reduce the risk of aerosol exposure.

Clinical Question/ PICO

Population: Neonates, children and adolescents 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 *[207]*. A simulation study is also included that evaluated the distance between a dummy's mouth and physician's face during intubation *[212]*.

Effectiveness and adverse events

Study design	Randomised trials
Population	Critically ill patients requiring emergency intubation in emergency departments or intensive care units. No studies available in patients with COVID-19.
Intervention	Videolaryngoscopy
Comparison	Direct laryngoscopy
Synthesis method	Meta-analysis
Results	We included six of the eight randomised trials (1023 patients) in the Rombey review *[205][206][208][209][210][211]*. (Two were excluded because patients were intubated before hospital admission.) We included an additional randomised trial of 163 patients that was published after the Rombey review *[204]*. This study did not change the overall results for the outcomes, but did improve the precision of the estimate for inadvertent oesophageal intubation.

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)

Study design	Crossover study
Population	25 doctors of mixed experience performing tracheal intubation on a high-fidelity manikin.
Intervention	Videolaryngoscopy
Comparison	Direct laryngoscopy
Results	Videolaryngoscopy may extend the mouth-to-mouth distance from laryngoscopist to patient comp

Certainty of the evidence is low to very low due to indirectness (not based on COVID-19 patients or exclusively patients with acute respiratory distress syndrome), risk of bias, lack of precision in some outcomes and small number of adverse events.

Outcome Timeframe	**Study results and measurements**	**Comparator** Direct laryngoscopy	**Intervention** Videolaryngoscopy	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
First-pass intubation success	Relative risk 1.05 (CI 95% 0.94 — 1.17) Based on data from 1,186 participants in 7 studies. [1] (Randomized controlled)	716 per 1000 Difference:	752 per 1000 **36 more per 1000** (CI 95% 43 fewer — 122 more)	**Very low** Due to serious risk of bias, inconsistency and indirectness [2]	We are uncertain whether videolaryngoscopy increases or decreases first-pass intubation success.
Oesophageal intubation	Relative risk 0.4 (CI 95% 0.17 — 0.93) Based on data from 795 participants in 4 studies. [3] (Randomized controlled)	50 per 1000 Difference:	20 per 1000 **30 fewer per 1000** (CI 95% 41 fewer — 3 fewer)	**Very low** Due to serious risk of bias and indirectness [4]	Videolaryngoscopy may decrease oesophageal intubation.
Operator distance in cm [5] 8 Critical	Measured by: distance analysed from videorecording High better Based on data from 25 participants in 1 studies. [6] (Randomized controlled)	16.4 centimetres (Mean) Difference:	35.6 centimetres (Mean) **MD 19.2 higher** (CI 95% 13.28 lower — 25.12 higher)	**Very low** Due to serious risk of bias, indirectness and imprecision [7]	Videolaryngoscopy may increase the operator distance.
Time to successful intubation 7 Critical	Based on data from 988 participants in 6 studies. [8] (Randomized controlled)	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.		**Very low** Due to serious risk of bias, indirectness and imprecision, and very serious inconsistency [9]	We are uncertain whether videolaryngoscopy increases or decreases time to successful intubation.

Attached Images

10.2.7 Extracorporeal membrane oxygenation (ECMO)

Consensus recommendation

Consider early referral to an extracorporeal membrane oxygenation (ECMO) centre for venovenous or venoarterial ECMO in mechanically ventilated neonates, children and adolescents with COVID-19 with refractory respiratory or cardiovascular failure despite optimising other critical care interventions.

Additional information

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 neonates, children and adolescents with severe or critical COVID-19 and no contraindications for ECMO, such as severe, irreversible organ dysfunction.

The decision on whether to use ECMO should be taken in consultation with the patient's, healthcare decision-maker or family/ carers. Key considerations include pre-existing conditions and the suitability of anticoagulation.

Early referral to an ECMO centre is preferred.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Extracorporeal membrane oxygenation (ECMO) is only used as a form of life support in selected neonates, children and adolescents who are severely ill; it aims to increase oxygenation and reduce ventilator-induced lung injuries. However, it may be associated with risk of serious side effects, such as neurological injury, major bleeding, disseminated intravascular coagulation and injuries from cannulation.

Certainty of the Evidence

No studies were identified involving neonates, children and adolescents with COVID-19 that compare ECMO to no ECMO.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families and guardians. However, the serious risk of side effects may be unacceptable for some children and adolescents, carers, families or guardians.

The Consumer Panel believes that in line with expert consensus and the available evidence, some informed patients, parents, carers, families and guardians would agree with the recommendation and consider this treatment, while others may not wish to have more invasive treatment initiated if this is consistent with their goals of care. The panel recognises that some patients, parents, carers, families and guardians may choose not to have this treatment based on reasons unrelated to COVID-19.

The Consumer Panel believes that most informed patients, parents, carers, families and guardians would agree that infection control precautions are optimised to minimise the risk of infection for others.

Resources Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. ECMO is resource-intensive and requires experienced centres, healthcare workers and infrastructure.

Equity Important issues, or potential issues not investigated

Paediatric ECMO is only available at some tertiary centres in Australia. Some neonates, children and adolescents live in states and territories where ECMO is not available.

Acceptability Important issues, or potential issues not investigated

There may be important issues with acceptability. ECMO could be considered less acceptable due to its possible harms and some may not consider its benefits are worth the risk.

Feasibility Important issues, or potential issues not investigated

There are likely to be feasibility issues due to the resource-intensive nature of ECMO. ECMO is likely to only be feasible in a limited number of centres.

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.

11. Venous thromboembolism (VTE) prophylaxis

Info Box

Patients with COVID-19 are at a higher risk of clotting conditions (e.g. pulmonary emboli, deep vein thrombosis) compared with patients without COVID-19. It is important to establish if patients with COVID-19 require enhanced clotting prevention methods to prevent clotting conditions. In addition to establish if the effect differs for patients with severe/critical COVID-19 (e.g. ICU admitted, mechanically ventilated) compared with non-severe/non-critical COVID-19 (e.g. ward-based, not mechanically ventilated).

Standard prophylactic methods exist to prevent clotting conditions in hospital in-patients (herein referred to as usual-care thromboprophylaxis). Recent research has explored the efficacy of methods used to treat clotting conditions (herein referred to as treatment-level thromboprophylaxis) for preventing clotting conditions in patients with COVID-19. The following recommendations have been developed from the evidence comparing these two methods.

The comparisons and outcomes referred to below were developed in consultation with members of our expert panels and, specifically, experts in the field of thromboprophylaxis. The Acute and Critical Care Panel is responsible for developing recommendations specific to VTE thromboprophylaxis in adults, whereas the Pregnancy and Perinatal care panel are responsible for developing recommendations specific to VTE thromboprophylaxis in pregnant and postpartum women.

Recommendations are subsequently reviewed by the Guidelines Leadership Group and approved by the Steering Committee prior to publication. In addition, all recommendations are reviewed by the Consumer Panel to establish acceptability to the patient population for which they are relevant.

11.1 VTE prophylaxis for adults

Conditional recommendation

Use prophylactic doses of anticoagulants, preferably low molecular weight heparin (LMWH) (e.g. enoxaparin 40 mg once daily or dalteparin 5000 units once daily), in **adults with moderate, severe or critical COVID-19 or other indications**, unless there is a contraindication, such as risk for major bleeding. Where the estimated glomerular filtration rate (eGFR) (see below) is less than 30 mL/min/1.73m2, unfractionated heparin or clearance-adjusted doses of LMWH may be used (e.g. enoxaparin 20 mg once daily).

Additional information

For body weights outside 50–90 kg or heights outside 150–180 cm, calculate the body surface area (BSA) and multiply the eGFR by BSA/1.73.

The Taskforce notes that in critical illness, creatinine-based estimation of kidney function can be unreliable.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

There is little to no difference in benefits for patients with COVID-19 and there may be important harms. The benefits as well as harms associated with the use of low molecular weight (LMW) heparin and other anticoagulants are well-known in other patient groups.

Certainty of the Evidence

Very low

In patients with severe or critical COVID-19, comparing standard/intermediate-dose anticoagulants with therapeutic-dose anticoagulants, the certainty of the evidence is low (due to serious imprecision and risk of bias) or very low (due to serious risk of bias and very serious imprecision) for all outcomes except for hospital survival, which is moderate (due to serious risk of bias). For standard-dose compared with intermediate-dose anticoagulants, certainty of the evidence is moderate (due to serious imprecision) for all outcomes. In non-critically ill hospitalised patients with COVID-19, comparing standard/intermediate-dose anticoagulants with therapeutic-dose anticoagulants, the certainty of the evidence is low (due to serious imprecision and risk of bias) for all outcomes.

Values and preferences

Substantial variability is expected or uncertain

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.

The Consumer Panel believes that, due to the known risk of thrombosis in hospitalised individuals with COVID-19, most informed patients would agree with the recommendation for prophylactic anticoagulation unless contraindicated.

Resources

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding equity.

Acceptability

Important issues, or potential issues not investigated

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

Feasibility

Important issues, or potential issues not investigated

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.

Conditional recommendation against

Do not prescribe apixaban prophylaxis after discharge from hospital for adult patients who have been hospitalised with COVID-19 unless they have developed a thromboembolic event in hospital, or have another clinical indication to start or restart prophylactic apixaban therapy.

For pregnant or postpartum women who are admitted to hospital (for any indication) and who have COVID-19 see section 10.2 VTE prophylaxis for pregnant and postpartum women.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

There is little or to difference in benefits for patients receiving prophylactic apixaban following discharge from hospital and there may be important harms. The benefits as well as harms associated with the use of apixaban and other anticoagulants are well-known in other patient groups.

Certainty of the Evidence

Low

In patients who have been hospitalised with COVID-19, comparing a prophylactic dose of 2.5 mg apixaban twice daily for 14 days with standard care (no anticoagulation), the certainty of the evidence is low (due to serious imprecision and risk of bias) for all outcomes.

We have no systematically collected information regarding the effectiveness of prophylactic doses of other anticoagulants after discharge from hospital following acute COVID-19.

Values and preferences

We expect few to want the intervention

We have no systematically collected information regarding patients' preferences and values. The panel believes that since there is no evidence of benefit but there may be potential harm that most patients would not want prophylactic

anticoagulation following discharge from hospital.

Resources

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding equity.

Acceptability

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding acceptability.

Feasibility

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding feasibility.

Clinical Question/ PICO

Population: Apixaban for thromboembolism following acute COVID-19
Intervention: Prophylactic anticoagulation with apixaban
Comparator: No anticoagulation

Summary

Evidence indicates that using a prophylactic dosage of apixaban at discharge from hospital probably has little or no effect on death or re-hospitalisation in patients who have been hospitalised with COVID-19.

This recommendation is based on one study with 801 patients *[576]*. This study included any patient who had been hospitalised and was not due to receive ongoing medication for a COVID-19-related condition. Of the included participants, approximately 15% did not require respiratory support, 57% received supplemental oxygen, 25% received non-invasive respiratory support and 3% received invasive mechanical ventilation. Approximately 10% of these patients had been admitted to ICU.

Outcome Timeframe	**Study results and measurements**	**Comparator** No anticoagulation	**Intervention** Prophylactic anticoagulation with apixaban	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality 9 Critical	Relative risk 1.51 (CI 95% 0.43 — 5.31) Based on data from 801 participants in 1 studies. [1] (Randomized controlled)	**10** per 1000 Difference:	**15** per 1000 **5 more per 1000** (CI 95% 6 fewer — 43 more)	**Low** Due to serious imprecision and serious risk of bias [2]	Prophylactic dose may have little or no difference on all-cause mortality (10 deaths).

Outcome Timeframe	**Study results and measurements**	**Comparator** No anticoagulation	**Intervention** Prophylactic anticoagulation with apixaban	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Rehospitalisation within 12 months 6 Important	Relative risk 1.04 (CI 95% 0.78 — 1.39) Based on data from 801 participants in 1 studies. [3] (Randomized controlled)	281 per 1000 Difference:	292 per 1000 **11 more per 1000** (CI 95% 62 fewer — 110 more)	**Low** Due to serious imprecision and serious risk of bias [4]	Prophylactic dose may have little or no difference on rehospitalisation (230 events).

Attached Images

Conditional recommendation against

Do not routinely offer therapeutic anticoagulant dosing in adults with moderate, severe or critical COVID-19. There is no additional indication for therapeutic dosing for anticoagulants in adults with severe or critical COVID-19 beyond current standard best practice.

Additional information

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

There is little to no difference in benefits for patients with COVID-19 and there may be important harms. The benefits as well as harms associated with the use of low molecular weight (LMW) heparin and other anticoagulants are well-known in other patient groups.

Certainty of the Evidence

Very low

In patients with severe or critical COVID-19, comparing standard/intermediate-dose anticoagulants with therapeutic-dose anticoagulants, the certainty of the evidence is low (due to serious imprecision and risk of bias) or very low (due to serious risk of bias and very serious imprecision) for all outcomes except for hospital survival, which is moderate (due to serious risk of bias). For standard-dose compared with intermediate-dose anticoagulants, certainty of the evidence is moderate (due to serious imprecision) for all outcomes. In non-critically ill hospitalised patients with COVID-19, comparing standard/ intermediate-dose anticoagulants with therapeutic-dose anticoagulants, the certainty of the evidence is low (due to serious imprecision and risk of bias) for all outcomes.

Values and preferences

We expect few to want the intervention

We have no systematically collected information regarding patients' preferences and values. The panel believes that since there is no evidence of benefit but there may be potential harm and that most patients would not want increased-dose anticoagulation.

The Consumer Panel believes that as there is no clear benefit in the use of therapeutic anticoagulation in hospitalised

patients with severe or critical COVID-19, most informed patients would agree with this recommendation and not opt for treatment.

Resources

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding equity.

Acceptability

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding acceptability.

Feasibility

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding feasibility.

Clinical Question/ PICO

Population: Patients with non-critical COVID-19
Intervention: Therapeutic-dose thromboprophylaxis
Comparator: Prophylactic-dose thromboprophylaxis

Summary

Evidence indicates that using therapeutic dosages instead of prophylactic dosages of anticoagulants probably has little or no effect on most critical outcomes in patients with non-critical COVID-19.

What is the evidence informing this recommendation?
Evidence comes from six ~~three~~ randomised trials in patients with non-critical COVID-19. With ~~One study of~~ 3749 ~~2221~~ patients ~~was an open-label, adaptive, multi-platform study that~~ includ ing ~~ed~~ data from ~~three~~ trials ~~(REMAP-CAP, ACTIV-4a, ATTACC)~~ comparing prophylactic-dose anticoagul ation ~~ants~~ with therapeutic-dose anticoagula tion ~~nts~~ *[341]*. ~~Two further studies—the RAPID trial of 465 patients~~ *~~[376]~~* ~~and the ACTION trial of 614 patients~~ *[332]* ~~—also compared prophylactic-dose with therapeutic-dose anticoagulants~~.

Study characteristics
Mean or median age of participants ranged from 56 to 60 years. The proportion of women ranged from 38% to 46%.

What are the main results?
Five ~~One~~ stu dies ~~dy~~ of including 3580 ~~2221~~ patients ~~people~~ with COVID-19 shows therapeutic-dose thromboprophylaxis may have little or no difference on all-cause mortality ~~found~~ ~~a small effect favouring prophylactic dosages on organ-support free days~~ *[341]*. Three studies of 3306 patients with COVID-19 found a small effect favouring therapeutic dosages on clotting events.

Our confidence in the results
Comparing prophylactic-dose anticoagulants with therapeutic-dose anticoagulants for patients with non-critical COVID-19 involved examination of inadequate quality evidence. The certainty we have in the evidence is very low (due to serious risk of bias, imprecision and inconsistency) to moderate (due to serious risk of bias). Thus, our confidence that the results reflect true differences in effect is low.

Outcome Timeframe	**Study results and measurements**	**Comparator** Prophylactic-dose thromboprophylaxis	**Intervention** Therapeutic-dose thromboprophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality 9 Critical	Relative risk 0.91 (CI 95% 0.51 — 1.63) Based on data from 3,580 participants in 5 studies. [1] (Randomized controlled)	75 per 1000 Difference:	68 per 1000 **7 fewer per 1000** (CI 95% 37 fewer — 47 more)	**Low** Due to serious imprecision and serious inconsistency [2]	Therapeutic-dose thromboprophylaxis may have little or no difference on new all-cause mortality.
Major bleeding 9 Critical	Relative risk 1.77 (CI 95% 1 — 3.14) Based on data from 3,749 participants in 6 studies. [3] (Randomized controlled)	10 per 1000 Difference:	18 per 1000 **8 more per 1000** (CI 95% 0 fewer — 21 more)	**Low** Due to serious risk of bias and serious inconsistency [4]	Therapeutic-dose thromboprophylaxis may have little or no difference on new major bleeding.
Clotting event [5] 8 Critical	Relative risk 0.62 (CI 95% 0.41 — 0.92) Based on data from 3,306 participants in 3 studies. [6] (Randomized controlled)	60 per 1000 Difference:	37 per 1000 **23 fewer per 1000** (CI 95% 35 fewer — 5 fewer)	**Moderate** Due to serious risk of bias [7]	Therapeutic-dose anticoagulants probably decreases thrombotic events (98 events).
Organ support not required [8] 21 days 7 Critical	Relative risk 1.05 (CI 95% 1 — 1.09) Based on data from 2,221 participants in 1 studies. [9] (Randomized controlled)	765 per 1000 Difference:	803 per 1000 **38 more per 1000** (CI 95% 0 fewer — 69 more)	**Moderate** Due to serious imprecision [10]	Therapeutic-dose anticoagulants probably improves organ support not being required (1721 events).

Attached Images

11.2 VTE prophylaxis for pregnant and postpartum women

Info Box

Pregnant women in general are at an increased risk of venous thromboembolism (VTE). Hospitalised pregnant women with an acute infective illness (such as COVID-19) are at even greater risk of VTE. However, the exact duration of increased risk of VTE in association with COVID-19 infection is not yet established.

All pregnant and postpartum women should undergo a documented assessment of risk factors for VTE on admission to hospital, if COVID-19 is diagnosed, if COVID-19 severity changes and postpartum.

The use of pharmacological prophylaxis in women should be accompanied by other measures to prevent VTE, such as anti-embolism stockings and sequential compression devices.

Consensus recommendation

For pregnant or postpartum women who are admitted to hospital (for any indication) and who have COVID-19, use prophylactic doses of anticoagulants, preferably low molecular weight heparin (LMWH) (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) unless there is a contraindication, such as risk for major bleeding or imminent birth.

Prophylactic anticoagulants should be continued for at least 14 days after discharge or until COVID-19-related morbidity (including immobility, dehydration and/or shortness of breath) has resolved.

Additional information

- *Dosing of LMWH is dependent on pre-pregnancy body weight and current renal function.*
- *For women with early pregnancy body weight outside of 50–90 kg, consider adjusted LMWH dosing.*
- *There is limited evidence to guide the most appropriate dose in obese patients but standard dosing may be inadequate.*

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Prophylactic anticoagulants are used routinely in pregnant and postpartum women who are at risk of VTE. There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19. However, acute infective illnesses such as COVID-19 are known to increase the risk of VTE.

Certainty of the Evidence

There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Caring for women and newborns with COVID-19 (irrespective of separation) requires greater resources than for those without COVID-19.

Equity

Important issues, or potential issues not investigated

There are likely no important equity issues.

Acceptability

No important issues with the recommended alternative

There is no systematically collected information regarding the acceptability of VTE prophylaxis in women with COVID-19 at this point. However, since prophylaxis with anticoagulants is commonly used in women with risk factors for VTE, it is likely to be acceptable to all stakeholders.

Feasibility

No important issues with the recommended alternative

There are likely no important feasibility issues.

Rationale

Prophylactic anticoagulants are used routinely in pregnant and postpartum women who are at risk of VTE. There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19, however, acute infective illnesses (such as COVID-19) are known to increase the risk of VTE.

Consensus recommendation

For pregnant women with severe or critical COVID-19, or where there are additional risk factors for venous thromboembolism (VTE), consider using increased prophylactic dosing of anticoagulants, preferably low molecular weight heparin (LMWH) (e.g. enoxaparin 40 mg twice daily or dalteparin 5000 IU twice daily) unless there is a contraindication, such as risk for major bleeding or platelet count < 30 x 109/L.

Prophylactic anticoagulants should be continued for at least four weeks after discharge or until COVID-19-related morbidity (including immobility, dehydration and/or shortness of breath) has resolved.

Additional information

- *Dosing is dependent on pre-pregnancy body weight and current renal function. For women with early pregnancy body weight outside of 50–90 kg, consider adjusted LMWH dosing.*
- *There is limited evidence to guide the most appropriate dose in obese patients but standard dosing may be inadequate.*
- *Clinicians should refer to their local or jurisdictional guidance on additional VTE risk factors.*
- *In some situations, continuation of LMWH throughout the rest of pregnancy and postpartum may be required. Involvement of specialist obstetricians, obstetric medicine physicians, haematologists or other physicians with expertise in VTE in pregnant women would be warranted.*

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Prophylactic anticoagulants are used routinely in pregnant and postpartum women who are at risk of venous thromboembolism (VTE). There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in

pregnant and postpartum women with COVID-19. However, acute infective illnesses such as COVID-19 are known to increase the risk of VTE.

Certainty of the Evidence

There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Caring for women and newborns with COVID-19 (irrespective of separation) requires greater resources than for those without COVID-19.

Equity

Important issues, or potential issues not investigated

There are likely no important equity issues.

Acceptability

No important issues with the recommended alternative

There is no systematically collected information regarding the acceptability of VTE prophylaxis in women with COVID-19 at this point. However, since prophylaxis with anticoagulants is commonly used in women with risk factors for VTE, it is likely to be acceptable to all stakeholders.

Feasibility

No important issues with the recommended alternative

There are likely no important feasibility issues.

Rationale

Prophylactic anticoagulants are used routinely in pregnant and postpartum women who are at risk of VTE. There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19, however, acute infective illnesses (such as COVID-19) are known to increase the risk of VTE.

Consensus recommendation

For pregnant or postpartum women who are self-isolating at home with mild COVID-19 and where additional risk factors for VTE are present, consider using prophylactic doses of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) unless there is a contraindication, such as risk for major bleeding or imminent birth. Prophylactic anticoagulants should be continued for at least 14 days or until COVID-19-related morbidity (including immobility, dehydration and/or shortness of breath) has resolved.

For pregnant or postpartum women who are self-isolating at home with mild COVID-19 and who have no additional risk factors for VTE, routine pharmacological prophylaxis is not recommended.

Additional information

- *Dosing of LMWH is dependent on pre-pregnancy body weight and current renal function. For women with early pregnancy body weight outside of 50–90 kg, consider adjusted LMWH dosing.*
- *There is limited evidence to guide the most appropriate dose in obese patients but standard dosing may be inadequate.*
- *Clinicians should refer to their local or jurisdictional guidance on additional VTE risk factors.*

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Prophylactic anticoagulants are used routinely in pregnant and postpartum women who are at risk of venous thromboembolism (VTE). There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19. However, acute infective illnesses such as COVID-19 are known to increase the risk of VTE.

Certainty of the Evidence

There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Caring for women and newborns with COVID-19 (irrespective of separation) requires greater resources than for those without COVID-19.

Equity

Important issues, or potential issues not investigated

There are likely no important equity issues.

Acceptability

No important issues with the recommended alternative

There is no systematically collected information regarding the acceptability of VTE prophylaxis in women with COVID-19 at

this point. However, since prophylaxis with anticoagulants is commonly used in women with risk factors for VTE, it is likely to be acceptable to all stakeholders.

Feasibility

No important issues with the recommended alternative

There are likely no important feasibility issues.

Rationale

Prophylactic anticoagulants are used routinely in pregnant and postpartum women who are at risk of VTE. There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19, however, acute infective illnesses (such as COVID-19) are known to increase the risk of VTE.

Consensus recommendation

For postpartum women who have had COVID-19 during pregnancy, consider using at least 14 days of prophylactic dosing of anticoagulants, preferably low molecular weight heparin (LMWH) (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) unless there is a contraindication, such as risk for major bleeding. Increased duration of 6 weeks should be considered if severe or critical COVID-19 and/or additional risk factors for venous thromboembolism (VTE) are present.

Additional information

- *Dosing of LMWH is dependent on pre-pregnancy body weight and current renal function. For women with early pregnancy body weight outside of 50–90 kg, consider adjusted LMWH dosing.*
- *There is limited evidence to guide the most appropriate dose in obese patients but standard dosing may be inadequate.*
- *Clinicians should refer to their local or jurisdictional guidance on additional VTE risk factors.*

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Prophylactic anticoagulants are used routinely in pregnant and postpartum women who are at risk of venous thromboembolism (VTE). There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19. However, acute infective illnesses such as COVID-19 are known to increase the risk of VTE.

Certainty of the Evidence

There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Caring for women and newborns with COVID-19 (irrespective of separation) requires greater resources than for those without COVID-19.

Equity

Important issues, or potential issues not investigated

There are likely no important equity issues.

Acceptability

No important issues with the recommended alternative

There is no systematically collected information regarding the acceptability of VTE prophylaxis in women with COVID-19 at this point. However, since prophylaxis with anticoagulants is commonly used in women with risk factors for VTE, it is likely to be acceptable to all stakeholders.

Feasibility

No important issues with the recommended alternative

There are likely no important feasibility issues.

Rationale

Prophylactic anticoagulants are used routinely in pregnant and postpartum women who are at risk of VTE. There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in pregnant and postpartum women with COVID-19, however, acute infective illnesses (such as COVID-19) are known to increase the risk of VTE.

11.3 VTE prophylaxis for children and adolescents

Consensus recommendation

For **all children and adolescents** hospitalised with COVID-19, the following are recommended to prevent thrombosis, based on age and risk assessment.

> In **children and adolescents aged 12 years and over** who are hospitalised specifically for COVID-19 treatment and with no contraindications to anticoagulants, use prophylactic doses of low molecular weight heparin* (LMWH) and mechanical thromboprophylaxis (TED stockings or calf compressors) until discharge from hospital.
>
> In **children under 12 years** who are hospitalised specifically for COVID-19 treatment and **with either D-dimer levels > 5 x upper limit normal or additional thrombosis risk factors** (including hospital-associated venous thromboembolism), use prophylactic doses of low molecular weight heparin* (LMWH) and mechanical thromboprophylaxis (TED stockings or calf compressors) where suitable based on size and mobility until discharge from hospital.

Additional information

Dose of low molecular weight heparin (LMWH):*

- *≥ 3 months old – enoxaparin 0.5 mg/kg BD (maximum of 60 mg BD, or at the standard adult prophylactic dose for your centre)*
- *< 3 months old – enoxaparin 0.75 mg/kg BD*
- ** Unfractionated heparin (UFH) is an alternative to LMWH and can be considered if there is potential for surgical intervention, renal impairment or other clinical factors that would normally favour UFH over LMWH. Dosing should be advised by paediatric haematology.*

Where the estimated glomerular filtration rate (eGFR) is less than 30 mL/min/1.73m2, UFH or clearance-adjusted doses of LMWH may be used (discuss with paediatric haematologist).

*Contraindications to thromboprophylaxis**

- *Stroke / intracranial haemorrhage*
- *Any bleeding from any site / uncontrolled bleeding*
- *Likely to need surgery in < 24 hours*
- *Congenital bleeding disorder (e.g. von Willebrand disease, haemophilia)*
- *Platelets < 50 x 10^9/L and/or INR > 1.8*
- *Uncontrolled hypertension*
- ** Consider UFH (unfractionated heparin)*

Thrombosis risk factors

- *Admission to paediatric intensive care unit (PICU)*
- *Obesity (BMI > 95 percentile)*
- *Central venous catheter*
- *Length of stay anticipated > 3 days*
- *Immobility that is not longstanding*
- *Personal history of VTE*
- *Known thrombophilia*
- *First degree relative with VTE*
- *Active malignancy*
- *Recent surgery / trauma*
- *Severe dehydration*
- *Underlying medical condition: nephrotic syndrome, cystic fibrosis, sickle cell disease, cardiac disease, chronic inflammatory disorder (juvenile idiopathic arthritis, inflammatory bowel disease), post splenectomy.*

In the absence of reliable evidence, the Taskforce has developed this recommendation based on their clinical expertise and experience.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Prophylactic anticoagulants are used in children and adolescents who are at risk of venous thromboembolism (VTE). The benefit of a modified thromboprophylaxis regimen for children and adolescents with COVID-19 is unclear. There are well-

known benefits of this strategy in selected children with risk factors for VTE. There are well-known harms of thromboprophylaxis such as major bleeding.

Certainty of the Evidence

There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in children and adolescents with COVID-19.

Values and preferences

No substantial variability expected

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians. However, we expect the intervention would be generally acceptable as it is regularly used in other procedures.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

Equity

No important issues with the recommended alternative

It is unlikely that the use of thromboprophylaxis will create equity issues as it is common practice.

Acceptability

No important issues with the recommended alternative

Thromboprophylaxis is generally a well-accepted intervention, and there are no important issues regarding acceptability.

Feasibility

No important issues with the recommended alternative

There are no major feasibility issues as the recommendation reflects usual practice.

12. Therapies for existing indications in patients with COVID-19

Info Box

The Primary and Chronic Care Panel is responsible for developing recommendations specific to therapies for existing indications in patients with COVID-19.

Recommendations are subsequently reviewed by the Guidelines Leadership Group and approved by the Steering Committee before publication. In addition, all recommendations are reviewed by the Consumer Panel to establish acceptability to the patient population for which they are relevant.

12.1 ACEIs/ARBs in patients with COVID-19

Recommended

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

Additional information

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

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Stopping angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (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.

Values and preferences

No substantial variability expected

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.

The Consumer Panel has considered issues around pre-existing conditions and treatments, and believes that in line with available evidence, informed patients would wish to continue with their current prescribed treatment for their pre-existing conditions.

Resources

No important issues with the recommended alternative

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

No important issues with the recommended alternative

There are no identified equity issues.

Acceptability

No important issues with the recommended alternative

Continued concomitant ACEI/ARB medication is likely to be acceptable to both patients and clinicians.

Feasibility

No important issues with the recommended alternative

There are likely no important feasiblity 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 *[426][427][428][429][430][431][432][433][434][435][436][437][438][439]*. 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 angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (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 *[261][262][263][264]*. These reviews conclude that continued use of ACEIs/ARBs is unlikely to be associated with an increased risk of disease severity or death in patients with COVID-19. The conclusions are based on very low certainty evidence due to serious risk of bias, imprecision and inconsistency in findings between studies.

Despite the very low certainty evidence that continued use of concomitant ACEIs/ARBs increases or decreases death 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Stopping concomitant ACEIs/ARBs	**Intervention** Continued use of concomitant ACEIs/ARBs	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 9 Critical	Odds ratio 0.86 (CI 95% 0.63 — 1.16) Based on data from 7,492 participants in 12 studies. [1] (Observational (non-randomized))	287 per 1000 Difference:	262 per 1000 **25 fewer per 1000** 72 fewer — 28 more	**Very low** Due to serious risk of bias, inconsistency and imprecision [2]	We are uncertain whether continued use of concomitant ACEIs/ARBs increases or decreases death in patients with COVID-19.
Risk of severe or lethal COVID-19	Odds ratio 1 (CI 95% 0.84 — 1.18)	309	309	**Very low** Due to serious	We are uncertain whether continued use

Outcome Timeframe	**Study results and measurements**	**Comparator** Stopping concomitant ACEIs/ARBs	**Intervention** Continued use of concomitant ACEIs/ARBs	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important	Based on data from 11,334 participants in 5 studies. [3] (Observational (non-randomized))	per 1000 Difference:	per 1000 **0 fewer per 1000** (CI 95% 36 fewer — 36 more)	risk of bias, inconsistency and imprecision [4]	of concomitant ACEIs/ ARBs increases or decreases the risk of death or progression to severe COVID-19.
Severity (narrative analysis) 6 Important	Based on data from 23,565 participants in 13 studies. [5] (Observational (non-randomized))	Continued use of ACEIs/ARBs in patients with COVID-19 does not appear to increase the likelihood of more severe COVID-19 illness.		**Very low** Due to serious risk of bias and imprecision [6]	We are uncertain whether continued use of concomitant ACEIs/ ARBs increases or decreases the risk of progression to severe COVID-19.

Attached Images

12.2 ACEIs in postpartum women

Consensus recommendation

In postpartum women with COVID-19 who have hypertension requiring treatment with angiotensin-converting enzyme inhibitors (ACEIs), there is currently no evidence to deviate from usual care. These medications should be initiated or continued unless otherwise contraindicated.

Additional information

ACEIs are contraindicated in the antenatal period due to risk of fetal and neonatal harm.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Angiotensin-converting enzyme inhibitors (ACEIs), such as enalapril, captopril and quinapril, are used for the management of postpartum hypertension and are considered compatible with breastfeeding *[265]*. Their use is contraindicated during pregnancy as they have been associated with fetal death and neonatal renal failure. There is currently no evidence to indicate that ACEIs should not be used postpartum in a woman with confirmed COVID-19.

Certainty of the Evidence

No studies were identified that address the use of ACEIs for postpartum women with COVID-19.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

The Consumer Panel has considered issues around pre-existing conditions and treatments, and believes that in line with available evidence, informed patients would wish to have treatment initiated, or to continue with prescribed treatment for their condition.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Caring for pregnant women with COVID-19 (irrespective of postpartum hypertension) requires greater resources than for women without COVID-19.

Equity

No important issues with the recommended alternative

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

Acceptability

Important issues, or potential issues not investigated

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

Feasibility

No important issues with the recommended alternative

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

12.3 Steroids for people with asthma or COPD with COVID-19

Consensus recommendation

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

Additional information

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

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.

Certainty of the Evidence

There is no available evidence about outcomes for inhaled or oral corticosteroids for patients with COVID-19 and asthma or COPD.

Values and preferences

No substantial variability expected

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.

The Consumer Panel has considered issues around pre-existing conditions and treatments, and believes that in line with available evidence, informed patients would wish to continue with their prescribed treatment for their pre-existing conditions.

Resources

No important issues with the recommended alternative

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.

Equity

No important issues with the recommended alternative

There are no identified equity issues.

Acceptability

No important issues with the recommended alternative

The treatment is likely to be acceptable to both patients and clinicians.

Feasibility No important issues with the recommended alternative

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

Rationale

Oral steroids and continuation of inhaled steroids reduce harms in patients experiencing exacerbations of asthma or COPD 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 *[266]*, NICE [NG168] *[267]* and NICE [NG 166] *[268]*. 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) *[266]*. 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 *[268]*.

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 chronic obstructive pulmonary disease (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 *[267]*. 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 *[269][270]*.

Abrupt withdrawal of corticosteroids can lead to acute adrenal insufficiency or exacerbation of symptoms of asthma or COPD.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Coticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
See summary					

Attached Images

12.4 Oestrogen-containing therapies

Consensus recommendation

In women who have COVID-19 and who are taking oral menopausal hormone therapy (MHT), **manage these medications as per usual care**. In women who stop or suspend oral MHT, review the indication for this and consider transitioning to a transdermal preparation. Manage transdermal MHT as per usual care.

Additional information

Decisions around stopping hormone therapy should be discussed with the patient, healthcare decision-maker or family/carers. The goals of patient care need to balance the preferences and values of the patient, based on discussion and consideration of the patient's individual circumstances.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

There is emerging evidence that menopausal hormone therapy (MHT) is associated with a reduced risk of mortality in post-menopausal women with COVID-19.

The risk of venous thromboembolism (VTE) is elevated in people with COVID-19 and who are receiving oral MHT, however the combined risk of VTE in post-menopausal women with COVID-19 who are receiving MHT is unknown. Current Taskforce guidelines recommend that VTE prophylaxis be given to all patients with severe or critical COVID-19. While there is a lack of direct evidence that the prophylactic anticoagulant doses prescribed in our VTE recommendations completely alleviate the risk of VTE in women taking oral MHT, it is likely that these doses are effective.

Certainty of the Evidence

Three cohort studies have associated a reduced risk of mortality with the use of menopausal hormone therapy (also known as hormone replacement therapy) in post-menopausal women with COVID-19. *[467][468][469]*

Values and preferences

Substantial variability is expected or uncertain

The Consumer Panel believes that in line with expert consensus and the available evidence, most informed patients would agree with this recommendation. The panel recognises that some informed patients may choose not to proceed with this recommendation based on reasons unrelated to COVID-19.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Use of oral or transdermal MHT as per usual care is unlikely to have an impact on availability of these drugs.

Equity

Important issues, or potential issues not investigated

There are no identified equity issues.

Acceptability

No important issues with the recommended alternative

The treatment is likely to be acceptable to both patients and clinicians.

Feasibility

No important issues with the recommended alternative

There are likely no important feasibility issues.

Rationale

Both COVID-19 (severe or critical) and oral MHT are associated with an increased risk of VTE. However, there is some evidence to suggest a reduction in risk of mortality in women with COVID-19 who are taking MHT. It is not known if this evidence pertains to oral or transdermal MHT.

The duration of elevated VTE risk after acute COVID-19 infection is uncertain. Current Taskforce guidelines recommend that VTE prophylaxis be given to all patients with severe or critical COVID-19. While there is a lack of direct evidence that the prophylactic anticoagulant doses prescribed in our VTE recommendations completely alleviate the risk of VTE in women taking oral MHT, it is likely that these doses are effective.

Consensus recommendation

In women who have COVID-19 and who are taking oestrogen-containing contraception, manage these medications as per usual care.

In women who stop or suspend contraception when they have COVID-19, restart contraception at the time of discharge or when acute symptoms have resolved.

Additional information

Decisions around stopping oestrogen-containing contraception should be discussed with the patient or their substitute / medical treatment decision-maker. The goals of patient care need to balance the preferences and values of the patient, based on discussion and consideration of the patients individual circumstances.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Both COVID-19 (severe or critical) and oestrogen-containing contraception are associated with an increased risk of venous thromboembolism (VTE). While the use of oestrogen-containing contraception is associated with an increased risk of VTE, this risk is assessed when prescribing oestrogen-containing contraceptives. Furthermore, it is recommended that VTE prophylaxis be given to all patients with severe or critical COVID-19.

While there is a lack of direct evidence that the prophylactic anticoagulant doses prescribed in our VTE recommendations completely alleviate the risk of VTE in women using oestrogen-containing contraception, it is likely that these doses are effective. Therefore, an increased risk of VTE during severe or critical COVID-19 is not considered a reason to stop oestrogen-containing contraception. Note that progestogen-only contraception methods are not associated with an increased VTE risk.

There is no evidence that women who are using oestrogen-containing contraception methods and who have mild or moderate COVID-19 have an increased risk of VTE. However, COVID-19 causes a hypercoagulable state in some people, which may worsen the VTE risk associated with combined hormonal contraception. The incidence of VTE in women of reproductive age with COVID-19 infection is currently not known.

There is a risk of unintended pregnancy when contraception is ceased. Women with severe or critical COVID-19 may not be well enough to take oral contraceptives, resulting in temporary cessation, but efforts should be made to ensure that recommencing contraception is not neglected. Where patients have stopped contraception, consider the need for emergency contraception.

Certainty of the Evidence

No studies were identified that address the risk of VTE associated with the use of oestrogen-containing contraception in women with COVID-19.

Values and preferences

Substantial variability is expected or uncertain

The Consumer Panel believes that in line with expert consensus and the available evidence, most informed patients would agree with this recommendation. The panel recognises that some informed patients may choose not to proceed with this recommendation based on reasons unrelated to COVID-19.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Use of contraception as per usual care is unlikely to have an impact on availability of these drugs.

Equity

Important issues, or potential issues not investigated

There are no identified equity issues.

Acceptability

No important issues with the recommended alternative

The treatment is likely to be acceptable to both patients and clinicians.

Feasibility

No important issues with the recommended alternative

There are likely no important feasibility issues.

Rationale

Severe or critical COVID-19 and oestrogen-containing contraceptives are both associated with an increased risk of venous thromboembolism (VTE). However, the increased risk is likely to be alleviated because (a) the risk of VTE is assessed when considering whether to prescribe oestrogen-containing contraceptives, and (b) it is recommended that patients with severe or critical COVID-19 are prescribed VTE prophylaxis.

While there is a lack of direct evidence that the prophylactic anticoagulant doses prescribed in our VTE recommendations completely alleviate the risk of VTE in women using oestrogen-containing contraception, it is likely that these doses are effective. Therefore, an increased risk of VTE during severe or critical COVID-19 is not considered a reason to stop oestrogen-containing contraception, and management as per usual care is recommended. It is useful to note, however, that usual care for people with severe or critical COVID-19 refers to stopping non-essential medications, as this reduces contact with patients thus reducing the risk of transmission to the healthcare worker. Note that progestogen-only contraception methods are not associated with an increased VTE risk.

There is no evidence that women who are using oestrogen-containing contraception methods and who have mild or moderate COVID-19 have an increased risk of VTE. However, COVID-19 causes a hypercoagulable state in some people, which may worsen the VTE risk associated with combined hormonal contraception. The incidence of VTE in women of reproductive age

with COVID-19 infection is currently not known. Patients should be advised of this theoretical risk to allow informed choice of contraceptive option, however, at this time there is no evidence to support routine cessation. Management as per usual care is, therefore, recommended—where usual care refers to continuing oestrogen-containing contraception, unless contraindicated.

There is a risk of unintended pregnancy when contraception is ceased. Women with severe or critical COVID-19 may not be well enough to take oral contraceptives, resulting in temporary cessation, but efforts should be made to ensure that recommencing contraception is not neglected. Where patients have stopped contraception, consider the need for emergency contraception.

13. Care after COVID-19

Info Box

This section applies to adults, adolescents and children with signs and symptoms that continue, or develop, after acute COVID-19 *[513][514]*. These signs and symptoms are commonly referred to as 'long COVID'.

A range of symptoms have been reported in both adults and children, with variation in the duration of symptoms and clinical sequelae *[382][384][503][504][505][506][507][508][509][510][511][512]*.

Growing evidence shows that these symptoms are driven by underlying immunological and biological changes. Symptoms may be experienced by people who had either mild, moderate or severe COVID-19. Some symptoms subside gradually with self-directed care alone, while other symptoms may require care from a health professional, and new symptoms may arise over time.

To obtain a summary of the following recommendations, we direct readers to the Care of people after COVID-19 flowchart.

The Primary and Chronic Care Panel is responsible for developing recommendations specific to care after COVID-19.

Recommendations are subsequently reviewed by the Guidelines Leadership Group and approved by the Steering Committee prior to publication. In addition, all recommendations are reviewed by the Consumer Panel to establish acceptability to the patient population for which they are relevant.

Info Box

CURRENT DEFINITIONS

Acute COVID-19

- Signs and symptoms of COVID-19 for up to 4 weeks.

Post-COVID-19 condition/syndrome

- Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body. Post COVID-19 condition may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed.

Adapted from *[513][514]*.

13.1 Goals of care

Good practice statement

Due to the broad range of symptoms and signs following acute COVID-19, a biopsychosocial approach to care, within the local context, is important. Take the time to listen to the patient, validate their experience and offer information about the symptoms that they are experiencing, including management options.

Good practice statement

The primary health care team is well placed to coordinate person-centred care and should remain a central point in the care team along with the patient's, healthcare decision-maker or family/carers. Best practice would include a multidisciplinary team. This could be accessed through general practice, community health, rehabilitation programs or post-COVID-19 clinics, where these are available.

Use case conferences to facilitate coordinated care.

Good practice statement

The following recommendations should be applied after considering features of the individual, their preferences and the context in terms of rurality/remoteness, public health responses and proximity to rehabilitation or higher-level care. For those needing active rehabilitation, involving a larger centre or specialist care could be considered. Use of virtual care, including telehealth, should be considered.

13.2 Assessment and diagnosis in patients with continuing symptoms after COVID-19

Good practice statement

Assessing the probability diagnosis

- Confirm that the person had COVID-19 (by checking that they had a positive PCR test), or is likely to have had COVID-19 (by checking that they have had symptoms consistent with a SARS-CoV-2 infection and/or known contact with a positive case or high-risk setting). Document details of the acute illness.
- Check the current symptoms and ask the person about their concerns, functioning and wishes in terms of their needs.
- Assess whether the current symptoms are likely to be related to acute COVID-19.
- Assess whether the symptoms may be related to, or are exacerbated by, comorbid conditions *[390]*.

Consensus recommendation

The following symptoms have been described by people after COVID-19 *[382][383][384]* [adapted from National Institute for Health and Care Excellence]:

Respiratory symptoms

- Shortness of breath
- Cough

Generalised symptoms

- Fatigue
- Fever
- Pain

Cardiovascular symptoms

- Chest tightness
- Chest pain
- Palpitations

Neurological symptoms

- Cognitive impairment ('brain fog', loss of concentration or memory issues)
- Headache
- Sleep disturbance
- Peripheral neuropathy (pins and needles and numbness)
- Dizziness
- Delirium (in older populations)
- Mobility impairment
- Visual disturbance

Gastrointestinal symptoms

- Abdominal pain
- Nausea and vomiting
- Diarrhoea
- Weight loss and reduced appetite

Musculoskeletal symptoms

- Joint pain
- Muscle pain

Ear, nose and throat symptoms

- Tinnitus
- Earache
- Sore throat
- Dizziness
- Loss of taste and/or smell

- Nasal congestion

Dermatological symptoms

- Skin rashes
- Hair loss

Psychological/psychiatric symptoms

- Depression
- Anxiety
- Post-traumatic stress disorder

This list of symptoms will be updated as new evidence emerges.

Info Box

Long COVID symptoms also manifest in ongoing complications from acute COVID-19, new symptoms following recovery of COVID-19, along with decompensation of pre-existing medical conditions.

Complications from acute COVID-19 include:

- Extrapulmonary medical complications of COVID-19 e.g. deep vein thrombosis (DVT), pulmonary embolism (PE), pulmonary fibrosis or scarring
- Myocarditis (cardiac muscle inflammation)

Conditions that can manifest following acute COVID-19 include:

- Post-intensive care syndrome (PICS). PICS refers to one or more of the following symptoms that people experience following care in ICU: anxiety, depression, cognitive impairment, memory loss, muscle weakness, dysphagia and reduced quality of life *[386][387]*.
- Multisystem inflammatory syndrome. In some people, both adults and children, symptoms corresponding to multisystem inflammatory syndrome have been reported *[385]*[Centers for Disease Control 2022].
- Cardiovascular dysautonomia such as Postural Orthostatic Tachycardia Syndrome (POTS)
- New and/or co-incident medical conditions
- De-stabilisation or exacerbation of pre-existing medical conditions.

13.3 Management in patients with continuing symptoms after COVID-19

Our understanding of effective management approaches is still emerging. As such, recommendations for the management of people with post-COVID-19 will be updated here as new evidence emerges. In the interim, we direct readers to the Care of people after COVID-19 flowchart. This flowchart outlines aspects of care and treatment based on current best-practice approaches.

Info Box

The Consumer Panel wish to emphasise the ongoing importance of preventing COVID infection (and reinfection) as the most effective way of minimising the risk of developing post-COVID condition.

Consensus recommendation

In patients with continuing symptoms after COVID-19, use established symptom management approaches (e.g. breathing retraining to improve symptoms of dyspnoea).

Evidence for specific management of post COVID-19 is not available. Established symptom management approaches are likely to be beneficial.

Use existing clinical guidelines [527][528][529][530][531][532][533][534][535][536][537][538][539][540] to guide symptom management.

Consensus recommendation

In patients with post-exertional fatigue, use a conservative physical rehabilitation plan involving consultation with physiotherapy or exercise physiology for cautious initiation and pacing of activity or movement. [Adapted from Centers for Disease Control and Prevention]

For most patients gradual return to exercise as tolerated may be beneficial.

Additional caution and specialist review should be sought before commencing exercise programs in patients who are known to have myocarditis. Clinicians should assess whether exercise exacerbates symptoms, and adjust rehabilitation plans as necessary.

A rehabilitation plan, where appropriate, might include physical and occupational therapy, speech and language therapy, vocational therapy, as well as neurological rehabilitation.

Consider individual factors and access issues in determining location for further treatment or rehabilitation (e.g. home-based, telehealth or face-to-face options).

Use local and regional protocols and HealthPathways to determine optimal referral pathways.

Consensus recommendation

Updated

In people with signs and symptoms of a new or exacerbated existing mental health condition following acute COVID-19, provide psychosocial support, and evidence-based psychological and psychiatric therapies for the relevant mental health condition.

Consensus recommendation

In patients with persistent symptoms or functional impairment following COVID-19, begin rehabilitation as soon as possible, as appropriate to the individual's circumstance, setting and tolerance.

Where appropriate, treatment may involve physical and occupational therapy, speech and language therapy, vocational therapy, as well as neurological rehabilitation and dietary interventions.

Consider using a chronic disease plan, mental health care plan or other enhanced care plan to facilitate access to multidisciplinary care.

Consider individual factors and access issues in determining location for further treatment or rehabilitation (e.g. home-based, telehealth or face-to-face options).

Use local and regional protocols and HealthPathways to determine optimal referral pathways.

Consensus recommendation

Use education and skills training on self-management strategies for symptoms.

The World Health Organization's patient resource page provides useful information about post-COVID-19 condition.

Consensus recommendation

New

At each consultation, ask the patient if they are taking any medications, supplements or therapies for their symptoms.

Consensus recommendation

In patients with continuing symptoms after COVID-19, monitor and optimise management of underlying medical conditions. [Adapted from Centers for Disease Control and Prevention]

Consensus recommendation

In patients with continuing symptoms after COVID-19, monitor and manage lifestyle factors (e.g. smoking, nutrition, sleep, alcohol use and physical activity).

Consensus recommendation

Schedule regular review as necessary and discuss patient function and symptomatology.

Where possible, use standardised tools to monitor changes in function and symptomology.

Consensus recommendation

Give people information on COVID-19 vaccines and encourage them to follow current official guidance for vaccination. Explain that it is not known if vaccines have any effect on ongoing symptomatic COVID-19 or post-COVID-19 condition. [Adapted from NICE]

Consensus recommendation

In patients with continuing symptoms after COVID-19, do not use unproven therapies outside of guidelines or randomised trials with appropriate ethical approval.

Numerous therapies are being evaluated to determine their effectiveness and safety in treating people with long COVID. We continually monitor new research for randomised trials that evaluate any treatments for long COVID. As new trials are published, our panels assess and make recommendations on whether the treatment should be used in the clinical care of patients.

Some symptoms of long COVID can be treated with well-established clinical approaches and clinicians should continue to use existing guidelines and clinical expertise when offering these approaches. For other treatments, however, the evidence is uncertain because there are too few trials or the overall patient numbers are low. These approaches are therefore only recommended for use in research, i.e. in randomised trials with appropriate ethical approval.

When sufficient evidence emerges that changes the recommendation from 'research only' we will update this in the guideline.

13.4 Therapies not recommended outside of clinical trials

New

Info Box

The Taskforce has reviewed high-quality evidence for several therapies used to prevent or treat post-COVID-19 condition. We continually monitor new research for randomised trials that evaluate any disease-modifying therapies for post-COVID-19 condition. As new trials are published, our panels assess and make recommendations on whether the therapy should be used in the clinical care of patients.

For many of these therapies, there is insufficient evidence to determine whether they are safe and/or effective in preventing or treating post-COVID-19 condition. As a result, the Taskforce recommends that these therapies are only used in research (i.e. in randomised trials with appropriate ethical approval), and are not used to prevent or treat post-COVID-19 condition until more definitive evidence is available.

Some symptoms of post-COVID-19 condition can be treated with well-established clinical approaches and clinicians should continue to use existing guidelines and clinical expertise when offering these approaches.

Only in research settings

New

For people with symptoms of post-COVID-19 condition, do not use fluvoxamine outside of randomised trials with appropriate ethical approval.

The COVID-OUT trial investigated whether fluvoxamine, metformin or ivermectin given during the acute illness prevented a diagnosis of post-COVID-19 condition [590]. We cannot use this study to develop an evidence-based recommendation because (1) the outcome of long COVID prevention was selected after the trial started, hence the trial was not adequately powered to detect a difference; (2) the self-reported outcome of a diagnosis of long COVID is not standardised and may result in variation; and (3) the study found large variation in the control arms of the study, with overlapping confidence intervals between control and intervention arms.

When sufficient evidence emerges that changes the recommendation from 'research only' we will update the guideline.

Only in research settings

Updated

For people with symptoms of post-COVID-19 condition, do not use hyperbaric oxygen therapy outside of randomised trials with appropriate ethical approval.

The panel also notes that the financial cost of attending hyperbaric oxygen therapy sessions is significant.

When sufficient evidence emerges that changes the recommendation from 'research only' we will update the guideline.

Only in research settings

New

For people with symptoms of post-COVID-19 condition, do not use ivermectin outside of randomised trials with appropriate ethical approval.

The COVID-OUT trial investigated whether fluvoxamine, metformin or ivermectin given during the acute illness prevented a diagnosis of post-COVID-19 condition [590]. We cannot use this study to develop an evidence-based recommendation because (1) the outcome of long COVID prevention was selected after the trial started, hence the trial was not adequately powered to detect a difference; (2) the self-reported outcome of a diagnosis of long COVID is not standardised and may result in variation; and (3) the study found large variation in the control arms of the study, with overlapping confidence intervals between control and intervention arms.

When sufficient evidence emerges that changes the recommendation from 'research only' we will update the guideline.

Only in research settings

New

For people with symptoms of post-COVID-19 condition, do not use metformin outside of randomised trials with appropriate ethical approval.

The COVID-OUT trial investigated whether fluvoxamine, metformin or ivermectin given during the acute illness prevented a diagnosis of post-COVID-19 condition [590]. We cannot use this study to develop an evidence-based recommendation because (1) the outcome of long COVID prevention was selected after the trial started, hence the trial was not adequately powered to detect a difference; (2) the self-reported outcome of a diagnosis of long COVID is not standardised and may result in variation; and (3) the study found large variation in the control arms of the study, with overlapping confidence intervals between control and intervention arms.

When sufficient evidence emerges that changes the recommendation from 'research only' we will update the guideline.

Only in research settings

Updated

For people with symptoms of post-COVID-19 condition, do not use naltrexone outside of randomised trials with appropriate ethical approval.

Side effects of naltrexone include nausea, headache, dizziness, anxiety, fatigue, insomnia and hepatotoxicity. After stopping naltrexone patients are more sensitive to the effects of opioids (tolerance is reduced) and the risk of opioid overdose and death are increased [175].

When sufficient evidence emerges that changes the recommendation from 'research only' we will update the guideline.

Only in research settings

New

For people with symptoms of post-COVID-19 condition, do not use multiple vitamin therapies outside of randomised trials with appropriate ethical approval, unless there are specific indications for using vitamins.

Overuse of multiple vitamin therapies can lead to a range of physical side effects including vitamin toxicity.

When sufficient evidence emerges that changes the recommendation from 'research only' we will update the guideline.

14. Timing of surgery following COVID-19 infection

Conditional recommendation against

Do not routinely perform elective surgery within 7 weeks of recovery from acute illness, following a diagnosis of SARS-CoV-2 infection, unless outweighed by the risk of deferring surgery, such as disease progression or clinical priority. Very low risk or low risk surgical procedures, such as endoscopy or skin incision, should be considered sooner if the clinical need warrants.

Informed consent and, where deemed necessary, shared decision-making with the patient's, healthcare decision-maker or family/carers, should include discussion about the potential increased risk of surgery following a diagnosis of COVID-19 and in the presence of post-acute COVID-19 symptoms.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

In patients with a preoperative diagnosis of SARS-CoV-2 infection, there may be an increase in mortality and morbidity in those who have elective surgery within 7 weeks. This risk needs to be considered with the individual patient's risk of deferring surgery, such as disease progression or clinical priority, to ensure any mortality benefit outweighs any potential harms associated with delaying surgery.

Certainty of the Evidence

Low

Certainty of the evidence is low due to serious imprecision (reliance on a single study) and risk of bias.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values. However, given the differing reasons individual patients will have for undergoing elective surgery, and the differing severity of acute and ongoing symptoms of COVID-19, substantial variablity is expected.

Resources

No important issues with the recommended alternative

We have no systematically collected evidence regarding cost-benefit.

Equity

No important issues with the recommended alternative

We have no systematically collected evidence regarding impact on equity. We acknowledge that multisystem preoperative assessment with a unit familiar with the assessment of people recovering from COVID-19 may be difficult to carry out in rural and remote areas. However, the recommendation considers it may be possible to be carried out via virtual consulation.

Acceptability

Important issues, or potential issues not investigated

Although we have no systematically collected evidence regarding acceptability, there may be important issues with acceptability given the differing reasons individual patients will have for undergoing elective surgery and the differing severity of acute and ongoing symptoms of COVID-19.

Feasibility

No important issues with the recommended alternative

We have no systematically collected evidence regarding feasibility.

Rationale

In patients with a preoperative diagnosis of SARS-CoV-2 infection, there may be an increase in mortality and morbidity in those who have elective surgery within seven weeks.

Clinical Question/ PICO

Population: People with a diagnosis of SARS-CoV-2 infection
Intervention: Surgery
Comparator: No surgery

Summary

Evidence indicates that there may be an increase in death and morbidity in patients who have elective surgery within 7 weeks of a diagnosis of SARS-CoV-2 infection.

What is the evidence informing this recommendation?
Evidence comes from a multi-centre, prospective, cohort study of patients undergoing elective or emergency surgery (140,231 patients from 116 countries) *[271]*. Surgical patients with preoperative SARS-CoV-2 infection (3127 patients) were compared with those without previous SARS-CoV-2 infection (137,104 patients).

The primary endpoint was 30-day postoperative death. The study reported adjusted analysis by patients whose symptoms had resolved. A sensitivity analysis was performed including only elective patients with preoperative SARS-CoV-2 infection (1762 patients) compared with those without previous SARS-CoV-2 infection (95,680 patients).

Study characteristics
The time from SARS-CoV-2 diagnosis to surgery was 0–2 weeks in 1138 patients (36%), 3–4 weeks in 461 patients (15%), 5–6 weeks in 326 patients (10%) and ≥ 7 weeks in 1202 patients (38%). Preoperative SARS-CoV-2 infection was confirmed with a RT-PCR swab in 80% (2486/3127) of patients. Symptomatic infection was reported in 55% (1726/3127) of preoperative SARS-CoV-2 infections. Of these symptomatic infections, 969 (56%) were not hospitalised, 497 (29%) were hospitalised for COVID-19 but did not require respiratory support, and 259 (15%) were hospitalised for COVID-19 and required respiratory support.

What are the main results?
In patients undergoing elective surgery, timing of surgery resulted in increased 30-day postoperative death at 0–2 weeks (OR 5.50, 95% CI 3.24 to 9.34), 3–4 weeks (OR 3.95, 95% CI 2.18 to 7.15) and at 5–6 weeks (OR 4.14, 95% CI 2.05 to 8.33) when compared with the reference standard (no preoperative SARS-CoV-2 diagnosis). However, this increase was not reported at ≥ 7 weeks (OR 1.03, 95% CI 0.50 to 2.09) from time of diagnosis with SARS-CoV-2. The trend was replicated in subgroup analyses by age, American Society of Anesthesiologists physical status, urgency, and grade of surgery.

The study also reported that deaths were higher among patients who reported ongoing symptoms at time of surgery at 0–2 weeks (OR 14.88, 95% CI 11.54 to 18.21), 3–4 weeks (OR 13.77, 95% CI 9.26 to 18.28), 5–6 weeks (OR 12.83, 95% CI 7.35 to 18.30) and at ≥ 7 weeks (OR 5.96, 95% CI 3.24 to 8.68). At ≥ 7 weeks, deaths were still higher among patients reporting ongoing symptoms (6.0%, 95% CI 3.2 to 8.7) than among patients whose symptoms had resolved (2.4%, 95% CI 1.4 to 3.4) or who had been asymptomatic (1.3%, 95% CI 0.6 to 2.0).

Our confidence in the results
Certainty of the evidence is low due to serious imprecision (only one study) and risk of bias.

Additional information
A rapid review by the Royal Australasian College of Surgeons (RACS) included 20 studies (12 peer reviewed) *[273]*. It included one case-control study and 18 case-series that reported on long-term clinical characteristics of COVID-19. The rapid review also included one prospective cohort study, which reported the risk of past SARS-CoV-2 infection on postoperative outcomes. (The study was a subgroup analysis of the previously reported prospective cohort study.) RACS recommends waiting 8–12 weeks, if possible.

The rapid review also identified five expert consensus guidance documents. The advice varied, with some advising a 2–4 week delay, some 8 weeks and others advising delaying until patients are no longer infectious and have recovered from COVID-19.

The Taskforce also notes another paper that contained recommendations from the Association of Anaesthetists, Centre for Peri-operative Care, Federation of Surgical Specialty Associations, Royal College of Anaesthetists and Royal College of Surgeons of England *[272]*. They recommended no elective surgery within 7 weeks of diagnosis with SARS-CoV-2 infection.

Outcome Timeframe	**Study results and measurements**	**Comparator** No surgery	**Intervention** Surgery	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
30-day postoperative mortality in elective surgery patients	Based on data from 1,762 participants in 1 studies. (Observational (non-randomized))	Timing of surgery was associated with an increased risk of mortality at 0–2 weeks (OR 5.50, 95% CI 3.24 to 9.34), 3–4 weeks (OR 3.95, 95% CI 2.18 to 7.15) and at 5–6 weeks (OR 4.14, 95% CI 2.05 to 8.33). No increased risk was reported at ≥7 weeks (OR 1.03, 95% CI 0.50 to 2.09) from time of diagnosis with SARS-CoV-2.		**Low** Due to serious imprecision and risk of bias [1]	Timing of surgery less than 7 weeks after COVID-19 diagnosis may increase risk of 30-day postoperative mortality in elective surgery patients.

Attached Images

Conditional recommendation

For people undergoing elective surgery following a diagnosis of SARS-CoV-2 infection, consider carrying out multisystem preoperative assessment in consultation with a unit familiar with the assessment of people recovering from COVID-19.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

In patients with a preoperative diagnosis of SARS-CoV-2 infection, there may be an increase in mortality and morbidity in those patients with ongoing symptoms following COVID-19 infection at the time of surgery. This risk needs to be considered with the individual patient's risk of deferring surgery, such as disease progression or clinical priority, to ensure any mortality benefit outweighs any potential harms associated with delaying surgery.

Certainty of the Evidence

Low

Certainty of the evidence is low due to serious imprecision (reliance on a single study) and risk of bias.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values. However, given the differing reasons individual patients will have for undergoing elective surgery, and the differing severity of acute and ongoing symptoms of COVID-19, substantial variability is expected.

Given the likely variability in practice, the Consumer Panel believes that patients would value discussion with the treating physicians regarding the outcomes of preoperative assessment.

Resources

No important issues with the recommended alternative

We have no systematically collected evidence regarding cost-benefit.

Equity

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity. We acknowledge that multisystem preoperative assessment with a unit familiar with the assessment of people recovering from COVID-19 may be difficult to carry out in rural and remote areas. However, the recommendation considers it may be possible to be carried out via virtual consulation.

Acceptability

Important issues, or potential issues not investigated

Although we have no systematically collected evidence regarding acceptability, there may be important issues with acceptability given the differing reasons individual patients will have for undergoing elective surgery and the differing severity of acute and ongoing symptoms of COVID-19.

Feasibility

No important issues with the recommended alternative

We have no systematically collected evidence regarding feasibility.

Clinical Question/ PICO

Population: People with a diagnosis of SARS-CoV-2 infection
Intervention: Surgery
Comparator: No surgery

Summary

Evidence indicates that there may be an increase in death and morbidity in patients who have elective surgery within 7 weeks of a diagnosis of SARS-CoV-2 infection.

What is the evidence informing this recommendation?
Evidence comes from a multi-centre, prospective, cohort study of patients undergoing elective or emergency surgery (140,231 patients from 116 countries) *[271]*. Surgical patients with preoperative SARS-CoV-2 infection (3127 patients) were compared with those without previous SARS-CoV-2 infection (137,104 patients).

The primary endpoint was 30-day postoperative death. The study reported adjusted analysis by patients whose symptoms had resolved. A sensitivity analysis was performed including only elective patients with preoperative SARS-CoV-2 infection (1762 patients) compared with those without previous SARS-CoV-2 infection (95,680 patients).

Study characteristics
The time from SARS-CoV-2 diagnosis to surgery was 0–2 weeks in 1138 patients (36%), 3–4 weeks in 461 patients (15%), 5–6 weeks in 326 patients (10%) and ≥ 7 weeks in 1202 patients (38%). Preoperative SARS-CoV-2 infection was confirmed with a RT-PCR swab in 80% (2486/3127) of patients. Symptomatic infection was reported in 55% (1726/3127) of preoperative SARS-CoV-2 infections. Of these symptomatic infections, 969 (56%) were not hospitalised, 497 (29%) were hospitalised for COVID-19 but did not require respiratory support, and 259 (15%) were hospitalised for COVID-19 and required respiratory support.

What are the main results?
In patients undergoing elective surgery, timing of surgery resulted in increased 30-day postoperative death at 0–2 weeks

(OR 5.50, 95% CI 3.24 to 9.34), 3–4 weeks (OR 3.95, 95% CI 2.18 to 7.15) and at 5–6 weeks (OR 4.14, 95% CI 2.05 to 8.33) when compared with the reference standard (no preoperative SARS-CoV-2 diagnosis). However, this increase was not reported at ≥ 7 weeks (OR 1.03, 95% CI 0.50 to 2.09) from time of diagnosis with SARS-CoV-2. The trend was replicated in subgroup analyses by age, American Society of Anesthesiologists physical status, urgency, and grade of surgery.

The study also reported that deaths were higher among patients who reported ongoing symptoms at time of surgery at 0–2 weeks (OR 14.88, 95% CI 11.54 to 18.21), 3–4 weeks (OR 13.77, 95% CI 9.26 to 18.28), 5–6 weeks (OR 12.83, 95% CI 7.35 to 18.30) and at ≥ 7 weeks (OR 5.96, 95% CI 3.24 to 8.68). At ≥ 7 weeks, deaths were still higher among patients reporting ongoing symptoms (6.0%, 95% CI 3.2 to 8.7) than among patients whose symptoms had resolved (2.4%, 95% CI 1.4 to 3.4) or who had been asymptomatic (1.3%, 95% CI 0.6 to 2.0).

Our confidence in the results
Certainty of the evidence is low due to serious imprecision (only one study) and risk of bias.

Additional information
A rapid review by the Royal Australasian College of Surgeons (RACS) included 20 studies (12 peer reviewed) *[273]*. It included one case-control study and 18 case-series that reported on long-term clinical characteristics of COVID-19. The rapid review also included one prospective cohort study, which reported the risk of past SARS-CoV-2 infection on postoperative outcomes. (The study was a subgroup analysis of the previously reported prospective cohort study.) RACS recommends waiting 8–12 weeks, if possible.

The rapid review also identified five expert consensus guidance documents. The advice varied, with some advising a 2–4 week delay, some 8 weeks and others advising delaying until patients are no longer infectious and have recovered from COVID-19.

The Taskforce also notes another paper that contained recommendations from the Association of Anaesthetists, Centre for Peri-operative Care, Federation of Surgical Specialty Associations, Royal College of Anaesthetists and Royal College of Surgeons of England *[272]*. They recommended no elective surgery within 7 weeks of diagnosis with SARS-CoV-2 infection.

Outcome Timeframe	**Study results and measurements**	**Comparator** No surgery	**Intervention** Surgery	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
30-day postoperative mortality in elective surgery patients	Based on data from 1,762 participants in 1 studies. (Observational (non-randomized))	Timing of surgery was associated with an increased risk of mortality at 0–2 weeks (OR 5.50, 95% CI 3.24 to 9.34), 3–4 weeks (OR 3.95, 95% CI 2.18 to 7.15) and at 5–6 weeks (OR 4.14, 95% CI 2.05 to 8.33). No increased risk was reported at ≥7 weeks (OR 1.03, 95% CI 0.50 to 2.09) from time of diagnosis with SARS-CoV-2.		**Low** Due to serious imprecision and risk of bias [1]	Timing of surgery less than 7 weeks after COVID-19 diagnosis may increase risk of 30-day postoperative mortality in elective surgery patients.

Attached Images

Info Box

The primary panels for the recommendations in this section are the Primary and Chronic Care Panel and the Acute and Critical Care Panel.

Recommendations are reviewed by the Guidelines Leadership Group and approved by the Steering Committee before being published. All our recommendations are reviewed by the Consumer Panel to establish acceptability and applicability to the clinical and patient populations they are most relevant to.

15. Pregnancy and perinatal care

Info Box

For recommendations on drug treatments, chemoprophylaxis, venous thromboembolism (VTE) prophylaxis and respiratory support in pregnant or breastfeeding women, and ACE inhibitors in postpartum women, please see sections above. We are continually working on updating all recommendations to reflect special populations, including pregnant and breastfeeding women.

The Pregnancy and Perinatal Care Panel is responsible for developing recommendations specific to pregnancy and perinatal care.

Recommendations are subsequently reviewed by the Guidelines Leadership Group and approved by the Steering Committee prior to publication. In addition, all recommendations are reviewed by the Consumer Panel to establish acceptability to the patient population for which they are relevant.

15.1 Antenatal corticosteroids

Consensus recommendation

The use of antenatal corticosteroids for women at risk of preterm birth is supported as part of standard care, independent of the presence of COVID-19.

Additional information

There are clear benefits to using antenatal corticosteroids for women at risk of preterm birth at less than 34 weeks' gestation. There is currently no evidence to suggest that antenatal corticosteroids cause additional maternal or fetal harm in the setting of COVID-19 when used for this indication. They should therefore be given where indicated.

The Taskforce has separate recommendations regarding the use of dexamethasone as a drug treatment in pregnant or breastfeeding women for COVID-19. Women with COVID-19 who are on oxygen and receiving dexamethasone do not require additional doses of corticosteroids for fetal lung maturation.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

There are substantial known benefits to using antenatal corticosteroids in preterm birth, which is supported as part of usual care. Antenatal corticosteroids reduce preterm newborn death and morbidities, including respiratory distress, necrotising enterocolitis and intra-ventricular haemorrhage *[274]*. There is currently no evidence to indicate that antenatal corticosteroids for preterm birth should not be used in a woman with confirmed COVID-19.

Certainty of the Evidence

No studies were identified that address the use of antenatal corticosteroids for women who have COVID-19 and are at risk of preterm birth.

Values and preferences

No substantial variability expected

There is no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

The Consumer Panel believes that most women would agree with the recommendation as the available evidence suggests no additional harm to mother or newborn.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Caring for pregnant women with COVID-19, irrespective of whether the baby is preterm or not, requires greater resources than for women without COVID-19.

Equity

Important issues, or potential issues not investigated

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

Acceptability

Important issues, or potential issues not investigated

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

Feasibility

No important issues with the recommended alternative

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

Rationale

There are substantial known benefits for using antenatal corticosteroids for this indication. There is currently no direct evidence to suggest additional harms of using antenatal corticosteroids for preterm birth in the setting of COVID-19. Antenatal corticosteroids should continue to be used as per usual care.

15.2 Magnesium sulfate

Consensus recommendation

The use of magnesium sulfate in pregnancy for fetal neuroprotection for women at risk of preterm birth is supported as part of standard care, independent of the presence of COVID-19.

The use of magnesium sulfate in pregnancy for the management of severe pre-eclampsia or eclampsia is supported as part of standard care, independent of the presence of COVID-19.

Additional information

There are clear benefits to using magnesium sulfate for fetal neuroprotection for women at risk of preterm birth, particularly prior to 32 weeks' gestation [364].

There are also clear benefits to using magnesium sulfate for women with severe pre-eclampsia or eclampsia [363].

There is currently no evidence to suggest that magnesium sulfate can cause additional maternal or fetal harm (such as pulmonary oedema) in the setting of COVID-19 when used for this indication. Magnesium sulfate should therefore be given where indicated.

In pregnant women with COVID-19 who are receiving magnesium sulfate, renal function and fluid balance should be monitored. If renal impairment develops, the dose of magnesium sulfate may need to be adjusted or withheld accordingly.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

There are substantial benefits to using magnesium sulfate for fetal neuroprotection in preterm birth and for women with severe pre-eclampsia or eclampsia. There is currently no evidence to indicate that magnesium sulfate should not be used in women with confirmed COVID-19.

Certainty of the Evidence

No studies were identified that address the use of magnesium sulfate for fetal neuroprotection in women who have COVID-19.

Values and preferences

No substantial variability expected

There is no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Caring for pregnant women with COVID-19, irrespective of whether the baby is preterm or not, requires greater resources than for women without COVID-19.

Equity

Important issues, or potential issues not investigated

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

Acceptability

Important issues, or potential issues not investigated

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

Feasibility

No important issues with the recommended alternative

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

Rationale

There are substantial benefits for using magnesium sulfate for fetal neuroprotection in preterm birth, and for management of pre-eclampsia and eclampsia. There is currently no direct evidence to suggest additional harms of using magnesium sulfate for fetal neuroprotection in the setting of COVID-19. This intervention should continue to be used as per usual care.

15.3 Mode of birth

Conditional recommendation

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

Additional information

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.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Decisions around mode of birth can include many factors. 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.

Certainty of the Evidence

Very low

- Certainty of the evidence is very low due to reliance observational data (particularly with the inclusion of case reports and case series) and the overall potential for the inclusion of confounding variables. Evidence informing this recommendation comes from a systematic review which assessed SARS-CoV-2 positivity in neonates and the association of mode of birth (vaginal or caesarean) in pregnant women with COVID-19 infection.

Values and preferences

No substantial variability expected

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.

The Consumer Panel believes that most women would agree with the recommendation as there is no available evidence to suggest harm to mother or newborn.

Resources

Important issues, or potential issues not investigated

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

Important issues, or potential issues not investigated

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.

Acceptability

Important issues, or potential issues not investigated

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

No important issues with the recommended alternative

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

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.

Clinical Question/ PICO

Population: Pregnant women with COVID-19
Intervention: Caesarean section
Comparator: Vaginal birth

Summary

There remains significant uncertainty whether mode of birth affects SARS-CoV-2 transmission.

What is the evidence informing this recommendation?
Evidence comes from a living systematic review published in March 2022 by Allotey et al. *[441]*.

Study characteristics
The living review assessed the rates of SARS-CoV-2 status in newborns and associated factors. 472 studies were included in the review (206 were cohort studies), with 49 studies contributing data on mode of delivery.

What are the main results?
Data were pooled from 49 studies with 4814 mother–baby dyads. 159 out of 2429 babies (6.6%) delivered vaginally tested positive for SARS-CoV-2 compared with 99 out of 2385 (4.2%) who were delivered via caesarean section (OR 1.38 95% CI 0.97 to 1.95) *[441]*.

Our confidence in the results
Certainty of the evidence is very low due to reliance on observational data (particularly with the inclusion of case reports and case series) and the overall potential for the inclusion of confounding variables.

Additional information
The Taskforce notes the publication of a WHO scientific brief in February 2021 on the definition and categorisation of the timing of mother-to-child transmission of SARS-CoV-2 *[277]*. The brief acknowledges the limited evidence on the extent of SARS-CoV-2 vertical transmission, due to limitations in existing studies around diagnostic testing and timely sample collection from women and newborns. The WHO brief proposes a classification system to help standardise and improve the detection of vertical transmission.

Outcome Timeframe	**Study results and measurements**	**Comparator** Vaginal birth	**Intervention** Caesarean section	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Number of infected newborns (Allotey 2022) 9 Critical	Based on data from 4,814 participants in 49 studies. (Observational (non-randomized))	159 out of 2429 babies (6.6%) delivered vaginally tested positive for SARS-CoV-2 compared with 99 out of 2385 babies (4.2%) delivered via caesarean section (OR 1.38 95% CI 0.97 to 1.95).		**Very low** Due to very serious risk of bias and serious imprecision and inconsistency. [1]	We are uncertain whether mode of birth increases or decreases the number of infected newborns.

Attached Images

15.4 Delayed umbilical cord clamping

Consensus recommendation

Delayed umbilical cord clamping is supported as part of standard care, independent of the presence of COVID-19.

Additional information

There is currently no evidence that delayed umbilical cord clamping affects the risk of vertical transmission of COVID-19.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

There is currently no evidence to indicate that delayed umbilical cord clamping increases the risk of SARS-CoV-19 transmission from mother to newborn. However, delayed umbilical cord clamping has several health benefits for term and preterm infants *[278][279]*.

Certainty of the Evidence

There is currently no direct evidence on the transmission risk of delayed cord clamping between mothers with COVID-19 and their newborns.

Values and preferences

No substantial variability expected

There is no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

The Consumer Panel believes that most women would agree with the recommendation as there is no available evidence to suggest harm to mother or newborn.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Caring for women or newborns with COVID-19 requires greater resources than for those without COVID-19.

Equity

Important issues, or potential issues not investigated

There are likely no important equity issues.

Acceptability

No important issues with the recommended alternative

Delayed umbilical cord clamping is often performed during the provision of neonatal care and is therefore likely to be acceptable to all stakeholders.

Feasibility No important issues with the recommended alternative

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

Rationale

There is currently no evidence to indicate that delayed umbilical cord clamping affects the risk of vertical transmission of COVID-19. Usual care practices regarding delayed cord clamping of preterm and term newborns should be used.

Clinical Question/ PICO

Population: Pregnant women with COVID-19
Intervention: Delayed cord clamping
Comparator:

Summary

There remains significant uncertainty whether delayed cord clamping affects SARS-CoV-2 transmission.

What is the evidence informing this recommendation?
Evidence comes from a systematic review by Kollikonda et al. *[350]* that assessed the success of different perinatal practices in preventing SARS-CoV-2 transmission between positive mothers and their infants and included cohort studies along with case series and case reports.

Study characteristics
The systematic review included five studies that documented early or delayed cord clamping practices (4 case series/ case reports and one observational study). It was generally not possible to assess how rigorously infection prevention and control practices had been implemented, though it is likely that such practices varied between studies.

The vaccination status of the mothers included in the studies was generally not reported, and none of the studies was conducted during the emergence of any SARS-CoV-2 variants of concern, such as Delta or Omicron.

What are the main results?
Overall, there is insufficient evidence to conclude whether cord clamping practices affect COVID-19 transmission. Diagnosis of COVID-19 occurred in 5/138 (3.6%) of babies in the delayed cord clamping group and 2/222 (0.9%) of babies in the early cord clamping group. All infants who tested positive were asymptomatic.

Our confidence in the results
Certainty of the evidence (across all reviews) is very low due to the inclusion of observational studies likely to be at high risk of bias and very few events. Heterogeneity between studies adds to the lack of clarity. In addition, inconsistent masking or hygiene protocols or inadequate ventilation may confound the overall findings. The studies provide no information about the vaccination status of the mother or the presence of SARS-CoV-2 variants.

Additional information
The Taskforce notes the publication of a WHO scientific brief in February 2021 on the definition and categorisation of the timing of mother-to-child transmission of SARS-CoV-2 *[277]*. The brief acknowledges the limited evidence on the extent of SARS-CoV-2 vertical transmission, due to limitations in existing studies around diagnostic testing and timely sample collection from women and newborns. The WHO brief proposes a classification system to help standardise and improve the detection of vertical transmission.

How up to date is this evidence?
The evidence in this summary was last updated on 28 March 2022. We continually monitor COVID-19 research and update our recommendations when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Outcome Timeframe	**Study results and measurements**	**Comparator**	**Intervention** Delayed cord clamping	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Number of infected newborns (Kollikonda 2022)	Based on data from 360 participants in 5 studies. (Observational (non-randomized))	5 out of 138 babies (3.6%) tested positive for SARS-CoV-2 in the delayed cord clamping group compared with 2 out of 222 babies (0.9%) in the early cord clamping group.		**Very low** Due to variations in outcome definitions, disease severity of infected mothers, and availability of different testing modalities.	We are uncertain whether delayed cord clamping increases or decreases the number of infected newborns.

Attached Images

15.5 Skin-to-skin contact

Consensus recommendation

Early skin-to-skin contact after birth and during the postnatal period is supported, independent of the presence of COVID-19. However, parents with COVID-19 should use infection prevention and control measures (mask and hand hygiene).

Additional information

Early skin-to-skin contact refers to placing the naked baby prone on the parent's bare chest immediately after birth.

Skin-to-skin contact should be encouraged and continue as per usual practice in other postnatal and neonatal settings, such as neonatal ICU and postnatal wards, providing infection prevention and control measures are maintained.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

There are substantial known benefits for skin-to-skin contact between mother and newborn, including significantly reduced newborn mortality and morbidity and improved newborn and parental attachment *[281][282]*. There is currently no evidence to indicate that a woman with a known COVID-19 infection should not practice skin-to-skin with her newborn to prevent transmission of COVID-19, provided they use infection prevention and control measures (mask and hand hygiene) *[350]*.

Certainty of the Evidence

There is currently no direct evidence on the transmission risk of skin-to-skin contact between mothers with COVID-19 and their newborns.

Values and preferences

No substantial variability expected

There is no systematically collected information regarding the preferences and values of women with COVID-19 at this point.

The Consumer Panel believes that most women would agree with the recommendation as there is no available evidence to suggest harm to mother or newborn.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Caring for women and newborns with COVID-19 (irrespective of separation) requires greater resources than for women and newborns without COVID-19.

Equity

Important issues, or potential issues not investigated

There are likely no important equity issues.

Acceptability

Important issues, or potential issues not investigated

Acceptability of skin-to-skin contact between mothers with COVID-19 and their newborns is expected to vary and individual preferences should be considered. Clear communication from health professionals regarding the benefits and harms of skin-to-skin contact is essential to aid discussion around individual preferences and acceptability.

Feasibility

Important issues, or potential issues not investigated

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

Rationale

There is currently no evidence to indicate that skin-to-skin contact affects the risk of vertical transmission of COVID-19. Usual care practices regarding skin-to-skin contact should be used.

Clinical Question/ PICO

Population: Women with COVID-19 who have given birth
Intervention: Skin-to-skin contact
Comparator: No skin-to-skin contact

Summary

There remains significant uncertainty whether early skin-to-skin contact affects SARS-CoV-2 transmission.

What is the evidence informing this recommendation?
Evidence comes from a systematic review that assessed success of different perinatal practices in preventing SARS-CoV-2 transmission between positive mothers and their infants *[350]*. The review included 28 studies (four prospective observational, one multicentre cohort, three retrospective chart reviews, seven case series, and 13 case reports). Six studies were rated as good quality, one as moderate, and 21 as poor quality.

Study characteristics
The review included 12 studies (38 newborns) that documented early skin-to-skin contact (variably described “kangaroo care”, “immediate skin-to-skin contact” or “immediate bonding”, as compared to “strict isolation measures” or “separated immediately after delivery”). It was generally not possible to assess how rigorously infection prevention and control practices had been implemented, though it is likely that such practices varied between studies. The vaccination status of women and the COVID-19 variant/s were not reported in these studies.

What are the main results?
In the early skin-to-skin contact group, 4/16 (25%) neonates tested positive for COVID-19, while in the comparator group 2/22 (9%) neonates tested positive. All infants who tested positive were asymptomatic. There is insufficient evidence to conclude whether early skin-to-skin contact affects COVID-19 transmission.

Our confidence in the results
Evidence comes from retrospective observational studies with very few events, which are likely to be at high risk of bias.

Additional information
The Taskforce notes the publication of a WHO scientific brief on 8 February 2021 on the definition and categorisation of the timing of mother-to-child transmission of SARS-CoV-2 *[277]*. The brief acknowledges the limited evidence on the extent of SARS-CoV-2 vertical transmission, due to limitations in existing studies around diagnostic testing and timely sample collection from women and newborns. The WHO brief proposes a classification system to help standardise and improve the detection of vertical transmission.

How up to date is this evidence?
The evidence in this summary was last updated on 6 September 2021. We continually monitor COVID-19 research and update our recommendations when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Outcome Timeframe	**Study results and measurements**	**Comparator** No skin-to-skin contact	**Intervention** Skin-to-skin contact	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Number of infected newborns [1] Within 30 days of exposure 9 Critical	Based on data from 106 participants in 1 studies. (Observational (non-randomized))	See summary for details. Included 106 newborns born to 116 mothers with confirmed SARS-CoV-2 infection. Newborns were tested for infection at 12–24 hours, 5–7 days and 14 days of life. All newborns returned negative test results at all timepoints.		**Very low** Due to very serious risk of bias and imprecision, and serious indirectness [2]	We are uncertain whether skin-to-skin contact increases or decreases the number of infected newborns.

Attached Images

15.6 Breastfeeding

Conditional 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.

Additional information

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. If the baby is being fed with expressed breast milk or formula, the same infection prevention and control measures (mask and hand hygiene) should be used.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

There are substantial known benefits for breastfeeding for the health and well-being of mothers and newborns, which is supported as part of usual care. Breastfeeding reduces child death, promotes newborn development and reduces the risk of infectious and chronic disease. For mothers, breastfeeding reduces the risk of ovarian and breast cancer *[284]*. There is currently no evidence to indicate that a woman with a known COVID-19 infection should not breastfeed her newborn to prevent transmission, provided they use infection prevention and control measures (mask and hand hygiene).

Certainty of the Evidence

Very low

Certainty of the evidence is very low due to reliance on case reports and case series.

Values and preferences

Substantial variability is expected or uncertain

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.

The Consumer Panel believes that most women would agree with the recommendation as there is no available evidence to suggest harm to mother or newborn. The panel notes that some women might still choose not to breastfeed based on reasons unrelated to COVID-19.

Resources

Important issues, or potential issues not investigated

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 are likely no important equity issues.

Acceptability

Important issues, or potential issues not investigated

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

No important issues with the recommended alternative

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

Population: Newborns of mothers with confirmed COVID-19
Intervention: Breastfeeding or breast milk
Comparator: No breastfeeding or breast milk

Summary

There remains significant uncertainty whether transmission of SARS-CoV-2 infection via breast milk is possible.

What is the evidence informing this recommendation?
A living systematic review by Allotey et al. *[441]* published in March 2022 provides the most up-to-date evidence on the transmission of SARS-CoV-2 through infant feeding and early care practices. The review only includes observational studies. The review findings are consistent with earlier systematic reviews *[350][285][286]* (see Study characteristics).

The impact of breastfeeding on transmission of SARS-CoV-2 can be examined in several ways—these approaches have been identified in the included studies:

1. Number of SARS-CoV-2 positive babies in breastfed cohorts compared with the number of SARS-CoV-2 positive babies within cohorts that are not breastfed.
2. Confirmation of SARS-CoV-2 in breast milk of SARS-CoV-2-infected breastfeeding mothers, which suggests the potential for transmission.

Study characteristics
The living review from Allotey assessed the rates of SARS-CoV-2 status in newborns and associated factors. Of the 472 studies included in the review, 206 were cohort studies—the remaining were case series and case reports. Thirteen cohort studies compared breastfed babies with babies who were not breastfed. The detection of SARS-CoV-2 within breast milk was also assessed. Heterogeneity in populations, tests and outcomes is noted.

A systematic review by Kollikonda et al. *[350]* published in June 2021 included 25 studies that assessed the success of different perinatal practices (including breastfeeding) in preventing SARS-CoV-2 transmission between positive mothers and their infants. The review included cohort, case series and case reports. The studies were largely of poor quality, and it was generally not possible to assess how rigorously infection prevention and control practices had been implemented, though it is likely that such practices varied between studies.

A systematic review by Zhu et al. *[286]* published in February 2021 assessed the presence of SARS-CoV-2 genome and antibodies in breast milk in SARS-CoV-2 infected mothers. The review included 50 studies (4 cohort studies, 1 case control, 18 case series and 27 case reports) in a qualitative synthesis and 48 studies (all observational, mostly case series and case reports) in a quantitative synthesis (meta-analysis).

A living systematic review by Centeno-Sablante et al. *[285]* published in August 2020 focused on newborn SARS-CoV-2 infection status and detection of SARS-CoV-2 in breast milk from mothers with confirmed SARS-CoV-2 infection. The review included 37 studies which were either case series or case reports.

Of note: across all reviews, the vaccination status of the mothers participating in the studies was generally not included and none of the included studies was conducted during the emergence of any SARS-CoV-2 variants of concern, such as Delta or Omicron.

What are the main results?

Overall, there is insufficient evidence to conclude whether breastfeeding affects COVID-19 transmission.

Allotey *[441]*: data were pooled from 13 studies with 1545 mother-baby dyads—43 out of 783 breastfed babies tested positive for SARS-CoV-2 compared with 39 out of 762 babies who were not breastfed (OR 0.74 95% CI 0.34 to 1.62). SARS-CoV-2 positivity was detected in the breast milk of eight women out of 328 women tested across 14 studies. The review did not find any association between breastfeeding practice and SARS-CoV-2 positivity in neonates, consistent with rare findings of RT-PCR positivity in breast milk samples.

Kollikonda *[350]*: 25 studies documented breastfeeding or bottle-feeding practices—the proportion of neonates who tested positive in the breastfed group was 11.5% (22/190) compared with 2.6% (4/152) in the bottle-fed group. Almost all infants who tested positive for COVID-19 were asymptomatic—two neonates developed low-grade fevers but without respiratory symptoms, and one preterm infant had respiratory symptoms, which were presumed to be related to prematurity rather than COVID-19—indicating that transmission did not translate into newborn harms.

Zhu *[286]*: 213 women with SARS-CoV-2 infection—183 women had SARS-CoV-2 genome testing of their breast milk, 30 had antibody testing of their breast milk and 89 had both genome and antibody testing. Twelve out of 183 women from 48 studies were positive for SARS-CoV-2 genome in their breastmilk (pooled proportion 5% (95% CI 2% to 15%)). Six infants of these 12 mothers tested positive for SARS-CoV-2, with one requiring respiratory support. The review concluded that SARS-CoV-2 genome presence in breastmilk is uncommon and is generally associated with mild symptoms in infants, while anti-SARS-CoV-2 antibodies may be a more common finding.

Centeno-Sablante *[285]*: 37 studies included 77 infants whose mothers were diagnosed with COVID-19 and provided a breast milk sample for analysis. Nineteen infants (2 years and younger) were confirmed COVID-19 cases—10 were reported to be breastfed, 4 were mix-fed (partly breastfed), and the rest were either formula-fed or data were lacking. Nine out of 68 breast milk samples analysed from mothers with COVID-19 were positive for SARS-CoV-2 RNA—four infants were positive and two were negative for COVID-19. The review concluded that there is no evidence of SARS-CoV-2 transmission through breast milk.

Our confidence in the results
Certainty of the evidence (across all reviews) is very low due to the reliance on observational studies, most of which are low-quality with few events and likely to be at high risk of bias. Heterogeneity between studies adds to the lack of clarity. In addition, inconsistent masking or hygiene protocols, or inadequate ventilation may be confounding factors. The impact on transmission of mothers' COVID-19 vaccination status and the role of SARS-CoV-2 variants is unclear.

Additional information
The Taskforce notes the publication of a WHO scientific brief in February 2021on the definition and categorisation of the timing of mother-to-child transmission of SARS-CoV-2 *[277]*. The brief acknowledges the limited evidence on the extent of SARS-CoV-2 vertical transmission, due to limitations in existing studies around diagnostic testing and timely sample collection from women and newborns. The WHO brief proposes a classification system to help standardise and improve the detection of vertical transmission.

Further, a WHO scientific brief on breastfeeding and COVID-19 from June 2020 concluded that data were insufficient to conclude that SARS-CoV-2 can be transmitted postnatally from an infected mother to her infant through breast milk and that the benefits of breastfeeding (with infection prevention and control measures) outweigh potential risks *[287]*.

How up to date is this evidence?
The evidence in this summary was last updated on 28 March 2022. We continually monitor COVID-19 research and update our recommendations when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Outcome Timeframe	**Study results and measurements**	**Comparator** No breastfeeding or breast milk	**Intervention** Breastfeeding or breast milk	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Number of infected newborns (Allotey 2022) End of follow-up 9 Critical	Based on data from 1,545 participants in 13 studies. (Observational (non-randomized))	43 out of 783 breastfed babies (5.5%) tested positive for SARS-CoV-2 compared with 39 out of 762 babies (5.1%) who were not breastfed (OR 0.74 95% CI 0.34 to 1.62).		**Very low** Due to very serious risk of bias, inconsistency and imprecision.	It is unclear whether breastfeeding increases or decreases number of infected newborns born to mothers with confirmed COVID-19.
Number of SARS-CoV-2 positive breast milk samples (Allotey 2022) End of follow-up 9 Critical	Based on data from 328 participants in 14 studies. (Observational (non-randomized))	SARS-CoV-2 positivity was detected in the breast milk of 8 out of 328 women tested.		**Very low** Due to very serious risk of bias, inconsistency and imprecision.	It is unclear whether breastfeeding increases or decreases number of infected newborns born to mothers with confirmed COVID-19.

Attached Images

15.7 Rooming-in

Conditional recommendation

For women with COVID-19 who have given birth, support rooming-in of mother and newborn in the birth suite and on the postnatal ward when both mother and baby are well. However, women with COVID-19 should use infection prevention and control measures (mask and hand hygiene).

Additional information

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 with COVID-19 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, these women should practice physical distancing when not feeding or caring for the baby.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

There are substantial known benefits for keeping mother and newborn together postpartum, which is supported as part of usual care. Rooming-in of mother and newborn promotes bonding and increases exclusive breastfeeding at discharge *[289]* as well as duration of breastfeeding *[290]*. 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, provided they use infection prevention and control measures (mask and hand hygiene).

Certainty of the Evidence

Very low

Certainty of the evidence is very low due to reliance on case reports and case series.

Values and preferences

No substantial variability expected

There is no systematically collected information regarding the preferences and values of women with COVID-19 at this point. The Consumer Panel believes that most women would agree with the recommendation as there is no available evidence to suggest harm to mother or newborn.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Caring for women and newborns with COVID-19 (irrespective of separation) requires greater resources than for women and newborns without COVID-19.

Equity

Important issues, or potential issues not investigated

There are likely no important equity issues.

Acceptability

Important issues, or potential issues not investigated

Acceptability of rooming-in is expected to vary and individual preferences should be considered. Clear communication from health professionals regarding the benefits and harms of rooming-in is essential to aid discussion around individual preferences and acceptability.

Feasibility

Important issues, or potential issues not investigated

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

Rationale

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, taking into consideration the 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

There remains significant uncertainty around whether rooming-in practices affect SARS-CoV-2 transmission.

What is the evidence informing this recommendation?
Evidence comes from a living systematic review published in March 2022 by Allotey et al. *[441]* and a systematic review by Kollikonda et al. *[350]* published in June 2021. The earlier Kollikonda review focused on the transmission of SARS-CoV-2 through infant feeding and early care practices, and included cohort studies along with case series and case reports. Although there is some overlap in the studies included in these reviews, the additional data captured in the Allotey review provides the most up-to-date information for this summary.

Study characteristics
The living review from Allotey compared SARS-CoV-2 positivity in infants separated or not separated from their mothers at birth. Of the 472 studies included in the review, 206 were cohort studies—the remaining were case series and case reports. Eleven cohort studies contributed to the data on rooming-in practices.

The systematic review from Kollikonda assessed the success of different perinatal practices in preventing SARS-CoV-2 transmission between positive mothers and their infants. Twenty-three studies compared rooming-in versus isolation measures, however these measures were not defined consistently across the studies. The studies were largely of poor quality, and it was generally not possible to assess how rigorously infection prevention and control practices had been implemented, though it is likely that such practices varied between studies.

The vaccination status of the mothers included in the studies was generally not reported, and none of the studies was conducted during the emergence of any SARS-CoV-2 variants of concern, such as Delta or Omicron.

What are the main results?
Allotey: Eleven studies contributed data on 1617 mother-baby dyads—of the 658 babies who were not separated at birth, 42 tested positive to COVID-19, and of the 959 babies who were separated at birth, 48 tested positive to COVID-19 (OR 1.37 95% CI 0.47 to 3.98). This review found no association between SARS-CoV-2 positivity in babies and mother-baby separation at birth.

Kollikonda: The review included relevant data on 403 mother-baby dyads—19.4% (20/103) of babies tested positive to COVID-19 in the rooming-in group and 1.7% (5/300) in the isolation group. After excluding case reports and short case series (< 5), the positivity rate was 15.5% (15/97) in the rooming-in group and 1.0% (3/289) in the isolation group. None of the infants who tested positive for COVID-19 exhibited symptoms, indicating that transmission did not translate into newborn harms.

Our confidence in the results
Certainty of the evidence (across both reviews) is very low due to the reliance on observational studies which are likely

to be at high risk of bias. Heterogeneity between studies adds to a lack of clarity. In addition, inconsistent masking or hygiene protocols, and inadequate ventilation may have confounded the overall findings. The impact on transmission of mothers' COVID-19 vaccination status and the role of SARS-CoV-2 variants is unclear.

Additional information
The Taskforce notes the publication of a WHO scientific brief in February 2021 on the definition and categorisation of the timing of mother-to-child transmission of SARS-CoV-2 *[277]*. The brief acknowledges the limited evidence on the extent of SARS-CoV-2 vertical transmission, due to limitations in existing studies around diagnostic testing and timely sample collection from women and newborns. The WHO brief proposes a classification system to help standardise and improve the detection of vertical transmission.

How up to date is this evidence?
The evidence in this summary was last updated on 28 March 2022. We continually monitor COVID-19 research and update our recommendations when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Outcome Timeframe	**Study results and measurements**	**Comparator** No rooming-in	**Intervention** Rooming-in	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Number of infected newborns (Allotey 2022) End of follow-up 9 Critical	Based on data from 1,617 participants in 11 studies. (Observational (non-randomized))	42 babies out of 658 mother-baby dyads (6.4%) not separated at birth tested positive for SARS-CoV-2 compared with 48 babies out of 959 mother-baby dyads (5.0%) who were separated at birth (OR 1.37 95% CI 0.47 to 3.98).		**Very low** Due to serious inconsistency and reliance on observational data. [1]	We are uncertain whether rooming-in increases or decreases the number of infected newborns.
Number of infected newborns (Kollikonda 2021) [2] Within 30 days of exposure 9 Critical	Based on data from 403 participants in 23 studies. (Observational (non-randomized))	20 out of 103 babies (19.4%) cared for in the same room as their mother tested positive for SARS-CoV-2 compared with 5 out of 300 babies (1.7%) who were kept isolated from their mother.		**Very low** Due to serious inconsistency and reliance on observational data. [3]	We are uncertain whether rooming-in increases or decreases the number of infected newborns.

Attached Images

16. Child and adolescent care

Info Box

For recommendations on drug treatments, chemoprophylaxis and respiratory support in children and adolescents please see sections above. We are continually working on updating all recommendations to reflect special populations, including children and adolescents.

The Paediatric and Adolescent Care Panel is responsible for developing recommendations specific to child and adolescent care.

Recommendations are subsequently reviewed by the Guidelines Leadership Group and approved by the Steering Committee prior to publication. In addition, all recommendations are reviewed by the Consumer Panel to establish acceptability to the patient population for which they are relevant.

16.1 Paediatric Inflammatory Multisystem Syndrome (PIMS-TS)

Info Box

Since late April, clinicians have described a condition among severely ill children and adolescents of fever and significant inflammation, often with abdominal pain, rash or shock. This condition has occurred in settings with substantial community incidence of COVID-19 and these children often have evidence of prior SARS-CoV-2 infection. The condition has provisionally been named paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) by clinicians from the United Kingdom *[294]*. The US Centers for Disease Control and Prevention has named it multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C) *[292]*. WHO has also defined this condition and used the label MIS-C *[293]*.

In Australia, the Acute Inflammatory Vasculitis working group, the Paediatric Active Enhanced Disease Surveillance (PAEDS) network and the Royal Australasian College of Physicians have issued a statement on PIMS-TS *[291]*. The Taskforce aligns with this statement, pending further evidence. In assessing the international literature on this condition, the Taskforce favours the PIMS-TS case definition from the Royal College of Paediatrics and Child Health (UK) *[294]* as we judge this to be most aligned with current Australian practice. The Taskforce will, however, review and include evidence to inform our recommendations from data using any of the three case definitions (listed below for comparison). Click here for a side-by-side comparison of the three definitions (adapted from *[295]*).

The Taskforce endorses the PIMS-TS case definition from the Royal College of Paediatrics and Child Health (United Kingdom) *[294]*.

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated C-reactive protein (CRP) and lymphopenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features*. This may include children fulfilling full or partial criteria for Kawasaki disease.
2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).
3. SARS-CoV-2 PCR testing may be positive or negative. All stable children should be discussed as soon as possible with specialist services to ensure prompt treatment (paediatric infectious disease / cardiology / rheumatology). There should be a low threshold for referral to paediatric intensive care using normal pathways.

* Additional features include:
Clinical

- All: persistent fever > 38.5°C
- Most: oxygen requirement, hypotension
- Some: abdominal pain, confusion, conjunctivitis, cough, diarrhoea, headache, lymphadenopathy, mucus membrane changes, neck swelling, rash, respiratory symptoms, sore throat, swollen hands and feet, syncope, vomiting

Imaging and electrocardiogram (ECG)

- Echocardiogram and ECG: myocarditis, valvulitis, pericardial effusion, coronary artery dilatation
- Chest x-ray: patchy symmetrical infiltrates, pleural effusion
- Abdominal ultrasound scan: colitis, ileitis, lymphadenopathy, ascites, hepatosplenomegaly
- Computed tomography (CT) chest: as for chest x-ray—may demonstrate coronary artery abnormalities if with contrast

Laboratory

- All: abnormal fibrinogen, absence of potential causative organisms (other than SARS-CoV-2), high CRP, high D-dimers, high ferritin, hypoalbuminaemia, lymphopenia, neutrophilia in most – normal neutrophils in some
- Some: acute kidney injury, anaemia, coagulopathy, high IL-10 (if available)**, high IL-6 (if available)**, neutrophilia, proteinuria, raised creatine kinase (CK), raised lactic acid dehydrogenase (LDH), raised triglycerides, raised troponin, thrombocytopaenia, transaminitis

** These assays are not widely available. CRP can be used as a surrogate marker for IL-6.

Additionally, in Australia the PAEDS network definition may be used for case reporting and identification of suspected cases.

For a comparison of PIMS-TS / MIS-C international definitions click here.

Consensus recommendation

Children and adolescents who have suspected or confirmed PIMS-TS should be managed by and their care discussed with a multidisciplinary team. Because of the potential for rapid deterioration, early consultation with experts and consideration of early transfer to a paediatric hospital with intensive care facilities to manage children are recommended for patients with suspected or confirmed PIMS-TS.

16.1.1 Aspirin and antithrombotic agents

Consensus recommendation

For children with PIMS-TS* who are treated with intravenous immunoglobulin, steroids (e.g. methylprednisolone) or biologic agents (e.g. anti IL-1; anti IL-6; anti-TNF), low-dose aspirin should be prescribed (3–5 mg/kg once daily for at least 6 weeks).

** paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2*

Additional information

If contraindications to aspirin therapy exist (e.g. active bleeding or platelets <100,000) seek expert advice, e.g. from haematology or cardiology, as relevant.

Additional measures to be considered to prevent venous thrombosis associated with PIMS-TS include:

- *Anticoagulation therapy*
- *Compression stockings (in children older than 12 years of age)*

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Aspirin is not routinely recommended in children due to the risk of Reye's syndrome. However, there are potential benefits of using aspirin in children and adolescents, particularly in Kawasaki disease, which shares common characteristics and partially overlaps with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS). There are also other well-known harms to consider when administering aspirin at higher doses, such as increased risk of gastrointestinal bleeding, acute kidney injury, tinnitus or bronchospasm.

Certainty of the Evidence

No randomised trials have been identified assessing the use of aspirin or antithrombotic agents for the treatment of PIMS-TS.

Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians. However, we expect the intervention would be generally acceptable as it is regularly used for the treatment of Kawasaki disease.

The Consumer Panel believes that in line with expert consensus and the available evidence, most informed patients, parents, carers, families and guardians would agree with the recommendation for this treatment. The panel recognises that some informed patients, parents, carers, families and guardians may choose not to proceed with this treatment based on reasons unrelated to COVID-19.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

Equity No important issues with the recommended alternative

It is unlikely that the use of aspirin will create equity issues as it is widely available.

Acceptability No important issues with the recommended alternative

Aspirin is generally a well-accepted intervention, and there are no important issues regarding acceptability.

Feasibility Important issues, or potential issues not investigated

Feasibility is affected by prompt diagnosis of PIMS-TS and access to a multidisciplinary team for discussion.

Rationale

Aspirin is used as an antithrombotic to prevent coronary artery thrombosis in Kawasaki disease.

16.1.2 Immunomodulatory agents

Consensus recommendation

In children under 5 years of age with PIMS-TS*:

With no haemodynamic compromise:

- give **intravenous immunoglobulin** 2 g/kg/dose – single dose (maximum 100 g/dose); **AND**
- give **intravenous methylprednisolone** 2 mg/kg/day (maximum 1000 mg/day) for 3 days

With haemodynamic compromise, and/or no/limited improvement with above:

- consider the following, in order, until improvement – please consult specialist as soon as possible:
  - **increase dose of intravenous methylprednisolone** 10 mg/kg/day (maximum 1000 mg/day) for 3 days
  - **add intravenous immunoglobulin** 2 g/kg/dose – single dose (maximum 100 g/dose)
  - **add biologics** anti-IL-1, anti-IL-6 or anti-TNF

Also consider **low-dose aspirin** for all children under 5 years of age with PIMS-TS* – refer to 15.1.1.

In children under 5 years of age with possible PIMS-TS* **and** Kawasaki disease-like clinical features, give **intravenous immunoglobulin** 2 g/kg/dose – single dose (maximum 100 g/dose).

** PIMS-TS: paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2*

Additional information

- *After 3 days of intravenous methylprednisolone, continue with oral prednisolone 2 mg/kg/day (maximum 60 mg/day) when tolerating oral intake and wean over 2–3 weeks. Children with mild illness and rapid response to therapy may be able to cease therapy after 3 days rather than having oral continuation therapy with prednisolone.*
- *Some children with milder illness who can tolerate oral prednisolone can commence therapy with oral prednisolone at 2 mg/kg/day (maximum 60 mg/day) in place of intravenous methylprednisolone.*
- *Kawasaki disease-like phenotype is more common in patients < 5 years of age.*
- *The oncotic load from a large intravenous immunoglobulin (IVIG) dose should be considered when administering this agent to children with myocardial dysfunction. For select cases of PIMS-TS with severe myocardial dysfunction, corticosteroid treatment alone and/or delayed use of IVIG may be beneficial.*

***PIMS-TS severity examples**:*

- *Mild PIMS-TS: no haemodynamic compromise*
  - *IV methylprednisolone 2 mg/kg/day (maximum 1000 mg/day) for 3 days*
- *Moderate PIMS-TS: haemodynamic compromise*
  - *IV methylprednisolone 10 mg/kg/day (maximum 1000 mg/day) for 3 days*
- *Severe PIMS-TS: ICU admission/need for vasoactive support*
  - *IV methylprednisolone 10 mg/kg/day (maximum 1000mg/day) for 3 days; **AND***
  - *IV immunoglobulin 2 g/kg/dose – single dose (maximum 100 g/dose)*
  - *If no improvement, add biologics*

The Taskforce is aware of the study published by Welzel et al (2023) in which 76 patients were treated with either methylprednisolone or IVIG. The median age was 9.1 years (IQR 6.2-12.2), neither treatment changed duration of hospitalisation, although lower respiratory support was observed in methylprednisolone group. One challenge not addressed in this study is differentiating Kawasaki Disease from PIMS-TS in younger children. As IVIG has been recommended for PIMS-TS in children and is routinely recommended in the treatment of Kawasaki Disease, we recommend IVIG as part of combination therapy for these children. We will continue to monitor for further evidence as it emerges and update this recommendation as new evidence becomes available.

Consensus recommendation

In children and adolescents 5 years and older with PIMS-TS*#:

With no haemodynamic compromise:

- give **intravenous methylprednisolone** 2 mg/kg/day (maximum 1000 mg/day) for 3 days

With haemodynamic compromise, and/or no/limited improvement with above:

- consider the following, in order, until improvement – please consult specialist as soon as possible:
  - **increase dose of intravenous methylprednisolone** 10 mg/kg/day (maximum 1000 mg/day) for 3 days
  - **add intravenous immunoglobulin** 2 g/kg/dose – single dose (maximum 100 g/dose)
  - **add biologics** anti-IL-1, anti-IL-6 or anti-TNF

Also consider **low-dose aspirin** for all children and adolescents 5 years and older with PIMS-TS* – refer to 15.1.1.

In children over 5 years of age with possible PIMS-TS* and Kawasaki disease-like clinical features, give **intravenous immunoglobulin** 2 g/kg/dose – single dose (maximum 100 g/dose) and **intravenous methylprednisolone** as initial therapy, doses as above.

** PIMS-TS: paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2*

If thought to be Kawasaki disease, give **intravenous methylprednisolone** 2 mg/kg/day (maximum 1000 mg/day) for 3 days and **intravenous immunoglobulin** 2 g/kg/dose – single dose (maximum 100 g/dose).

Additional information

- *After 3 days of intravenous methylprednisolone, continue with oral prednisolone 2 mg/kg/day (maximum 60 mg/day) when tolerating oral intake and wean over 2–3 weeks. Children with mild illness and rapid response to therapy may be able to cease therapy after 3 days rather than having oral continuation therapy with prednisolone.*
- *Some children with milder illness who can tolerate oral prednisolone can commence therapy with oral prednisolone at 2 mg/kg/day (maximum 60 mg/day) in place of intravenous methylprednisolone.*
- *The oncotic load from a large intravenous immunoglobulin (IVIG) dose should be considered when administering this agent to children with myocardial dysfunction. For select cases of PIMS-TS with severe myocardial dysfunction, corticosteroid treatment alone and/or delayed use of IVIG may be beneficial.*

***PIMS-TS severity examples**:*

- *Mild PIMS-TS: no haemodynamic compromise*
  - *IV methylprednisolone 2 mg/kg/day (maximum 1000 mg/day) for 3 days*
- *Moderate PIMS-TS: haemodynamic compromise*
  - *IV methylprednisolone 10 mg/kg/day (maximum 1000 mg/day) for 3 days*
- *Severe PIMS-TS: ICU admission/need for vasoactive support*
  - *IV methylprednisolone 10 mg/kg/day (maximum 1000 mg/day) for 3 days; **AND***
  - *IV immunoglobulin 2 g/kg/dose – single dose (maximum 100 g/dose)*
  - *If no improvement, add biologics*

The Taskforce is aware of the study published by Welzel et al (2023) in which 76 patients were treated with either methylprednisolone or IVIG. The median age was 9.1 yeas (IQR 6.2-12.2), neither treatment changed duration of hospitalisation, although lower respiratory support was observed in methylprednisolone group. One challenge not addressed in this study is differentiating Kawasaki Disease from PIMS-TS in younger children. As IVIG has been recommended for PIMS-TS in children and is routinely recommended in the treatment of Kawasaki Disease, we recommend IVIG as part of combination therapy for these children. We will continue to monitor for further evidence as it emerges and update this recommendation as new evidence becomes available.

16.1.3 VTE prophylaxis

Consensus recommendation

For **all children and adolescents** hospitalised with COVID-19, the following are recommended to prevent thrombosis, based on age and risk assessment.

> In **children and adolescents aged 12 years and over** who are hospitalised specifically for PIMS-TS / MIS-C treatment and with no contraindications to anticoagulants, use prophylactic doses of low molecular weight heparin* (LMWH) and mechanical thromboprophylaxis (TED stockings or calf compressors) until discharge from hospital.
>
> In **children under 12 years** who are hospitalised specifically for PIMS-TS / MIS-C treatment and **with either D-dimer levels > 5 x upper limit normal or additional thrombosis risk factors** (including hospital-associated venous thromboembolism), use prophylactic doses of low molecular weight heparin* (LMWH) and mechanical thromboprophylaxis (TED stockings or calf compressors) where suitable based on size and mobility until discharge from hospital.

Additional information

In children with PIMS-TS / MIS-C, the presence of myocardial dysfunction or giant coronary artery aneurysms might be an indication for extended duration therapeutic anticoagulation that continues post discharge.

Dose of low molecular weight heparin (LMWH):*

- *≥ 3 months old – enoxaparin 0.5 mg/kg BD (maximum of 60 mg BD, or at the standard adult prophylactic dose for your centre)*
- *< 3 months old – enoxaparin 0.75 mg/kg BD*
- ** Unfractionated heparin (UFH) is an alternative to LMWH and can be considered if there is potential for surgical intervention, renal impairment or other clinical factors that would normally favour UFH over LMWH. Dosing should be advised by paediatric haematology.*

Where the estimated glomerular filtration rate (eGFR) is less than 30 mL/min/1.73m2, UFH or clearance-adjusted doses of LMWH may be used (discuss with paediatric haematologist).

*Contraindications to thromboprophylaxis**

- *Stroke / intracranial haemorrhage*
- *Any bleeding from any site / uncontrolled bleeding*
- *Likely to need surgery in < 24 hours*
- *Congenital bleeding disorder (e.g. Von Willebrand disease, haemophilia)*
- *Platelets < 50 x 10^9/L and/or INR > 1.8*
- *Uncontrolled hypertension*
- ** Consider UFH (unfractionated heparin)*

Thrombosis risk factors

- *Admission to paediatric intensive care unit (PICU)*
- *Obesity (BMI > 95 percentile)*
- *Central venous catheter*
- *Length of stay anticipated > 3 days*
- *Immobility that is not longstanding*
- *Personal history of VTE*
- *Known thrombophilia*
- *First degree relative with VTE*
- *Active malignancy*
- *Recent surgery / trauma*
- *Severe dehydration*
- *Underlying medical condition: nephrotic syndrome, cystic fibrosis, sickle cell disease, cardiac disease, chronic inflammatory disorder (juvenile idiopathic arthritis, inflammatory bowel disease), post splenectomy.*

In the absence of reliable evidence, the Taskforce has developed this recommendation based on their clinical expertise and experience.

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

Prophylactic anticoagulants are used in children and adolescents who are at risk of venous thromboembolism (VTE). The benefit of a modified thromboprophylaxis regimen for children and adolescents with PIMS-TS is unclear. There are well-known benefits of this strategy in selected children with risk factors for VTE. There are well-known harms of thromboprophylaxis such as major bleeding.

Certainty of the Evidence

There is currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in children and adolescents with PIMS-TS.

Values and preferences

No substantial variability expected

We have no systematically collected information regarding preferences and values for children and adolescents, their parents, carers, families or guardians. However, we expect the intervention would be generally acceptable as it is regularly used in other procedures.

Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

Equity

No important issues with the recommended alternative

It is unlikely that the use of thromboprophylaxis will create equity issues as it is common practice.

Acceptability

No important issues with the recommended alternative

Thromboprophylaxis is generally a well-accepted intervention, and there are no important issues regarding acceptability.

Feasibility

No important issues with the recommended alternative

There are no major feasibility issues.

Rationale

Three observational studies on the management of PIMS-TS have been identified *[299][327][328]*.

McArdle 2021 is an international observational cohort study that compared treatment of intravenous immunoglobulin (IVIG) plus glucocorticoids with IVIG alone and glucocorticoids alone in children with multisystem inflammatory syndrome after suspected COVID-19 infection *[328]*. The primary outcomes were a composite of inotropic support or mechanical ventilation (invasive or non-invasive) by day 2 or later or death, and reduction in disease severity. The study found that IVIG plus steroids compared with IVIG alone made no difference to receipt of inotropic or ventilatory support or death (OR 0.77, 95% CI 0.33 to 1.82; 410 patients) or when compared with steroids alone (OR 0.54, 95% CI 0.22 to 1.33; 307 patients).

Son 2021 is a cohort study conducted in the USA that compared IVIG plus glucocorticoids with glucocorticoids alone *[327]*. The primary outcome was cardiovascular dysfunction on or after day 2 until discharge, or shock that resulted in the use of vasopressors. The study found that IVIG plus steroids compared with IVIG alone was associated with lower cardiovascular dysfunction after day 2 (RR 0.56, 95% CI 0.34 to 0.94; 212 patients).

Data from these two studies were pooled with the previously included study by Ouldali 2021 *[299]*. IVIG combined with

steroids compared with IVIG alone probably reduces the need for escalation or adjunctive immunomodulatory therapy (moderate certainty evidence – upgraded due to large treatment effect) and may decrease left ventricular dysfunction (low certainty evidence).

17. Abbreviations and Acronyms

ACE	Angiotensin-converting enzyme
ACEIs	Angiotensin-converting enzyme inhibitors
AEs	Adverse events
AHPPC	Australian Health Protection Principal Committee
ALT	Alanine aminotransferase
ANZICS	Australian and New Zealand Intensive Care Society
ANZPID	Australia and New Zealand Paediatric Infectious Diseases Group
ARBs	Angiotensin receptor blockers
ARDS	Acute respiratory distress syndrome
BiPAP	Bilevel positive airway pressure
BSA	Body surface area
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
CMA	Combined metabolic activators
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019 (disease caused by the virus SARS-CoV-2)
CPAP	Continuous positive airway pressure
CPR	Cardiopulmonary resuscitation
CRP	C-reactive protein
CSR	Clinical study report
CT	Computed tomography
CXR	Chest x-ray
DMARDs	Disease-modifying anti-rheumatic drugs
DMTs	Disease-modifying treatments
DOI	Digital Object Identifier
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECHO	Echocardiogram
ECMO	Extracorporeal membrane oxygenation
eGFR	Estimated glomerular filtration rate
FiO2	Fraction of inspired oxygen
FDA	US Food and Drug Administration

GRADE	Grading of recommendations, assessment, development and evaluation
HCP	Healthcare professionals
HFNC	High-flow nasal cannula
HFNO	High-flow nasal oxygen
HFOV	High-frequency oscillatory ventilation
HRT	Hormone replacement therapy
hUC-MSCs	Human umbilical cord mesenchymal stem cells
HR	Hazard ratio
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
IFN-κ	Interferon kappa
IgG	Immunoglobulin G
IHPS	Infantile hypertrophic pyloric stenosis
IL	Interleukin
IQR	Interquartile range
IU	International units
IV	Intravenous
LMWH	Low molecular weight heparin
MDRD	Modification of diet in renal disease
MERS	Middle East respiratory syndrome
MET	Medical Emergency Team
MIS-C	Multisystem inflammatory syndrome in children
mIU	Milli-international units
MHT	Menopausal hormone therapy
NAb	Neutralising antibodies
NC19CET	National COVID-19 Clinical Evidence Taskforce
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Care Excellence
NIPPV	Non-invasive positive pressure ventilation
NIV	Non-invasive ventilation
NMBAs	Neuromuscular blocking agents
NSAIDs	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
OR	Odds ratio
PaO2	Partial pressure of arterial oxygen

PCR	Polymerase chain reaction
PEEP	Positive end-expiratory pressure
PICU	Paediatric intensive care unit
PICS	Post-intensive care syndrome
PIMS-TS	Paediatric multisystem inflammatory syndrome - temporally associated with SARS-CoV-2
PPE	Personal protective equipment
RACS	Royal Australasian College of Surgeons
rhG-CSF	Recombinant human granulocyte colony-stimulating factor
RR	Risk ratio
RT-PCR	Reverse transcription-polymerase chain reaction
SAEs	Serious adverse events
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2 (the virus that causes the disease COVID-19)
SOT	Supplementary oxygen therapy
SpO2	Oxygen saturation
SSRIs	Selective serotonin reuptake inhibitors
TFF2	Trefoil factor 2
TID	Three times a day
TNF	Tumour necrosis factor
ULN	Upper limit of normal
VA ECMO	Venoarterial extracorporeal membrane oxygenation
VTE	Venous thromboembolism
VV ECMO	Venovenous extracorporeal membrane oxygenation
WHO	World Health Organization

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